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Increased neural differentiation after a single session of aerobic exercise in older adults

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ABSTRACT

Aging is associated with decreased cognitive function. One theory posits that this decline is in part due to multiple neural systems becoming dedifferentiated in older adults. Exercise is known to improve cognition in older adults, even after only a single session. We hypothesized that one mechanism of improvement is a redifferentiation of neural systems. We used a within-participant, cross-over design involving 2 sessions: either 30 minutes of aerobic exercise or 30 minutes of seated rest (n = 32; ages 55–81 years). Both functional Magnetic Resonance Imaging (fMRI) and Stroop performance were acquired soon after exercise and rest. We quantified neural differentiation via general heterogeneity regression. There were 3 prominent findings following the exercise. First, participants were better at reducing Stroop interference. Second, while there was greater neural differentiation within the hippocampal formation and cerebellum, there was lower neural differentiation within frontal cortices. Third, this greater neural differentiation in the cerebellum and temporal lobe was more pronounced in the older ages. These data suggest that exercise can induce greater neural differentiation in healthy aging.

1. Introduction

The decline of cognitive and neural systems in older adults is a major risk factor for neurodegenerative diseases such as Alzheimer's disease (Albert et al., 2001; Small, 2000, 2001) and one of the most important public health issues of our day (Plassman et al., 2008). Cognitively, these declines tend to be associated with processing speed, memory, and executive functions (Yam et al., 2014). A central aspect to the cognitive neuroscientific study of aging is to better understand the neural underpinnings of this decline.

One prominent neural theory is that cognitive and neural decline in older adults is due to multiple neural systems becoming increasingly dedifferentiated with age (Carp et al., 2011; Dennis and Cabeza, 2011; Koen et al., 2020; Koen and Rugg, 2019; Park et al., 2004). The health of a neural system is in part based on its capacity to differentiate amongst similar stimuli and task states, which is an indicator that information is well-encoded within these neural networks (e.g., Favila et al., 2016; Glezer et al., 2015; Jiang et al., 2017; Perez-Nieves et al., 2021; Purcell et al., 2019; Purcell and Rapp, 2018). One can consider well-differentiated neural signals as being

Abbreviations: A/PCC, Anterior/Posterior Cingulate Cortex; AAL3, Authenticator Assurance Level 3; AFNI, Analysis of Functional NeuroImages; Ant, Anterior; BMM, Bayesian Multilevel Modeling; BOLD, Blood Oxygenation Level Dependent; BPM, Beats Per Minute; CA, Cornu Ammonis; FG, Gusiform Gyrus; fMRI, functional Magnetic Resonance Imaging; FNT, Famous Name Task; FWHM, Full Width Half Max; GABA, Gamma-Aminobutyric Acid; HO, Harvard Oxford; HR, Heart Rate; Hreg, Heterogeneity Regression; I/M/SFG, Inferior/Middle/Superior Frontal Gyrus; I/M/STG, Inferior/Middle/Superior Temporal Gyrus; IAPS, International Affective Picture System; ICC, Intraclass Correlation Coefficient; Min-Max, mean interclass correlations; MNI, Montreal Neurological Institute; MR, Magnetic Resonance; MRI, Magnetic Resonance Imaging; MTL, Medial Temporal Lobe; PHG, Parahippocampal Gyrus; ROI, Region of Interest; RPE, Rating of Perceived Exertion; RT, Reaction Time; S/I-post, Superior/Inferior Posterior; S/IPL, Superior/Inferior Parietal Lobule; SAM, Self-Assessment Manikin; SL, Search Light; SLOMOCO, Slice-Oriented Motion Correction; SMA, Supplementary Motor Area; TP, Temporal Pole; TR, Repetition Time

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necessary to instantiate cognitive skills that include discriminating similar sensory stimuli or discriminating between similar memory traces. One method used to quantify this dedifferentiation involves the demonstration of the relative lessening of distinctness in spatial patterns of functional Magnetic Resonance Imaging (fMRI) signal responses for different stimuli (Carp et al., 2011; Srokova et al., 2020). The preponderance of studies identifying this pattern have focused on either sensory (e.g., scene discrimination) or memory (e.g., episodic memory)-based tasks and are primarily associated with posterior brain regions involved in sensory and memory processing (Koen and Rugg, 2019). There are a few, likely interrelated, neural mechanisms that could underlie dedifferentiation in older adults: (1) declines in Gamma-aminobutyric acid (GABA) neurotransmission, which may lead to reduced lateral inhibitory signals important for local signal differentiation (Koen and Rugg, 2019); (2) declines in neuromodulatory catecholamine signals that are known to be important for high neural signal-to-noise ratios (Li and Rieckmann, 2014; Mather and Harley, 2016); or (3) possibly a general decline in neurotrophic factors that stimulate local neural plasticity, which may lead to impoverished capacity for maintaining local neural circuitry that can differentiate neural signals sufficiently well (Budni et al., 2015).

