BRAIN CONNECTIVITY
Volume 00, Number 00, 2024

DOI: 10.1089/brain.2024.0003

Acute Exercise Improves Large-Scale Brain Network Segregation in Healthy Older Adults

Yash Kommula,[1,2] Daniel D. Callow,[1,4] Jeremy J. Purcell,[1,3] and J. Carson Smith[1–3]

Abstract

Introduction: Age-related cognitive decline and mental health problems are accompanied by changes in resting-state functional connectivity (rsFC) indices, such as reduced brain network segregation. Meanwhile, exercise can improve cognition, mood, and neural network function in older adults. Studies on effects of exercise on rsFC outcomes in older adults have chiefly focused on changes after exercise training and suggest improved network segregation through enhanced within-network connectivity. However, effects of acute exercise on rsFC measures of neural network integrity in older adults, which presumably underlie changes observed after exercise training, have received less attention. In this study, we hypothesized that acute exercise in older adults would improve functional segregation of major cognition and affect-related brain networks.
Methods: To test this, we analyzed rsFC data from 37 healthy and physically active older adults after they completed 30 min of moderate-to-vigorous intensity cycling and after they completed a seated rest control condition. Conditions were performed in a counterbalanced order across separate days in a within-subject crossover design. We considered large-scale brain networks associated with cognition and affect, including the frontoparietal network (FPN), salience network (SAL), default mode network (DMN), and affect-reward network (ARN).
Results: We observed that after acute exercise, there was greater segregation between SAL and DMN, as well as greater segregation between SAL and ARN.
Conclusion: These findings indicate that acute exercise in active older adults alters rsFC measures in key cognition and affect-related networks in a manner that opposes age-related dedifferentiation of neural networks that may be detrimental to cognition and mental health.

Keywords: aging; exercise; functional connectivity; network segregation; resting-state fMRI

Impact Statement

Our findings contribute novel insight on changes in large-scale functional brain network organization after acute exercise in healthy, active older adults. We argue that these effects of acute exercise may benefit cognition and mental health during older age by countering age-related rsFC changes in major functional brain networks (e.g., salience, default mode, and affect-reward networks). Our multilayered analysis approach of large-scale network rsFC (e.g., between-network segregation; within- and between-network connectivity) and novel between-network segregation index formula can feasibly be employed by the field in the future.

[1]Department of Kinesiology, School of Public Health, University of Maryland, College Park, Maryland, USA.
[2]Program in Neuroscience and Cognitive Science, University of Maryland, College Park, Maryland, USA.
[3]Maryland Neuroimaging Center, University of Maryland, College Park, Maryland, USA.
[4]Department of Psychiatry and Behavioral Sciences, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA.

Introduction

The number of older adults is growing rapidly worldwide because of lower birth rates and longer lifespans (Khavinson et al., 2020). While a triumph for humanity, longer lives also raise urgency for a public health response to age-related health issues (Beard et al., 2016). Declines in cognition (Murman, 2015) and greater prevalence of poor mental health (Reynolds et al., 2015) are two major age-related health problems that may be related to changes in how strongly distinct large-scale brain networks are connected (Baez-Lugo et al., 2023; Chong et al., 2019). According to research using resting-state functional connectivity (rsFC) metrics from resting-state functional magnetic resonance imaging (rsfMRI), aging is associated with lower connectivity within brain networks (Varangis et al., 2019) and greater connectivity between brain networks (Iordan et al., 2017). The former reflects deterioration of normal functional brain organization (Varangis et al., 2019), whereas the latter may reflect behaviorally compensatory or harmful dedifferentiation of neural activity (Park and Reuter-Lorenz, 2009; Won et al., 2023). Age-related changes in within- and between-network connectivity combine to result in lower segregation of brain networks, which is indicative of a loss of functional specialization and more shared connections among brain networks (Chan et al., 2014).

Changes in rsFC measures of large-scale brain networks have been shown to be useful predictors of present or impending cognitive decline (Damoiseaux, 2017), as well as mood disorders and their treatment outcomes (Taylor et al., 2021). As growing evidence suggests that aerobic exercise can improve cognition and emotional well-being in older adults (Alfini et al., 2020; Basso and Suzuki, 2017; Busse et al., 2009), it is plausible that these benefits reflect the impacts of exercise on network segregation in older adults. In this study, we report the effects of a single session of aerobic exercise compared to a seated rest control condition on rsFC measures (between-network segregation, within/between-network connectivity, and region of interest-region of interest [ROI-ROI] connectivity) among four major brain networks in healthy and physically active older adults.

Studies of rsFC patterns in the human brain have identified several major functional networks, which likely play crucial roles in subserving cognitive or affect-related processes across the lifespan (Menon, 2011). These major networks each consist of several brain regions and include the default mode network (DMN), frontoparietal network (FPN), salience network (SAL), and affect-reward network (ARN) (Menon, 2011; Weng et al., 2017). Evidence suggests that each of these brain networks has a unique function. For instance, DMN supports introspection and mediates self-referential thoughts and feelings (Mak et al., 2017); FPN is involved with higher-order cognition (Seeley et al., 2007); SAL is important for detecting and integrating salient sensory stimuli, as well as facilitating switching between DMN and FPN engagement (Menon, 2011); and ARN is implicated in affect and reward processing (Weng et al., 2017). DMN, FPN, SAL, and ARN are examples of associative networks that perform cognitive or affect-related processes that require directing and integrating information in a wide range of tasks and across multiple modalities (Mesulam, 1990). Aberrant rsFC patterns among these networks may be implicated in cognitive dysfunction and/or emotional instability (Baez-Lugo et al., 2023; Menon, 2011), highlighting the need for greater understanding of the effects of behavioral interventions such as exercise on rsFC measures in older adults.

Participating in repeated bouts of exercise and exercise training may alter rsFC by increasing functional coherences within age-susceptible brain networks and driving associated improvements in cognitive performance (Won et al., 2021). Notably, the cumulative effects of repeated bouts of exercise are hypothesized to be built on responses to individual exercise sessions (Basso and Suzuki, 2017), and thus, it is important to document the acute effects of exercise on rsFC. One study found that a session of active moderate-intensity cycling (compared to passive cycling) led to greater within-network integration of ARN, hippocampal, SAL, and right executive control (ECN) networks and greater between-network connectivity between SAL and ARN and SAL and ECN in young and older adults (Weng et al., 2017). Effects of acute exercise in that study were focused on associative networks, which may have a greater propensity to exhibit age-related rsFC changes (Chan et al., 2014). Older age positively moderated the strength of acute exercise effects on functional networks in that study as well (Weng et al., 2017). Acute exercise may also enhance positive affect in older adults and reduce rsFC between SAL hubs (left or right anterior insula) and left hippocampus (Alfini et al., 2020).

Previous studies on the effects of acute exercise on rsFC in older adults have reported seed-to-voxel analyses and have not used large-scale network analyses, which limit inferences regarding interactions between distinct larger scale brain networks. A segregation analysis overcomes this limitation by including data from all the major hubs of large-scale networks. Although we have recently shown that acute exercise leads to lower local neural differentiation in frontal cortices and greater local neural differentiation in central and posterior regions of the brain (Purcell et al., 2023), we did not characterize large-scale functional brain organization after acute exercise. In this study, we hypothesized that acute exercise would lead to greater large-scale network segregation between network pairs, which would be driven by greater within-network connectivity and lower between-network connectivity.

Methods

Participants

Forty-one physically active, healthy, cognitively normal, and community-dwelling older adults (ages 60 to 89 years) were recruited from the local community to participate in the study in accordance with the Helsinki Declaration. Participants were excluded if they reported a history of stroke, neurological disease, major psychiatric disorder, diabetes, untreated hypertension, contraindications to exercising on a bike, or any contraindications to undergoing an MRI scan (e.g., claustrophobia, ferromagnetic implant). All included participants completed a telephone screening, baseline session day, acute exercise condition day, and an acute seated rest condition day (order of exercise and rest sessions was counterbalanced across participants).

Baseline session

On a day prior to the two experimental days (acute exercise day, acute rest day), all participants attended a baseline visit. At this baseline session, participants first provided written informed consent approved by the institutional review board. Next, participants completed the Montreal Cognitive Assessment [MoCA; (Nasreddine et al., 2005)], a 30-point questionnaire typically used to screen for potential cognitive impairment. A MoCA score of at least 26 points was required to participate in the study. Participants then completed several questionnaires to provide information about their health history, sleep habits [PSQI, (Buysse et al., 1989)], physical activity [Stanford 7-day Physical Activity Recall questionnaire; (Sallis et al., 1985)], anxiety symptoms [Geriatric Anxiety Scale, (Segal et al., 2010)], and depression symptoms [Geriatric Depression Scale, (Yesavage et al., 1982)]. Finally, participants performed a submaximal exercise stress test to determine baseline cardiorespiratory fitness levels (see procedural details in Supplementary Data S1) and were familiarized with a task that they would perform during task fMRI acquisitions on the two experimental days (Mnemonic Similarity Task).

Exercise and rest conditions

Participants completed two experimental conditions (acute exercise and acute rest) on separate days spaced 1–7 days apart in counterbalanced order [for further details on protocol, see (Callow et al., 2023)]. A within-subject crossover design was used in which each participant completed both conditions. Conditions were performed at the Maryland Neuroimaging Center in the room adjacent to the scanner to minimize the time gap between condition completion and scan initiation to approximately 10 min. Given scheduling restrictions, some participants performed the experimental conditions at slightly different times of day for each condition, although this time difference was a maximum of 2 h. Before each condition, participants were provided standardized instructions for the Borg 6–20 ratings of perceived exertion (RPE) and Self-Assessment Manikin (SAM) scales (Bradley and Lang, 1994; Borg, 1982).

For the acute exercise condition, participants performed a continuous bout of cycling on a Monark cycle ergometer (Varberg, Sweden). Participants completed a 5-min warm-up at a self-selected pace, followed by a 20-min bout of cycling at a target RPE of 13–15 on the Borg 6–20 RPE scale (corresponding to moderate–vigorous intensity and associated with the verbal anchor of “somewhat hard” to “hard”), and finally a 5-min cooldown. Participants were permitted to adjust the resistance of the bike while maintaining a 60–80 revolutions per min cadence to achieve the target RPE during the 20-min bout of moderate–vigorous cycling. Heart rate, RPE, and a subjective valence (pleasantness) and arousal measure using the SAM scale were recorded every 5 min along the condition. Water was provided to participants *ad libitum*, and a towel and clean dry clothing were available after the condition in preparation for the scan. Participants were encouraged not to talk excessively during the condition.

During the acute rest condition, participants were seated on the same cycle ergometer they had used for the acute exercise condition and asked to sit quietly for 30 min. Similar to the acute exercise condition, HR, RPE, subjective valence, and subjective arousal were measured every 5 min along the condition, water was provided *ad libitum*, and participants were encouraged not to talk excessively. Participants did not have access to cell phones or reading materials during their acute seated rest.

MRI assessment

Following each condition, participants were prepared for MRI, and MRI data were then acquired using a Siemens Prisma 3.0 Tesla MR scanner and a 32-channel head coil. Details on structural and functional scanning protocols, rsfMRI data preprocessing and denoising steps, and rsFC measurement units are included in Supplementary Data S1. All rsfMRI pre- and postprocessing was volume based.

We defined four networks for our analyses as follows: the frontoparietal network (FPN), salience network (SAL), default mode network (DMN), and affect-reward network (ARN) (see Table 3 and Fig. 1). We aimed to keep the number of ROIs per network as concise and representative as possible, so we defined ROIs using major nodes identified for each of those rsFC networks in prior literature (Weng et al., 2017; Whitfield-Gabrieli and Nieto-Castanon, 2012). Briefly, left and right hippocampus, amygdala, and nucleus accumbens ROIs were taken directly from CONN’s default atlas regions and derived originally from the Harvard-Oxford atlas (Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006), whereas all other ROIs were taken directly from CONN’s default network regions derived originally from CONN’s independent component analysis of 497 healthy individuals of the Human Connectome Project dataset (Whitfield-Gabrieli and Nieto-Castanon, 2012) (see Supplementary Data S1 for additional details). All network analyses involved obtaining rsFC connectivity values across ROI pairs that could either be within- or between-networks. The network-based measures were calculated using averaging of the rsFC values for all of the within-network (e.g., FPN within-network connectivity) or between-network (e.g., SAL&DMN between-network connectivity) ROI pairs.

Between-network segregation index analysis

A novel between-network segregation index (SI) was calculated for each subject and each condition using mean Pearson’s bivariate correlation coefficients ($\bar{r}$ values). The equation for calculating it was $SI = \frac{(\bar{r}_w + 1) - (\bar{r}_b + 1)}{(\bar{r}_w + 1) + (\bar{r}_b + 1)}$, where $\bar{r}_w$ represents mean within-network connectivity of a network, and $\bar{r}_b$ represents the mean between-network connectivity between the network considered for $\bar{r}_w$ and a different network. This SI formula was adapted from previous research (Chan et al., 2014), but we modified the formula to avoid distortion that could occur from $\bar{z}$ *values* outside of the range of −1 to 1, exceptionally high or low $\bar{z}$ values due to r values close to ±1 (e.g., r = 0.9999), and small near-zero denominator values (e.g., 0.0002). The modified formula scales between a range from −1 (minimum segregation) to 1 (maximum segregation). Furthermore, unlike all previous studies that have calculated network segregation of a single network from nodes of all other considered brain networks, our modified segregation formula was designed to measure segregation between two networks. The conn_withinbetweenROItest function of CONN toolbox was used to attain $\bar{z}_w$ and $\bar{z}_b$ values, which were