Given these known cognitive and neural declines in aging, there is growing interest in understanding lifestyle behaviors such as exercise that can help to improve cognitive and neural function in older adults (Livingston et al., 2020). Such work has reported that, over the long term (i.e., weeks to years), physical exercise does help to reduce the risk of cognitive decline in older adults (Angevaren et al., 2008; Colcombe and Kramer, 2003; Gomez-Pinilla and Hillman, 2013; Heyn et al., 2008; Hillman et al., 2008; Yaffe et al., 2009). The long-term adaptations in the brain following exercise training are hypothesized to result from the accumulation of neurophysiological changes driven by numerous consecutive single sessions of exercise (El-Sayes et al., 2019; Loprinzi et al., 2021). It is imperative, therefore, to better understand the neural and cognitive effects of a single session of exercise. The preponderance of research exploring improved cognitive function after a single session of exercise has focused on episodic memory (Coelho-Júnior et al., 2021; Loprinzi, 2019; Sng et al., 2018; Suwabe et al., 2018; Weinberg et al., 2014) or executive function (Herold et al., 2020; Won et al., 2019a). Specifically, the executive function *inhibitory control* has been reported to be increased immediately following aerobic exercise as measured with the flanker task (Kamijo et al., 2009) or the Stroop task (Barella et al., 2010; Chang et al., 2019; Hogervorst et al., 1996; Lichtman and Poser, 1983; Sibley et al., 2006).

Building on these cognitive findings, fMRI studies have examined changes in the brain due to acute exercise using either executive function or memory fMRI tasks (Herold et al., 2020). Generally, these fMRI effects after a single session of exercise tend to heighten at subsets of regions typically active during a given task. For instance, both the left frontal and parietal regions that are typically active during a flanker task (Siemann et al., 2016, 2018) show different activation levels due to acute exercise (Won et al., 2019a). Likewise, the hippocampus and parahippocampal gyri have been associated with typical semantic memory processing (Douville et al., 2005) and were shown to be differentially active due to acute exercise (Won et al., 2019b). However, the interpretation of which brain areas *generally* change due to exercise may be limited in part by the fMRI task used (e.g., flanker or semantic memory task discussed above). This leads to the question of whether there are brain regions or networks independent of specific functional tasks that are altered after a single exercise session.

Given the aforementioned relevance of age-dependent neural dedifferentiation, we hypothesize that a contributing factor to neural and cognitive improvements due to exercise is an increase in neural differentiation, which can be detected using a minimally task-biased neural measure after a single session of aerobic exercise. These effects of exercise would be expected to be seen in multiple systems associated with age-dependent neural dedifferentiation such as sensory, motor, or memory systems (Koen et al., 2020). Some possible neural mechanisms of increased neural differentiation after acute exercise include (1) modulation of the GABAergic system (Maddock et al., 2016), (2) neuromodulatory catecholamine signaling (Weng et al., 2017), and (3) mild neuroinflammation, which stimulates local glial function and local neural signaling (Callow et al., 2021, 2023; DiSabato et al., 2016; Whitney et al., 2009).

We anticipate multiple neural systems to be associated with increased neural differentiation after a single session of exercise. First, we anticipate the ventral occipital temporal cortices seeing increases based on previous work reporting local differences in neural distinctness (differentiation) in visual association cortices after 6 months of aerobic exercise training in older adults (Kleemeyer et al., 2017). Second, we anticipate greater neural differentiation in the hippocampal formation based on previous work indicating that this region is important for processing distinct neural episodic memory patterns (i.e., pattern separation) (Koen and Rugg, 2019; Yassa et al., 2011; Yassa and Stark, 2011), and because this function has been associated with improvements after exercise in both younger (Suwabe et al., 2018) and older adults (Callow et al., 2022). This region has also been associated with proneuroplastic function after exercise (Jennen et al., 2022). Finally, the cerebellum has been associated with processing distinct neural patterns for sensory stimuli (Cayco-Gajic and Silver, 2019) and has been associated with proneuroplastic functions after exercise (Isaacs et al., 1992; Neeper et al., 1996; Won et al., 2021). Given this confluence of evidence, we predict the visual association cortex, medial temporal lobe regions, and cerebellar regions will be associated with higher neural differentiation due to acute aerobic exercise, and these regions will be particularly pronounced in relatively older ages.