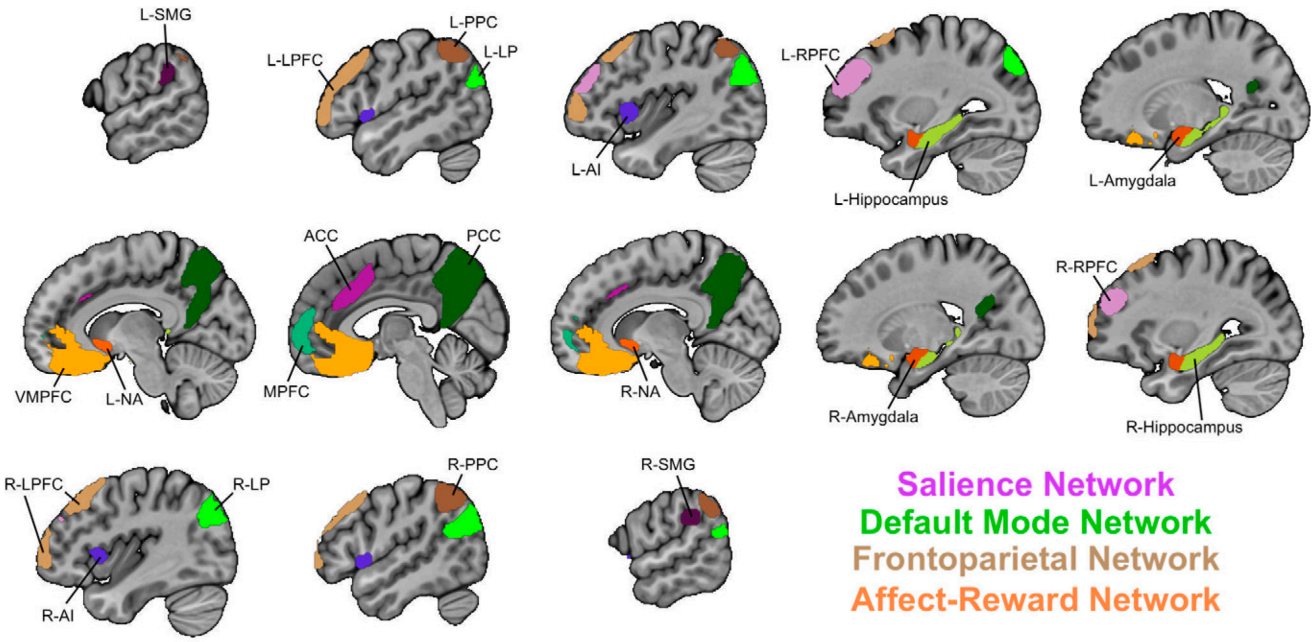

FIG. 1. Regions of defined networks. Colored areas represent the 22 regions of 4 defined networks where connectivity was compared between the exercise and rest conditions (n = 37). As shown in the figure legend (bottom right corner), each network is assigned a color, with different shades within that color representing regions comprising that network (purple = salience network, green = default mode network, brown = frontoparietal network; orange = affect-reward network). L, left; R, right; ACC, anterior cingulate; AI, anterior insula; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus; MPFC, medial prefrontal cortex; LP, lateral parietal region; PCC, precuneus cortex; LPFC, lateral prefrontal cortex; PPC, posterior parietal cortex; NA, nucleus accumbens; VMPFC, ventromedial prefrontal cortex. Sagittal view from left hemisphere to right hemisphere is presented.

then untransformed to the $\overline{r}_w$ and $\overline{r}_b$ values needed for SI calculation. Six network pairs were tested—SAL&DMN, SAL&FPN, SAL&ARN, DMN&FPN, DMN&ARN, and ARN&FPN. Since our modified SI calculation depends on which of the two networks comprising a pair is considered for the $\overline{r}_w$ value, each network in a network pair was considered for $\overline{r}_w$ in two separate SI calculations per network pair. Then, SI calculations were compared between conditions while controlling for sex, condition order, and mean-centered age using a general linear model [CONN_glm function; (Nieto-Castanon, 2020)]. Finally, the p-values for each of the two SI calculations for a network pair were combined using the Simes method (Simes, 1986) for combining p-values (simes.test function in R). Thus, one p-value representing the average and unbiased between-conditions SI difference was achieved per each of the six network pairs.

Within-network and between-network connectivity analyses

The conn_withinbetweenROItest function of CONN toolbox was used to test for between-condition differences in mean within-network ($\overline{z}_w$) and mean between-network ($\overline{z}_b$) connectivity while controlling for sex, condition order, and mean-centered age. This function is an implementation of a general linear model [CONN_glm, (Nieto-Castanon, 2020)]. Within-network connectivity was analyzed for DMN, FPN, SAL, and ARN. Meanwhile, between-network connectivity was assessed for SAL&DMN, SAL&FPN, SAL&ARN, DMN&FPN, DMN&ARN, and ARN&FPN.

Statistical analyses

Statistical analyses were performed using R (R Core Team, 2020). We computed descriptive statistics (e.g., mean, standard deviation, percentage of sample) of baseline demographic variables. Mean and standard deviation for condition-associated variables (e.g., HR, RPE, Valence, Arousal) were calculated using data acquired during the final 10 min of either experimental condition. Furthermore, we ran paired t-tests to test for significant differences on condition-associated variables between the final 10 min of the acute exercise condition and the final 10 min of the seated rest control condition.

For any significant result of any rsFC analysis, the significance of interactions (condition*mean-centered age, condition*condition order, condition*sex) was further investigated. To test each of the three interactions, mixed-effects models, including an outcome variable, interaction term (e.g., condition*mean-centered age), the remaining fixed effects variables (e.g., condition order and sex, when assessing interaction between condition and mean-centered age), and a random effect of subject, were used.

Results

Participants

Of the 41 participants who completed the study, four subjects (3 female, 1 male) were excluded from rsFC analyses because they did not undergo rsfMRI at either or both the postexercise and postrest scan sessions. The final sample for rsFC analyses included 37 participants who were cognitively healthy (MOCA ≥26), had an average age of 66.8 years, and were

Table 1. Participant Characteristics for Demographics, Health, Cardiorespiratory Fitness, Leisure-Time Physical Activity, Cognitive Status, and Depression and Anxiety Symptoms ($N = 37$)

Characteristics	*Mean (SD) [range]*
Age (years)	66.8 (4.6) [60–76]
Female	32 (86.5%)[a]
White	32 (86.5%)[a]
Education (≥ graduate school)	29 (78.4%)[a]
BMI (kg/m^2)	25.6 (4.1) [18.4–40.1]
HRresting (bpm)	67.2 (10.5) [45–86]
VO$_2$max (mL/kg/min)	22.5 (7.2) [9.1–46]
7-day physical activity (MET-hours/week)[b]	91.6 (33.0) [23–175]
MoCA	28.0 (1.35) [26–30]
Geriatric Depression Score	2.8 (2.8) [0–13]
Geriatric Anxiety Score	7.2 (7.8) [0–44]

[a]Female, White, and education are expressed as n (%).
[b]Energy expenditure relative to the resting metabolic rate (1 MET = 1 metabolic equivalent of task = 1 kilocalorie per kilogram of body weight per hour).
SD, standard deviation; BMI, body mass index; kg/m^2, kilograms of body weight per meters of height squared; HRresting, resting heart rate computed as the mean resting heart rate on the acute seated rest day; bpm, beats per minute; VO$_2$max, maximal rate of oxygen consumption; mL/kg/min, milliliters of oxygen per kilogram of body weight per min estimated from submaximal exercise stress test; MoCA, Montreal Cognitive Assessment.

predominantly female ($n = 32$, 86.5%), White ($n = 32$, 86.5%), and highly educated with a graduate-level education ($n = 29$, 78.4%) (see Table 1). Furthermore, the mean ± standard deviation for several baseline measures describing the current sample are as follows: body mass index (kg/m^2) = 25.6 ± 4.1; Geriatric Depression Scale score = 2.8 ± 2.8; Geriatric Anxiety Scale score = 7.2 ± 7.8; MET/week (expended for 7-day Physical Activity) = 91.6 ± 33.0 (see Table 1). No adverse events were reported for any participant throughout the study.

Manipulation check

As a precursor to hypothesis testing, we verified that ratings of perceived exertion (RPE) and heart rate (HR) were significantly greater during the acute exercise condition compared with during the acute seated rest condition. Mean ± standard deviation, as well as results of paired t-tests comparing each measure between conditions, is as follows: exercise RPE = 12.9 ± 1.2, rest RPE = 6.2 ± 0.4, $p \leq 2.2 \times 10^{-16}$; exercise HR = 126.5 ± 24.8, rest HR = 69.2 ± 10.8, $p \leq 2.2 \times 10^{-16}$ (see Table 2). Subjective ratings of arousal were also higher during exercise compared with rest (exercise SAM-A = 5.7 ± 1.6, rest SAM-A = 4.5 ± 1.6, $p = 5.21 \times 10^{-4}$). Valence (pleasantness) was not significantly different between the two conditions (exercise SAM-V = 7.1 ± 1.7, rest SAM-V = 6.8 ± 1.6, $p = 0.161$) (see Table 2).

Between-network segregation index analysis

Between-network segregation index was significantly greater after acute exercise compared with after acute seated rest for the SAL&DMN (combined $p = 0.004$), as well as SAL&ARN (combined $p = 0.012$) (see Table 4 and Fig. 2). These results survived the false discovery rate (FDR) threshold ($p < 0.008$ and $p < 0.017$, respectively). Meanwhile, between-network segregation index was not significantly different between conditions for all other network pairs (all $p > 0.05$) (see Table 4 and Fig. 2).

The significant results for the between-network segregation analysis showed a significant or near-significant interaction between condition and sex ($p = 0.037$ for DMN-SAL segregation and $p = 0.056$ for ARN-SAL segregation); however, these p values would not survive FDR-correction even if significant and were not close to significance when calculating segregation index using the other network within the pair for $\bar{z}_w$ (SAL-DMN and SAL-ARN). Other interactions for the two segregation analysis results (condition*mean-centered age, condition*condition order) were not statistically significant (all $p \geq 0.156$).

Within-network and between-network connectivity analyses

Within-network connectivity was not significantly different between the acute exercise and acute seated rest conditions for any network (all $p > 0.05$) (see Table 5 and Fig. 4). Meanwhile, two pairs of networks had significantly lower between-network connectivity after the acute exercise condition, compared with the acute seated rest condition—SAL-DMN ($p = 0.001$, $t = -3.53$), as well as SAL-ARN ($p = 0.011$, $t = -2.69$) (see Table 6 and Figs. 3 and 4). The significant between-condition difference in between-network connectivity for SAL-DMN and SAL-ARN both survived the

Table 2. Experimental Condition Outcomes and Manipulation Check ($N = 37$)

	Exercise		*Rest*		*Exercise–rest*		
Measure	*Mean*	*SD*	*Mean*	*SD*	*Mean difference*	t *statistic*	p *value*[a]
HR (bpm)	126.5	24.8	69.2	10.8	57.3	16.4	**<2.2e-16**
RPE	12.9	1.2	6.2	0.4	6.7	34.5	**<2.2e-16**
Valence	7.1	1.7	6.8	1.6	0.3	1.4	0.16
Arousal[b]	5.7	1.6	4.5	1.6	1.2	3.8	**5.2 e-4**

Bold font indicates statistical significance at $p < 0.05$.
[a]p-value, p value from paired t-tests performed between exercise and rest conditions.
[b]Arousal, subjective measure of arousal; All measures were averaged and compared over the final 10 min of the moderate-to-vigorous intensity exercise session (minutes 15–25 of the experimental conditions); Average participant heart rate in the final 10 min of the exercise condition was approximately 82.4% (SD = 15.3%) of age predicted maximal heart rate, which corresponds to a moderate-to-hard intensity rating based on ACSM guidelines (Gordon et al., 2010).
SD, standard deviation; HR, heart rate; bpm, beats per minute; RPE, ratings of perceived exertion; Valence, subjective measure of valence.

Table 3. Defined Networks; 22 Regions Comprising Four Networks Were Used for Network-Level and ROI-Level Analyses ($n = 37$)

Region label	*x*[a]	*y*	*z*	*BA*	*Vox*
Salience Network					
ACC	2	34	18	32, 24	1063
L-AI	–44	10	–8	48, 45, 38	446
R-AI	50	14	–8	48, 45	388
L-RPFC	–32	50	12	46, 9, 45, 10	1166
R-RPFC	32	48	16	46, 9, 45	581
L-SMG	–60	–36	22	48, 40	233
R-SMG	64	–38	24	48, 40, 2	284
Default Mode Network					
MPFC	0	40	–16	10, 11	830
L-LP	–46	–76	20	39, 19, 7	1041
R-LP	54	–66	16	39, 19, 7	1326
PCC	8	–50	4	23, 7, 5	4833
L-Hippocampus	–24	–9	–30	—	6199
R-Hippocampus	27	–10	–29	—	5692
Frontoparietal Network					
L-LPFC	–48	42	–10	46, 45, 10, 44, 8, 9	1703
R-LPFC	48	46	–8	46, 45, 10, 44, 8, 9	1758
L-PPC	–54	–60	38	40, 39, 7	832
R-PPC	60	–54	32	40, 39, 7	837
Affect-Reward Network					
L-NA	–9	7	–13	—	770
R-NA	10	7	–12	—	586
VMPFC	±2	25	–32	11, 25, 10	35459
L-Amygdala	–25	–4	–29	—	2651
R-Amygdala	26	–3	–29	—	2739

[a]The (x), (y), and (z) represent neurological coordinates on MNI space.

BA, Brodmann area; Vox, number of 2 mm isotropic voxels in cluster; ACC, anterior cingulate; L, left; R, right; AI, anterior insula; RPFC, rostral prefrontal cortex; SMG, supramarginal gyrus; MPFC, medial prefrontal cortex; LP, lateral parietal region; PCC, precuneus cortex; LPFC, lateral prefrontal cortex; PPC, posterior parietal cortex; NA, nucleus accumbens; VMPFC, ventromedial prefrontal cortex.

false discovery rate (FDR) threshold ($p < 0.008$ and $p < 0.017$). Between-network connectivity for all other network pairs was not significantly different between conditions (all $p > 0.05$) (see Table 6 and Figs. 3 and 4).

The significant results for the between-network connectivity analyses did not show significant interaction between condition and mean-centered age, condition order, or sex (all $p \geq 0.108$).

Discussion

The present study examined the effects of a single session of moderate-to-vigorous intensity cycling exercise, compared to a seated rest control condition, on rsFC measures (between-network segregation, within- and between-network connectivity) of four major functional brain networks (DMN, FPN, SAL, and ARN) in healthy, physically active older adults. Our findings indicate that acute exercise led to greater between-network segregation by way of lower between-network connectivity for two network pairs (between SAL&DMN and between SAL&ARN). There were no significant FDR-surviving interactions between condition and mean-centered age, condition order, or sex. Thus, the observed effects of acute exercise on between-network segregation and between-network connectivity in healthy, active older adults were consistent across ages of the sample included in the rsFC analyses ($n = 37$; 60–76 years), order of condition completion across testing days, and between men and women. Overall, these findings suggest that compared with a session of seated rest, acute exercise may lead to greater segregation between age-susceptible brain networks. This effect of acute exercise on neural network function may help to explain the well-documented benefits of exercise on cognition and mental health during older age.

Between-network segregation analysis

In line with our hypothesis, two network pairs (SAL&DMN and SAL&ARN) exhibited greater between-network segregation after the session of acute cycling exercise compared with after the seated rest condition. Given that SAL&DMN and SAL&ARN are pairings between external (SAL) and internal (ARN, DMN) state circuitry, this suggests that the segregation results for these network pairs may have implications for the processing of broad classes of information. It is likely that decoupling internal and external state-focused networks, as we observed after acute exercise, is behaviorally advantageous given that desegregation between these networks has been associated with worse cognition and psychiatric health (Mattfeld et al., 2014; Ng et al., 2016; Whitfield-Gabrieli and Ford, 2012). Greater segregation among SAL&DMN and SAL&ARN could therefore reflect better attention and processing during internal or external state-related behaviors, with less extraneous activity unrelated to the behavior that could adversely impact network function.

Studies suggest that enhancing segregation of brain networks may provide cognitive benefits for older adults. One

Table 4. Results of the Network Segregation[a] Analysis ($n = 37$)

	Exercise		Rest		Exercise–rest			
Network pair	*Mean*	*SD*	*Mean*	*SD*	*Mean difference*	t *statistic*	p *value*[b]	*Combined* p *values*[c]
SAL-DMN	0.214	0.062	0.191	0.064	0.023	2.69	**0.011***	**0.004***
DMN-SAL	0.176	0.068	0.149	0.070	0.027	3.38	**0.002***	
SAL-ARN	0.171	0.044	0.160	0.046	0.011	2.10	**0.043**	**0.012***
ARN-SAL	0.068	0.036	0.055	0.031	0.013	2.95	**0.006***	
SAL-FPN	0.159	0.068	0.154	0.072	0.005	0.74	0.465	0.930
FPN-SAL	0.151	0.074	0.157	0.077	–0.006	0.02	0.983	
DMN-ARN	0.058	0.024	0.054	0.029	0.004	0.94	0.355	0.651
ARN-DMN	–0.007	0.021	–0.008	0.021	0.001	0.46	0.651	
FPN-ARN	0.140	0.055	0.151	0.047	–0.011	–1.01	0.322	0.639
ARN-FPN	0.045	0.037	0.043	0.036	0.002	0.47	0.639	
FPN-DMN	0.111	0.055	0.115	0.044	–0.004	–0.04	0.967	0.380
DMN-FPN	0.080	0.049	0.069	0.047	0.011	1.34	0.190	

Bold font indicates statistical significance at $p < 0.05$, and asterisks (*) are appended to the significant findings that also survived the false discovery rate (FDR) threshold.