In this study, we focus on an approach to estimate (de)-differentiation of local neural responses by directly quantifying the relative (dis)-similarity of adjacent fMRI signals, independent of specific task responses. This approach focuses on quantifying local neural heterogeneity with fMRI signals (Jiang et al., 2017; Purcell et al., 2019; Purcell and Rapp, 2018) and is motivated by sparse coding theory, which posits that well-learned (encoded) neural representations have sparsely distributed neural codes (Rolls and Tovee, 1995), and these codes produce locally heterogeneous neural signals (Vinje and Gallant, 2000). Here, we build upon previous work by introducing an implementation of this approach termed general heterogeneity regression (Hreg), which can be applied to any fMRI

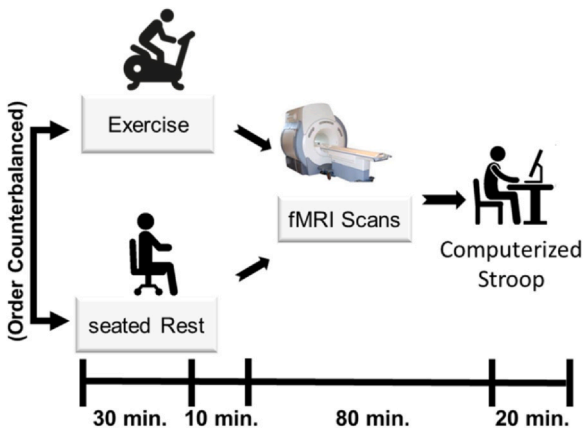

Fig. 1. Data acquisition summary. Each participant performed the exercise and seated rest condition on separate days (order was counterbalanced).

Table 1
Participant information (N = 32)

Demographics	Mean (Min-Max)	(n, %)
Age (years)	66.3 (55–81)	
Gender (n, %)		
Male		8 (25%)
Female		24 (75%)
Education (n, %)		
High school		2 (6.25%)
College or higher		30 (93.75%)
Physical characteristics		
Height (cm)	166.6 (147.3–188)	
Weight (kg)	71.3 (45.4–103.4)	
BMI (kh/m^2)	25.6 (18.2–36.8)	
Physical activity recall score (kJ/kg/d)	132.7 (105.6–175.2)	
Resting HR (BPM)	73.3 (49–89)	
Cognitive performance		
MMSE	29.2 (26–30)	

Physical activity recall score = kilojoule per kilogram per day (kJ/kg/day) derived from the approximate number of hours spent in light to very hard physical activities over the past 7 days; resting HR = resting heart rate measured in average beats per minute (BPM) at the start of each visit (averaged across visits).
Key: BMI, body mass index; BPM, beats per minute; HR, heart rate; MMSE, Mini-Mental State Exam.

dataset irrespective of its task design and can be used to examine neural differentiation across multiple neural systems. One advantage of this approach is that it does not require a specific task design and can be used to examine effects in the entire brain, that is, not just specific to a single region, such as the hippocampal formation (e.g., Reagh et al., 2018).

We applied the Hreg method to fMRI data from a within-participant cross-over design involving either 30 minutes of rest or moderate-intensity aerobic exercise on a cycle ergometer (Fig. 1) in a sample of healthy late middle age to older adults (Table 1). We tested 4 hypotheses. (1) In confirmation of previous work (Chang et al., 2015), 30 minutes of aerobic exercise will improve executive function. (2) A single exercise session will increase levels of neural differentiation in the brain, including hippocampal, cortical, and cerebellar regions. (3) There will be an age-dependent interaction such that the beneficial neural effects of exercise will be more pronounced for older ages. (4) Differences in neural differentiation between the exercise and seated rest control conditions will be associated with exercise-related improvements in executive function.

2. Materials and methods

2.1. Participants

A total of 32 middle-aged to older adults (ages 55–81 years) were selected to participate in the study after meeting the eligibility criteria (Supplementary Fig. S1). Participants were recruited from local senior fitness classes, recreation centers, and swimming clubs. Prior to selection, participants completed a phone interview to determine eligibility based on the following exclusion criteria: any contraindications of MRI scanning (e.g., ferromagnetic metallic implants or claustrophobia), a history of heart attack; stroke; diabetes; high blood pressure; neurological disease; major psychiatric disturbance; hypertension; seizures; neurological disorder; or taking psychotropic medications. Next, participants attended an in-person screening session in which they provided informed consent approved by the Institutional Review Board at the University of Maryland. Participants were excluded if they had a score less than 24 on the Mini-Mental State Examination (Folstein et al., 1975), were left-handed using the Edinburgh Handedness Inventory (< 0) (Oldfield, 1971), were severely obese (body mass index ≥40 kg/m^2), or had low levels of physical activity (< 30 minutes of physical activity 3 times per week during the past 6 months) as per the 7-day physical activity recall (Paffenbarger et al., 1978) used to estimate physical activity energy expenditure. All eligible participants obtained physician approval before engaging in moderate-intensity exercise. This study was conducted according to the Helsinki Declaration of 1975. Demographic, physical, and cognitive data for all participants are shown in Table 1. Further details about the participant recruitment process are illustrated in our prior work (Alfini et al., 2020; Won et al., 2019a).