[a]Network segregation index values were calculated with a formula that uses mean Pearson's correlation-coefficient values ($\bar{r}$): SI = $\frac{(\bar{r}_w + 1) - (\bar{r}_b + 1)}{(\bar{r}_w + 1) + (\bar{r}_b + 1)}$, where $\bar{r}_w$ is mean within-network connectivity and $\bar{r}_b$ is mean between-network connectivity.

[b]*p*-value, *p* values for between-condition network segregation comparisons, in which each network within a network pair was considered as the "within"-network in separate segregation calculations (e.g., SAL-DMN uses SAL as the within-network, DMN-SAL uses DMN as the within-network).

[c]Combined *p*-values, *p* values were combined across both segregation calculations of a given network pair.

SD, standard deviation; SAL, salience network; DMN, default mode network; FPN, frontoparietal network; ARN, affect-reward network.

study reported that greater network segregation among associative brain networks was correlated with better long-term episodic memory, regardless of age (Chan et al., 2014). It has also been found that higher baseline whole-brain modularity [another graph-theoretical network measure that is considered representative of the degree of segregation of all brain networks (Newman and Girvan, 2004)] predicts greater executive function improvement after both cognitive training (Gallen et al., 2016) and aerobic exercise training (Baniqued et al., 2017) in healthy older adults. Greater segregation among SAL, DMN, and ARN suggests that each of these networks can perform their diverse functions more

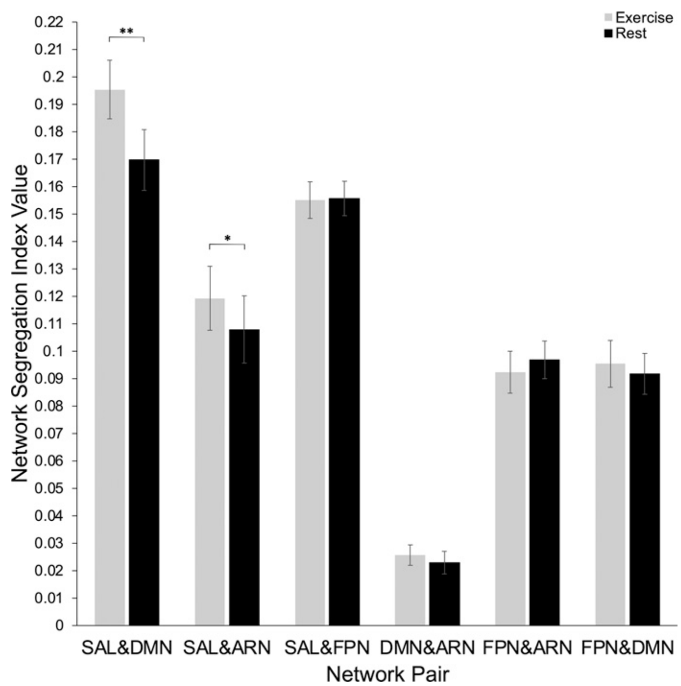

FIG. 2. Results of network segregation analysis ($n = 37$). Between-conditions difference in network segregation index (SI) for 2 network pairs (SAL&DMN and SAL&ARN). SAL, salience network; DMN, default mode network; ARN, affect-reward network; FPN, frontoparietal network. Asterisks indicate statistical significance as follows: *$p < 0.05$; **$p < 0.01$. Data for SAL&DMN reflect segregation values and SEM averaged for SAL-DMN and DMN-SAL, whereas data for SAL&ARN reflect segregation values and SEM averaged for SAL-ARN and ARN-SAL. Between-condition difference in segregation for SAL&DMN and SAL&ARN both survived the false discovery rate (FDR) threshold.

Table 5. Results of the Within-Network Connectivity[a] Analysis ($N = 37$)

	Exercise		Rest		Exercise–rest		
Network	Mean	SD	Mean	SD	Mean difference	t statistic	p value[b]
SAL	0.398	0.102	0.393	0.105	0.005	0.39	0.698
DMN	0.281	0.098	0.265	0.103	0.016	1.49	0.147
FPN	0.380	0.150	0.406	0.130	−0.026	−0.60	0.554
ARN	0.116	0.060	0.107	0.054	0.009	1.38	0.176

[a]Within-network connectivity units are mean Fisher-transformed correlation-coefficient values ($\overline{z}$).
[b]*p*-value, *p* value from between-condition comparison of within-network connectivity using a general linear model.
SD, standard deviation; SAL, salience network; DMN, default mode network; FPN, frontoparietal network; ARN, affect-reward network.

effectively and with less competing ‘noise’ from adjacent networks.

The current segregation findings have implications as proposed mechanisms by which exercise promotes improved mental health in older adults (Alfini et al., 2020). More independent functioning of SAL and ARN may presumably reduce focus on currently salient stimuli, which can be unpleasant, during affect and reward processing. This decoupling of the networks may support the classically observed anxiolytic and mood-enhancing effects of exercise (Basso and Suzuki, 2017). Adults with major depressive disorder (MDD) have shown significantly lower DMN segregation and modestly lower SAL segregation compared with healthy controls (Fan et al., 2019). Lower salience network segregation has been associated with higher levels of perseverative negative thinking in middle-aged adults (Solé-Padullés et al., 2022). This suggests that greater segregation among SAL, DMN, and ARN after acute exercise is a plausible network-level mechanism for the beneficial effects of exercise on affective processing in older adults. While we did not report exercise-related changes in subjective affect in the current study, these effects have been consistently reported in the literature and have been previously linked to the SAL and ARN (Alfini et al., 2020; Kommula et al., 2023).

Within- and between-network connectivity

The analysis of within- and between-network connectivity allowed the examination of specific network-level connectivity changes that determined the changes in network segregation after acute exercise. Between-network connectivity for SAL&DMN and SAL&ARN was lower after acute exercise compared with after seated rest. This supports the interpretation that greater network segregation for SAL&DMN and SAL&ARN after acute exercise is chiefly explained by lower between-network connectivity in these network pairs following the exercise session. These results suggest that acute exercise may be a behavioral approach to oppose greater connectivity between networks due to aging (Iordan et al., 2017). However, most exercise intervention studies suggest that exercise training leads to greater *within*-network connectivity (Won et al., 2021), not necessarily lower between-network connectivity. Nevertheless, both greater within-network connectivity and lower between-network connectivity support greater network segregation. One of the few previous studies of acute exercise on rsFC found that acute exercise led to greater connectivity between SAL&ARN (Weng et al., 2017). This finding is contrary to our finding of reduced SAL&ARN between-network connectivity after exercise, and there are several possibilities that may explain these disparate results. For example, Weng et al. used seed-to-voxel analyses to measure within- and between-network FC. In contrast, in the current study we used whole-network connectivity metrics to test for between-condition differences in within- and between-network FC, enabling us to focus on larger-scale functional organization of the brain while avoiding potential bias associated with seed selection (Cole et al., 2010). We also recruited physically active older adults, whereas Weng et al. included younger adults and did not specify physical activity status of the participants.

Contrary to the hypothesis, within-network connectivity did not differ between the experimental conditions for any defined networks. It is worth mentioning the nonsignificant within-network connectivity effects, however, because directions of

Table 6. Results of the Between-Network Connectivity[a] Analysis ($N = 37$)

	Exercise		Rest		Exercise–rest		
Network pair	Mean	SD	Mean	SD	Mean difference	t statistic	p value[b]
SAL&DMN	−0.111	0.080	−0.070	0.085	−0.041	−3.53	**0.001***
SAL&ARN	−0.027	0.062	−0.010	0.056	−0.017	−2.69	**0.011***
SAL&FPN	−0.001	0.108	0.007	0.118	−0.008	−0.70	0.491
DMN&ARN	0.131	0.055	0.126	0.052	0.005	0.79	0.433
FPN&ARN	0.019	0.059	0.016	0.054	0.003	0.60	0.552
FPN&DMN	0.084	0.084	0.095	0.079	−0.011	−0.73	0.473

Bold font indicates significance at $p < 0.05$, and an asterisk (*) is appended to the significant findings since they also survived the false discovery rate (FDR) threshold.
[a]Between-network connectivity units are mean Fisher-transformed correlation-coefficient values ($\overline{z}$).
[b]*p*-value, *p* value from between-condition comparison of between-network connectivity using a general linear model.
SD, standard deviation; SAL, salience network; DMN, default mode network; ARN, affect-reward network; FPN, frontoparietal network.

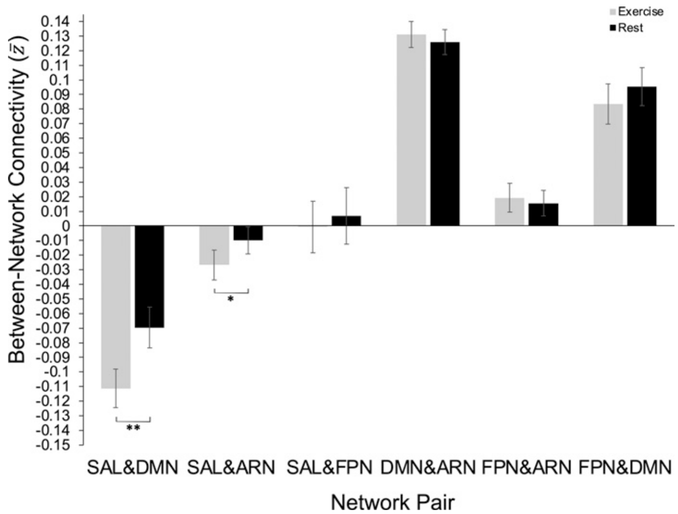

FIG. 3. Results of the between-network connectivity analysis ($n = 37$). Between-conditions difference in between-network connectivity for 2 network pairs (SAL&DMN and SAL&ARN). Between-network connectivity units are mean Fisher-transformed correlation-coefficient values ($\bar{z}$). SAL, salience network; DMN, default mode network; FPN, frontoparietal network; ARN, affect-reward network. Asterisks indicate statistical significance as follows: $*p < 0.05$; $**p < 0.01$. Between-condition difference in between-network connectivity for SAL&DMN and SAL&ARN both survived the false discovery rate (FDR) threshold.

trending effects could provide clues for future investigation. Moreover, the direction of the nonsignificant differences in within-network connectivity after acute exercise compared with seated rest (greater for DMN, ARN, and SAL; lower for FPN) is consistent with recent evidence that acute exercise may lead to greater similarity of fMRI signals across adjacent voxels in frontal cortices, but lower similarity of fMRI signals across adjacent voxels in more posterior brain regions (Purcell et al., 2023). The null effects of acute exercise on within-network connectivity in the present study are inconsistent with

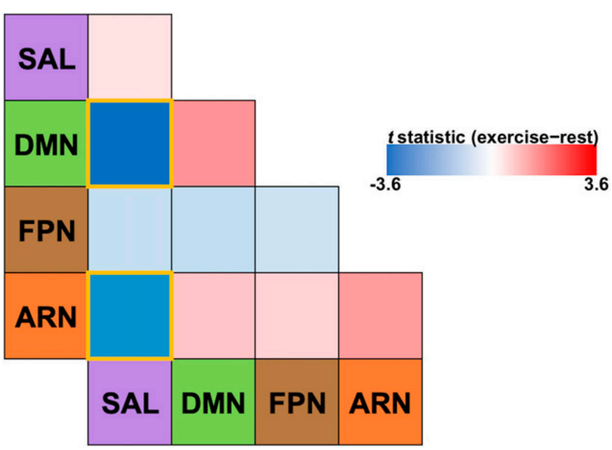

FIG. 4. Results of the within- and between-network connectivity analyses ($n = 37$). Between-conditions difference in between-network connectivity for 2 network pairs (SAL&DMN and SAL&ARN). SAL, salience network; DMN, default mode network; FPN, frontoparietal network; ARN, affect-reward network. The heatmap ranges from −3.6 to 3.6 in units of exercise–rest t statistic. Between-condition difference in between-network connectivity for SAL&DMN and SAL&ARN both survived the false discovery rate (FDR) threshold.

the prior report of greater within-network FC in the ARN, hippocampal, SAL, and ECN networks (Weng et al., 2017). Despite the lack of within-network differences in the current study, research suggests that the significant between-network connectivity differences after acute exercise may represent mechanisms of improved cognition or mental health in older adults. For example, one study found that better executive functioning, psychomotor speed, and verbal memory were related to more anticorrelated coupling between SAL and DMN in both healthy older adults and older Parkinson's disease patients (Putcha et al., 2016). Greater SAL&DMN between-network connectivity can be problematic for older adults' cognition as cognitive tasks requiring attention to external stimuli typically require engagement of SAL and FPN (Dosenbach et al., 2006) but suppression of the more internal environment-associated DMN (Raichle et al., 2001). Furthermore, studies suggest that greater SAL&DMN connectivity is related to MDD (Balaev et al., 2018; Manoliu et al., 2013). Our findings of reduced SAL&ARN between-network connectivity may also have implications for emotional reactivity and affect in older adults. As previously discussed, greater connectivity between SAL&ARN nodes can plausibly elicit sensory focus on negatively salient stimuli through SAL during reward and affect-related processes by ARN. Overactivity in key SAL and ARN hubs, such as anterior insula and amygdala, has also been linked to higher anxiety and neuroticism (Hamilton et al., 2013; Stein et al., 2007), further suggesting that greater SAL&ARN connectivity with aging may negatively influence mental health in older adults. SAL hyperactivity has also been correlated with greater subjectively perceived levels of pain (Legrain et al., 2011). Taken together, the existing evidence suggests that lower between-network connectivity for SAL&DMN and SAL&ARN may benefit older adults' cognition and mental health.

Potential mechanisms, strengths, and limitations

Although our study was not designed to identify the cellular mechanisms for acute exercise to influence rsFC, which in older adults remain inconclusive, there are several candidates that should be mentioned. One possibility is that change in amount of galaninergic inhibition of noradrenergic circuits plays a role in altered rsFC after a session of exercise (Sciolino and Holmes, 2012). Neurochemical changes involving lactate, cortisol, neurotrophins, neuromodulators, or other neurotransmitters might also mediate the relationship between acute exercise and rsFC change, but more research using animal models is needed to clarify the precise mechanism (Basso and Suzuki, 2017). Changes in rsFC after exercise also may be related to changes in neural differentiation after acute exercise, effects which may be dependent on modulation of the GABAergic system, neuromodulatory catecholamine signaling, and mild neuroinflammation (Callow et al., 2023; Purcell et al., 2023).

Strengths of our study include the use of rsFC analyses in older adults without depending on seed-to-voxel analyses. Furthermore, our finding that acute exercise leads to greater network segregation in healthy older adults provides novel insight and adds to this growing literature. We performed a two-level rsFC analysis (network segregation, within- and between-network connectivity) that allowed us to understand nuanced mechanisms of how acute exercise may influence large-scale network rsFC. One limitation of our study is that only one exercise intensity was used (i.e., moderate-to-vigorous intensity cycling), and there is evidence that lower and higher exercise intensities may differentially influence rsFC (Schmitt et al., 2019). In addition, we only studied associative networks that may perform complex cognitive or affect-related processes and did not investigate sensorimotor networks. Next, we interpret that the current effects of acute exercise on rsFC measures in older adults could underlie commonly observed changes over time in response to exercise training (e.g., greater coherence within networks); however, our study did not administer repeated sessions over the course of an intervention. Future studies of older adults should assess rsFC changes after both acute and chronic exercise in the same sample. That future research direction would be especially worthwhile given that not every existing exercise training study has found greater within-network connectivity. Namely, a few studies report instances of lower within-network connectivity (Chirles et al., 2017; Flodin et al., 2017; McFadden et al., 2013) or greater between-network connectivity (McGregor et al., 2018; Won et al., 2023) after exercise training, but those effects co-occurred with benefits such as lower fat mass or greater cardiorespiratory fitness and cognitive stability. Finally, we did not observe a relationship between our behavioral data from the Mnemonic Similarity Task, fitness, or self-rated mood and the connectivity results to support suspected cognitive and affect-related effects of the currently supported rsFC changes after acute exercise. It could be that greater statistical power is needed or that other cognitive domains could be related to the differences in rsFC outcomes we observed. This is a limitation of the study that warrants caution in the interpretation. Brain-behavior relationships would have been particularly interesting to study as much research encourages that the current rsFC findings may benefit older adults' cognition and mental health, whereas other research also suggests that the relationship between functional measures and behavior may generally weaken with age (Ghisletta and Lindenberger, 2003).