2.2. Exercise and rest experimental conditions

Participants came in for a scanning session during which they either were at rest or exercised prior to scanning (Fig. 1). This was carried out using a within-participant cross-over design where each participant underwent 2 experimental visits (exercise and rest) on separate days (mean of 12 days between visits; min-max = 1–91 days). Participants were scheduled at approximately the same time of day at each session (e.g., if the first was in the morning, then the other session would also be in the morning). Prior to participation for either visit, participants were fitted with a heart rate (HR) monitor (Polar Electro, Kempele, Finland) and were provided with standard instruction using the Borg 6–20 ratings of perceived exertion (RPE) scale (Borg, 1970), scaled between 6 and 20 (6–7 = "very, very light"; 15 = "hard"; 19–20 = "very, very hard").

During the exercise visit condition, participants sat on a stationary bike ergometer (Monark 828E, Varbro, Sweden) and proceeded to cycle as follows: a 5-minute warm-up session with self-selected intensity, 20-minutes continuous moderate-intensity cycling, a 5-minute cool-down, and a 5-minute recovery period. Participants were instructed to maintain a pedal cadence of 60–80 rpm during exercise and instructed to select a flywheel resistance that maintained their intensity at an RPE of 15 (associated with the verbal anchor "hard").

During the rest condition visit, participants were instructed to sit in a chair for a total of 30 minutes to match the full duration of the exercise condition. Participants were instructed not to read, write, use technology (e.g., phones), or talk excessively during the rest session.

For both the exercise and the rest conditions, HR, RPE, and self-assessment manikin (SAM) for valence and arousal (Bradley and Lang, 1994) were recorded just prior to and then every 5 minutes of the session. To quantify the effects of each condition for each measure, we compared the measurements obtained just prior to the start of the condition to that of the average measurements across the third- and fourth-time interval (i.e., between 15 and 25 minutes of the session). This average provides a stable measure of the 10-minute performance period during a physiological steady-state just prior to the 5-minute cool-down period in the exercise condition. The data from the other 2 5-minute time intervals were not included due to it taking up to 10 minutes to reach a physiological steady-state exercise intensity. That stated, obtaining these regular, 5-minute interval measurements were considered important for encouraging participant task engagement and consistent vigilance to their subjective states throughout the sessions.

After either condition, there was approximately a 10-minute set-up time for the scanning session. Then, participants underwent 80 minutes of structural and functional MRI data collection and then participated in a computerized version of the Stroop task.

2.3. fMRI scans

The protocol involved the acquisition of 4 different functional runs during the scanning session. Three were obtained during the performance of a task and one was a resting state scan. It is worth noting that the task components were not directly examined in this work because only the fMRI signal residuals for each of the runs were used in the below analysis (i.e., task components of the time series were included as regressors but ignored in the analyses). Thus, only a brief description of the tasks is included (Supplementary Text S1). For discussion of in-scanner task performance, see Supplementary Text S2.

2.4. fMRI data acquisition

Whole-brain, fMRI was conducted on a Siemens 3.0 Tesla MR scanner (Magnetom Trio Tim Syngo, Munich, Germany). A 32-channel head coil was used for radio frequency transmission and reception, and foam padding was positioned within the head coil to minimize head movement within the coil. A high-resolution T1-weighted anatomical image was acquired for coregistration with the following sequence parameters: magnetization prepared rapid acquisition of gradient echo, matrix = 256, field of view = 230 mm, voxel size = 0.9 × 0.9 × 0.9 mm, slices = 192 (sagittal plane, acquired right to left), slice thickness = 0.9 mm, repetition time (TR) = 1900 ms, echo time = 2.32 ms, inversion time = 900 ms, flip angle = 9°, and sequence duration = 4:26 minutes. All of the fMRI runs were acquired using the same following sequence parameters: single-shot gradient echo-planar images, matrix = 64, field of view = 192 mm, voxel size = 3 × 3 × 3 mm, slices = 36, slice thickness = 3.0 mm, TR/echo time = 2000/24 ms, volumes = 175, flip angle = 70°, bandwidth = 2232 Hz/Px, and multislice mode = interleaved. The scan durations are noted in Supplementary Table S1. Although most (75%) of the participants received all 4 of these runs, some runs were missed for a few participants due to technical issues. The scan session began approximately 15 minutes after the completion of either experimental condition (rest or exercise).