Conclusion

The present study suggests that a single bout of aerobic exercise may influence brain rsFC in healthy older adults through greater between-network segregation and lower between-network connectivity for two network pairs (SAL&DMN and SAL&ARN). Given that the directions of these effects oppose deleterious age-related changes in network function, these findings have implications for the commonly reported improvements in cognition and mental health after acute exercise in older adults (Alfini et al., 2020; Basso and Suzuki, 2017; Busse et al., 2009). Our findings provide neuroimaging evidence to support the widely reported recommendation that physical activity may be useful as a lifestyle intervention to address the public health challenge of cognitive and mental health intervention in an ever-expanding population of older adults around the world. Although the durability of the impact of acute exercise on rsFC measures in older adults remains to be determined, our data suggest that lower between-network connectivity after acute exercise may be an effect that, when repeated, leads to long-term adaptations that protect brain health. Future work should replicate the present findings in older adults with clinical disorders and varied physical activity levels, investigate whether changes in network segregation after exercise correlate with cognitive and affect-related behavioral measures, and compare different exercise intensities on these outcomes of interest.

Harvard-Oxford Acknowledgment

The CMA provided data for an atlas distributed with FSL. We are very grateful for the training data for FIRST, particularly to David Kennedy at the CMA, and also to: Christian Haselgrove, Center for Morphometric Analysis, Harvard; Bruce Fischl, Martinos Center for Biomedical Imaging, MGH; Janis Breeze and Jean Frazier, Child and Adolescent Neuropsychiatric Research Program, Cambridge Health Alliance; Larry Seidman and Jill Goldstein, Department of Psychiatry of Harvard Medical School; and Barry Kosofsky, Weill Cornell Medical Center.

Acknowledgments

This work was supported by the Department of Kinesiology at the University of Maryland, College Park. The authors thank the participants for their time and dedication to this study. Data and analysis code that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Y.K.: Data curation; project administration; formal analysis; investigation; visualization; writing—original draft; and writing—review and editing. D.D.C.: Data curation; project administration; funding acquisition; and writing—review and editing. J.J.P.: Supervision; visualization; and writing—

review and editing. J.C.S.: Conceptualization; data curation; funding acquisition; methodology; project administration; resources; supervision; validation; and writing—review and editing.

Author Disclosure Statement

All authors have no conflicts of interest.

Funding Information

This work was supported by the Department of Kinesiology at the University of Maryland, College Park. Daniel D. Callow contributions to this research were supported, in part, by National Institute of Health (NIH) award F31 AG074670-01.

Supplementary Material

Supplementary Data S1

References

Alfini AJ, Won J, Weiss LR, et al. Impact of exercise on older adults' mood is moderated by sleep and mediated by altered brain connectivity. Soc Cogn Affect Neurosci 2020;15(11): 1238–1251; doi: 10.1093/scan/nsaa149

Baez-Lugo S, Deza-Araujo YI, Maradan C, et al. Exposure to negative socio-emotional events induces sustained alteration of resting-state brain networks in older adults. Nat Aging 2023;3(1):105–120; doi: 10.1038/s43587-022-00341-6

Balaev V, Orlov I, Petrushevsky A, et al. Functional connectivity between salience, default mode and frontoparietal networks in post-stroke depression. J Affect Disord 2018;227: 554–562; doi: 10.1016/j.jad.2017.11.044

Baniqued PL, Gallen CL, Voss MW, et al. Brain network modularity predicts exercise-related executive function gains in older adults. Front Aging Neurosci 2017;9:426; doi: 10.3389/fnagi.2017.00426

Basso JC, Suzuki WA. The effects of acute exercise on mood, cognition, neurophysiology, and neurochemical pathways: A review. Brain Plast 2017;2(2):127–152; doi: 10.3233/BPL-160040

Beard JR, Officer A, de Carvalho IA, et al. The world report on ageing and health: A policy framework for healthy ageing. Lancet 2016;387(10033):2145–2154; doi: 10.1016/S0140-6736(15)00516-4

Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377–381.

Bradley MM, Lang PJ. Measuring emotion: The Self-Assessment manikin and the semantic differential. J Behav Ther Exp Psychiatry 1994;25(1):49–59.

Busse AL, Gil G, Santarém JM, et al. Physical activity and cognition in the elderly: A review. Dement Neuropsychol 2009;3(3):204–208; doi: 10.1590/S1980-57642009DN303 00005

Buysse DJ, Reynolds CF, Monk TH, et al. The pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213; doi: 10.1016/0165-1781(89)90047-4

Callow DD, Kommula Y, Stark CEL, et al. Acute cycling exercise and hippocampal subfield function and microstructure in healthy older adults. Hippocampus 2023;33(10):1123–1138; doi: 10.1002/hipo.23571

Chan MY, Park DC, Savalia NK, et al. Decreased segregation of brain systems across the healthy adult lifespan. Proc Natl Acad Sci U S A 2014;111(46):E4997–5006; doi: 10.1073/pnas.1415122111

Chirles TJ, Reiter K, Weiss LR, et al. Exercise training and functional connectivity changes in mild cognitive impairment and healthy elders. J Alzheimers Dis 2017;57(3):845–856; doi: 10.3233/JAD-161151

Chong JSX, Ng KK, Tandi J, et al. Longitudinal changes in the cerebral cortex functional organization of healthy elderly. J Neurosci 2019;39(28):5534–5550; doi: 10.1523/JNEUROSCI.1451-18.2019

Cole DM, Smith SM, Beckmann CF. Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. Front Syst Neurosci 2010;4:8; doi: 10.3389/fnsys.2010.00008

Damoiseaux JS. Effects of aging on functional and structural brain connectivity. NeuroImage 2017;160:32–40; doi: 10.1016/j.neuroimage.2017.01.077

Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 2006;31(3):968–980; doi: 10.1016/j.neuroimage.2006.01.021

Dosenbach NU, Visscher KM, Palmer ED, et al. A core system for the implementation of task sets. Neuron 2006;50(5): 799–812; doi: 10.1016/j.neuron.2006.04.031

Fan J, Tso IF, Maixner DF, et al. Segregation of salience network predicts treatment response of depression to repetitive transcranial magnetic stimulation. NeuroImage Clin 2019;22: 101719; doi: 10.1016/j.nicl.2019.101719

Flodin P, Jonasson LS, Riklund K, et al. Does aerobic exercise influence intrinsic brain activity? An aerobic exercise intervention among healthy old adults. Front Aging Neurosci 2017;9:267; doi: 10.3389/fnagi.2017.00267

Frazier JA, Chiu S, Breeze JL, et al. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry 2005;162(7):1256–1265; doi: 10.1176/appi.ajp.162.7.1256

Gallen CL, Baniqued PL, Chapman SB, et al. Modular brain network organization predicts response to cognitive training in older adults. PLoS One 2016;11(12):e0169015; doi: 10.1371/journal.pone.0169015

Ghisletta P, Lindenberger U. Age-based structural dynamics between perceptual speed and knowledge in the Berlin Aging Study: Direct evidence for ability dedifferentiation in old age. Psychol Aging 2003;18(4):696–713; doi: 10.1037/0882-7974.18.4.696

Goldstein JM, Seidman LJ, Makris N, et al. Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. Biol Psychiatry 2007;61(8):935–945; doi: 10.1016/j.biopsych.2006.06.027

Gordon NF, Pescatello LS, Thompson WR, (eds). ACSM's guidelines for exercise testing and prescription (8th ed.). Lippincott Williams & Wilkins: United States; 2010.