2.5. Behavioral task and analysis

Approximately 90 minutes after each experimental condition, a computerized version of the color-naming Stroop task was administered using E-Prime 2.0 (Psychology Software Tools, Pittsburgh, PA), which took a total of approximately 6.5 minutes. Other brief neuropsychological tests were also administered before the Stroop task but are not discussed in this study. Participants sat at a desk in front of a computer monitor and were instructed to press 1 of 4 keyboard keys relabeled to represent each color (e.g., "B" for blue, "Y" yellow, "G" for green, and "R" for red). Participants were instructed to use their left and right index and middle fingers to indicate the color of the stimulus as quickly and accurately as possible. A total of 64 color-word trials consisting of 28 congruent (font color and written word refer to the same color), 28 incongruent (font color and written word conflict), and 8 neutral (written word does not refer to a color) conditions were presented. Before beginning the test, a short (2 minutes) practice session consisting of 20 trials (8 congruent, 8 incongruent, and 4 neutral stimuli) was administered. To minimize practice effects, 2 versions of the Stroop task comprising unique orders of color-word stimuli were counterbalanced across experimental visits. Of the 32 total participants who completed the entire study protocol, 2 participants were excluded from analyses involving the Stroop data due to a technical failure at the time of data acquisition.

The Stroop reaction times (RT) in milliseconds and percentage (%) accuracy were calculated for the conditions of interest, including the congruent and incongruent trials. The primary measure of interest is the interference measure for both the RT and the % accuracy, which compares the behavior on the congruent trials relative to the incongruent trials. The interference effect was obtained from the % accuracy RT scores. Estimates of the interference effect are typically obtained from the comparison of performance on the congruent and incongruent trials, that is, relatively low performance (% accuracy or RT) on the incongruent relative to the congruent trials. This is thought to quantify the ability to selectively attend to task-relevant information (color) while excluding irrelevant information (written word) (Algom and Chajut, 2019). The measure of interest for this study is the interaction between trial type and that of the exercise and rest condition. To measure this, we ran mixed effects models including fixed effects for condition and trial type (congruent and incongruent), along with random effect intercepts and slopes. An example R (r-project.org) code for the mixed-model used for the Stroop accuracy is as follows: Stroop_Accuracy ~ Rest_Exercise * Congruent_Incongruent + (1 + Rest_Exercise + Congruent_Incongruent | Participant_ID). In this formula, Rest_Exercise is a categorical variable for the experimental conditions and Congruent_Incongruent is a categorical variable for the Stroop trial type. Interference score accuracy statistics (t and p values) are based on *Rest_Exercise * Congruent_Incongruent* interaction effect estimate.

It is worth noting that there were additional behavioral measures acquired for this study at one time point, including mood-based measures (e.g., the Beck Depression Inventory), basic cognition (e.g., Mini-Mental State Exam), and sleep (e.g., total sleep time). These measures are not relevant to this project and thus not discussed further. Further details can be found in previous reports on these data (Alfini et al., 2020; Won et al., 2019b).

2.6. MRI data preprocessing

First, both anatomical and functional images were converted into a 3D space using the Analysis of Functional NeuroImages (AFNI)'s Dimon program (Cox, 1996). Second, the anatomical images were processed using Freesurfer's (version 5.3.0) cortical reconstruction process for cortical parcellation and subcortical segmentation (Fischl et al., 2002). The functional data were realigned using slice-oriented motion correction (SLOMOCO), a highly effective method to reduce motion artifact effects in a slicewise manner (i.e., relative to the more traditional volume-wise motion correction) (Beall and Lowe, 2014). The time-series data were then aligned with the Freesurfer-processed anatomical images using AFNI's anatomical and echo-planar imaging alignment function (align_epi_anat). These aligned anatomical and functional data were visually inspected and submitted to the AFNI's preprocessing program (proc.py). Functional data were despiked (3dDespike) and each volume of the time series was time-shifted to the beginning of the TR (3dTshift). TRs with excessive motion (> 0.5 mm scan-to-scan motion) were indexed and censored from the analysis described below. If a run had greater than 25% of time points with excessive motion then that run was excluded from analysis (1 run of the International Affective Picture System task was excluded). Nonlinear transformation of the anatomical images to the standard space (AFNI's MNI152_T1_2009c) was performed (3dQwarp). The resulting nonlinear transformation matrices were used to normalize and resample the functional data. The resolution of the final image was 3 × 3 × 3 mm (corresponding to the original functional acquisition resolution).

We also ensured that there were equal numbers of runs at both the rest and exercise sessions for all participants. That is, if 1

participant had a run at the rest session missing, that equivalent run was ignored at the exercise session for that participant (and vice versa).

2.7. General Hreg analysis

Heterogeneity regression (Hreg) was initially developed to examine task-specific differentiation in the brain (Purcell and Rapp, 2018). In the present study, it was adapted to examine the local differentiation of resting state and task-residuals (i.e., the fMRI time series after task effects have been regressed out). This analysis quantifies the relative similarity of adjacent fMRI signals while accounting for any similarity due to both within- and cross-voxel noise. See Fig. 2 for a schematic summary of the searchlight analysis performed on unsmoothed, preprocessed, Montreal Neurological Institute (MNI) normalized data. Each searchlight contains 7 voxels: a central voxel and the 6 shared-face voxels. This approach essentially takes each pair of voxels in the search light and uses a regression analysis to identify the similarity of 2 adjacent time series. It also uses the general psychophysiological interaction approach (McLaren et al., 2012) to account for BOLD signal similarity due to noise across adjacent voxels (e.g., the similarity of signal *across adjacent voxels* due to motion). In more detail, for each combination of voxel pairs, the following equation was used: $Y_i = [Y_k H(x)N]^* B_G + [(Y_k{}^*N)]^* B_i + e$. Y_i is the voxel time series of 1 voxel. Y_k is the predictor voxel time series; $H(x)$ corresponds to the condition regressors (x, e.g., famous names) convolved with the hemodynamic function H; N corresponds to the nuisance regressors (e.g., motion parameters). The $Y_k{}^*N$ interaction term is used to estimate and control for the interaction between the time series and nuisances regressors (e.g., if adjacent signals change in sync due to motion). In this manner, the unstandardized Y_k B estimate quantifies the relative similarity between the voxel (Y_i) and this adjacent voxel while accounting for the mean task-related BOLD response, noise, and task by noise interaction terms. The Hreg value is simply the inverse of the mean of all of the Y_k unstandardized B coefficients for each of the unique pairwise voxel-voxel combinations (7!/(7−2)! = 42) in each searchlight multiplied by negative one. Thus, higher Hreg values correspond to higher relative differentiation, while lower Hreg values correspond to lower relative differentiation. These values are then assigned to the searchlight center voxel.

In this work, we advanced upon this Hreg measure by developing an Hreg. This approach builds directly from the general functional connectivity approach that was recently introduced, which concatenates both task and resting state data in order to leverage as much data as possible in fMRI connectivity analyses (Elliott et al., 2019). The key difference is that the general Hreg approach examines *local* adjacent voxel-voxel similarity instead of long-distance connectivity, as discussed by Elliott et al. (2019).

A general Hreg analysis was run using a whole-brain gray matter cortical, subcortical, and cerebellar mask based on the Harvard Oxford (HO; 0.25 probability) (Desikan et al., 2006) and cerebellar atlas (Diedrichsen et al., 2009). The general Hreg models discussed above included the concatenated time series from all of the functional runs for each participant (see Supplementary Table S1 for a summary of the amount of data used). Some runs were excluded due to technical issues at the time of acquisition or due to excessive motion. Most (75%) of the participants had the full 933 timepoints (31:06 minutes of data) for the analysis prior to censoring. Post-censoring, there was an average of 28:15 minutes for the rest condition and 28:26 minutes for the exercise condition used for analysis. There was no significant difference between the number of timepoints censored due to motion across the conditions ($t(31) = -1.06$,