Hamilton JP, Chen MC, Gotlib IH. Neural systems approaches to understanding major depressive disorder: An intrinsic functional organization perspective. Neurobiol Dis 2013;52: 4–11; doi: 10.1016/j.nbd.2012.01.015

Iordan AD, Cooke KA, Moored KD, et al. Aging and network properties: Stability over time and links with learning during working memory training. Front Aging Neurosci 2017;9:419; doi: 10.3389/fnagi.2017.00419

Khavinson V, Popovich I, Mikhailova O. Towards realization of longer life. Acta Biomed 2020;91(3):e2020054; doi: 10.23750/abm.v91i3.10079

Kommula Y, Purcell JJ, Callow DD, et al. Emotional processing and positive affect after acute exercise in healthy older adults. Psychophysiology 2023;60(11):e14357; doi: 10.1111/psyp.14357

Legrain V, Iannetti GD, Plaghki L, et al. The pain matrix reloaded: A salience detection system for the body. Prog Neurobiol 2011;93(1):111–124; doi: 10.1016/j.pneurobio.2010.10.005

Mak LE, Minuzzi L, MacQueen G, et al. The default mode network in healthy individuals: A systematic review and meta-analysis. Brain Connect 2017;7(1):25–33; doi: 10.1089/brain.2016.0438

Makris N, Goldstein JM, Kennedy D, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res 2006;83(2–3):155–171; doi: 10.1016/j.schres.2005.11.020

Manoliu A, Meng C, Brandl F, et al. Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder. Front Hum Neurosci 2013;7:930; doi: 10.3389/fnhum.2013.00930

Mattfeld AT, Gabrieli JD, Biederman J, et al. Brain differences between persistent and remitted attention deficit hyperactivity disorder. Brain 2014;137(Pt 9):2423–2428; doi: 10.1093/brain/awu137

McFadden KL, Cornier MA, Melanson EL, et al. Effects of exercise on resting-state default mode and salience network activity in overweight/obese adults. Neuroreport 2013;24(15):866–871; doi: 10.1097/WNR.0000000000000013

McGregor KM, Crosson B, Krishnamurthy LC, et al. Effects of a 12-Week aerobic spin intervention on resting state networks in previously sedentary older adults. Front Psychol 2018;9:2376; doi: 10.3389/fpsyg.2018.02376

Menon V. Large-scale brain networks and psychopathology: A unifying triple network model. Trends Cogn Sci 2011;15(10):483–506; doi: 10.1016/j.tics.2011.08.003

Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990;28(5):597–613; doi: 10.1002/ana.410280502

Murman DL. The impact of age on cognition. Semin Hear 2015;36(3):111–121; doi: 10.1055/s-0035-1555115

Nasreddine ZS, Phillips NA, Bedirian V, et al. The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695–699; doi: 10.1111/j.1532-5415.2005.53221.x

Newman ME, Girvan M. Finding and evaluating community structure in networks. Phys Rev E Stat Nonlin Soft Matter Phys 2004;69(2 Pt 2):026113; doi: 10.1103/PhysRevE.69.026113

Ng KK, Lo JC, Lim JKW, et al. Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. Neuroimage 2016;133:321–330; doi: 10.1016/j.neuroimage.2016.03.029

Nieto-Castanon A. General Linear Model. In: Handbook of functional connectivity Magnetic Resonance Imaging methods in CONN. Hilbert Press: 2020.

Park DC, Reuter-Lorenz P. The adaptive brain: Aging and neurocognitive scaffolding. Annu Rev Psychol 2009;60:173–196; doi: 10.1146/annurev.psych.59.103006.093656

Purcell J, Wiley R, Won J, et al. Increased neural differentiation after a single session of aerobic exercise in older adults. Neurobiol Aging 2023;132:67–84; doi: 10.1016/j.neurobiolaging.2023.08.008

Putcha D, Ross RS, Cronin-Golomb A, et al. Salience and default mode network coupling predicts cognition in aging and parkinson's disease. J Int Neuropsychol Soc 2016;22(2):205–215; doi: 10.1017/S1355617715000892

R Core Team. R: A Language and Environment for Statistical Computing. In: R Foundation for Statistical Computing. R Core Team: Vienna, Austria; 2020.

Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. Proc Natl Acad Sci U S A 2001;98(2):676–682; doi: 10.1073/pnas.98.2.676

Reynolds K, Pietrzak RH, El-Gabalawy R, et al. Prevalence of psychiatric disorders in U.S. older adults: Findings from a nationally representative survey. World Psychiatry 2015;14(1):74–81; doi: 10.1002/wps.20193

Sallis JF, Haskell WL, Wood PD, et al. Physical activity assessment methodology in the Five-City Project. Am J Epidemiol 1985;121(1):91–106; doi: 10.1093/oxfordjournals.aje.a113987

Schmitt A, Upadhyay N, Martin JA, et al. Modulation of distinct intrinsic resting state brain networks by acute exercise bouts of differing intensity. Brain Plast 2019;5(1):39–55; doi: 10.3233/BPL-190081

Sciolino NR, Holmes PV. Exercise offers anxiolytic potential: A role for stress and brain noradrenergic-galaninergic mechanisms. Neurosci Biobehav Rev 2012;36(9):1965–1984; doi: 10.1016/j.neubiorev.2012.06.005

Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 2007;27(9):2349–2356; doi: 10.1523/JNEUROSCI.5587-06.2007

Segal DL, June A, Payne M, et al. Development and initial validation of a self-report assessment tool for anxiety among older adults: The geriatric anxiety scale. J Anxiety Disord 2010;24(7):709–714; doi: 10.1016/j.janxdis.2010.05.002

Simes RJ. An improved Bonferroni procedure for multiple tests of significance. Biometrika 1986;73(3):751–754; doi: 10.1093/biomet/73.3.751

Solé-Padullés C, Cattaneo G, Marchant NL, et al. Associations between repetitive negative thinking and resting-state network segregation among healthy middle-aged adults. Front Aging Neurosci 2022;14:1062887; doi: 10.3389/fnagi.2022.1062887

Stein MB, Simmons AN, Feinstein JS, et al. Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry 2007;164(2):318–327; doi: 10.1176/ajp.2007.164.2.318

Taylor JJ, Kurt HG, Anand A. Resting state functional connectivity biomarkers of treatment response in mood disorders: A review. Front Psychiatry 2021;12:565136; doi: 10.3389/fpsyt.2021.565136

Varangis E, Habeck CG, Razlighi QR, et al. The effect of aging on resting state connectivity of predefined networks in the brain. Front Aging Neurosci 2019;11:234; doi: 10.3389/fnagi.2019.00234

Weng TB, Pierce GL, Darling WG, et al. The acute effects of aerobic exercise on the functional connectivity of human brain networks. Brain Plast 2017;2(2):171–190; doi: 10.3233/BPL-160039

Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. Annu Rev Clin Psychol 2012;8:49–76; doi: 10.1146/annurev-clinpsy-032511-143049

Whitfield-Gabrieli S, Nieto-Castanon A. Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2012;2(3):125–141; doi: 10.1089/brain.2012.0073

Won J, Callow DD, Pena GS, et al. Evidence for exercise-related plasticity in functional and structural neural network connectivity. Neurosci Biobehav Rev 2021;131:923–940; doi: 10.1016/j.neubiorev.2021.10.013

Won J, Nielson KA, Smith JC. Large-Scale network connectivity and cognitive function changes after exercise training in older adults with intact cognition and mild cognitive impairment. J Alzheimers Dis Rep 2023;7(1):399–413; doi: 10.3233/ADR-220062

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatr Res 1982;17(1):37–49; doi: 10.1016/0022-3956(82)90033-4

Address correspondence to:
J. Carson Smith
Department of Kinesiology
School of Public Health
University of Maryland
4200 Valley Dr
College Park, MD 20742
USA

E-mail: carson@umd.edu