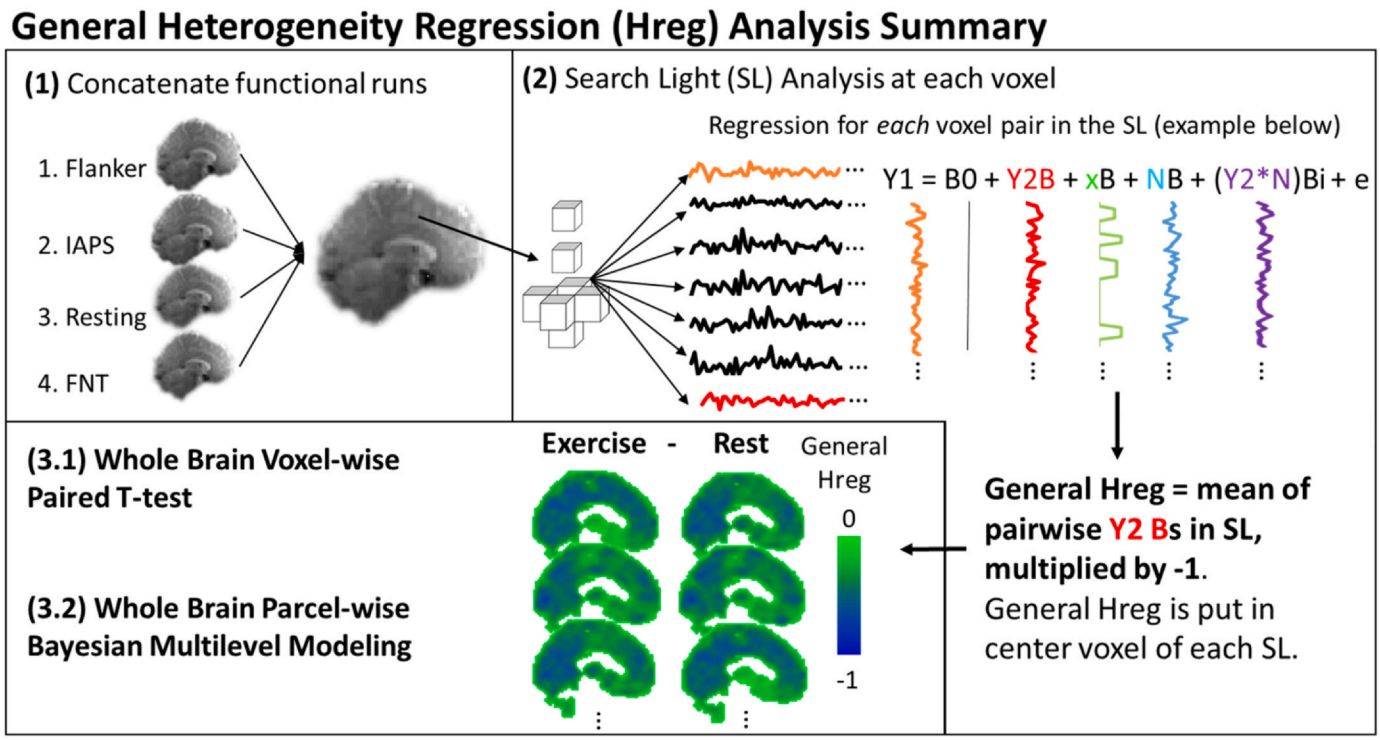

Fig. 2. General heterogeneity regression (Hreg) analysis summary. (1) After standard preprocessing, concatenate all functional runs for each participant into a single time series. (2) Run an SL analysis on each voxel with 7 voxels in each SL. For each SL, run pairwise regression analyses where 1 voxel is the dependent variable and, in turn, each other is an independent variable. The general Hreg value is the mean of the pairwise unstandardized B coefficients for each dependent variable time series, multiplied by −1; thus, higher general Hreg equals greater local neural differentiation. (3) Run 2 group-level analyses to quantify the differences between exercise and rest maps. (3.1) Whole-brain voxel-wise paired *t*-test: compare Hreg values in each voxel between exercise and rest conditions, and (3.2) whole-brain parcel-wise Bayesian multilevel modeling: compare Hreg values in each parcel between exercise and rest conditions. Notes: FNT, Famous Name Task; IAPS, International Affective Picture System.

$p = 0.299$); this indicates that there was not a clear difference in movement across conditions. There was also no significant difference between the amount of data used across conditions ($t(31) = -1.1$, $p = 0.299$). Besides including the concatenated voxel time series, condition regressors for each task (which were subsequently ignored) and the following noise covariates were included. First, a single motion regressor recommended for use with SLOMOCO was included—termed slomoco.volumetric.TDzmetric and quantified the average voxel displacement generated from the slicewise out-of-plane motion parameters (Beall and Lowe, 2014). In addition, the top 5 principal components from the cerebral spinal fluid mask were defined via the HO atlas (Desikan et al., 2006) as per the compcor approach (Behzadi et al., 2007). Thus, there were 6 noise covariates (this is along with the corresponding 6 noise interaction term covariates as discussed above).

The voxel-wise group-level maps were generated by smoothing the general Hreg maps using an 8 mm Full Width Half Max and then by running a paired *t*-test comparing the exercise minus the rest condition maps (Fig. 2). A regression-based paired *t*-test was used as described here (Hedberg and Ayers, 2015) since it is more efficient than the traditional paired *t*-test. Two additional participant-level noise nuisance covariates were included in the paired *t*-test. First, the average whole-brain (i.e., gray matter mask) general Hreg value was extracted for each participant and included to ensure that no global differentiation signal or noise was accounting for the regional differences between the experimental conditions. Second, the number of total timepoints postcensoring was also included as a noise covariate to avoid differences that could be driven by the amount of data or excessive motion. A stringent threshold-free cluster enhancement (Smith and Nichols, 2009) was used to correct for multiple comparisons using a two-tailed alpha level of 0.05. Results are reported in MNI space as peak coordinates and use anatomical labels either from the HO atlas (Desikan et al., 2006) or a standard cerebellar atlas (Diedrichsen et al., 2009).

Whole-brain split half intraclass correlation coefficients (ICCs) waculated in order to quantify the group reliability of the general Hreg maps. See Supplementary Text S3 for more details. Brain images in the results are presented either in sagittal slices in MNI space generated in MRIcroGl: https://www.nitrc.org/projects/mricrogl, surface projections for the cortex generated in Surf ICE: www.nitrc.org/projects/surfice/), or a flattened map of the cerebellar surface generated in SUITE flatmap: www.diedrichsenlab.org/imaging/suit_flatmap.htm.

2.8. Bayesian multilevel modeling analyses

In addition to more traditional frequentist approaches, we also employed a Bayesian multilevel modeling (BMM) approach on brain parcels. This approach uses the same Hreg data as discussed in the voxel-wise group-level maps, except that it extracts data from entire brain parcels (e.g., the entire inferior temporal gyrus). This method has been used recently as a way to avoid issues of multiplicity associated with whole-brain univariate modeling and instead includes all of the whole-brain data within a single model (Chen et al., 2019a, 2019b). In order to do this, we used a whole-brain BMM (Gelman et al., 2012), which leverages random effects estimates obtained from a single mixed effects model. The goal of the BMM approach is to estimate the probability of the hypothesis given the data. Thus, this approach does not necessitate a binary thresholding (e.g., alpha level) and allows for the presentation of the posterior probability density distribution associated with each effect of interest. These posterior distributions reflect the relative probabilities of the range of possible parameters and allow for the comparison of the entire effect-of-interest distribution relative to a null point—in this case 0. For example, in the first analysis discussed below (2.8.1), we are interested in whether there is an effect of condition. If, for instance, 90% of the area under the curve of the posterior distribution for this parameter (i.e., the difference between exercise and rest) is greater than 0, then the 90% credible interval indicates a positive effect. Within the frequentist framework, this is conceptually analogous to significance at alpha = 0.10 one-tailed. In this work, we follow previously reported conventions (Limbachia et al., 2021) and will call these posterior probability values P+, such that the previous example the P+ would be 0.9 (i.e., 90%). For a minimally technical description of the logic of this approach, see here Chen et al. (2020).

For this analysis, we first parsed the brain into standard anatomical regions based on the AAL3 atlas; this was chosen because it is one of the few standard atlases that includes both cortical, subcortical, and cerebellar parcellations (Rolls et al., 2020). We then identified 2 levels of regions, termed level 1 and level 2. The level 1 regions included major gyri, subcortical, and cerebellar parcellations. The level 2 regions were more broadly defined and focused on the lobes (e.g., entire temporal lobe). See Supplementary Table S3 for the full list of regions. The smaller level 1 regions were modeled hierarchically; that is, they were nested within their corresponding larger level 2 regions. For example, the level 1 region left inferior frontal gyrus was nested within the level 2 region frontal lobe. It is

Table 2
Stroop performance (N = 30)

Measures	Rest mean (SEM)	Exercise mean (SEM)	Exercise minus rest		Interference effect: trial type by condition interaction		
			Raw	Cohen's d	*t*-stat	*p*	R^2 full model
% Accuracy							
Congruent	99.3% (.3%)	99% (.7%)					
Incongruent	95.8% (1.1%)	97.9% (.9%)					
Interference	**−3.5% (.98%)**	**−1.2% (.6%)**	**2% (1.1–3.5)**	**0.38**	**2.49**	**0.02**	**0.69**
RT (ms)							
Congruent	1125 (55.5)	1146 (49.2)					
Incongruent	1317 (54.4)	1336 (56.9)					
Interference	19.2 (2.6)	17 (2.5)	−2 (−6.2 to 2.7)	−0.13	−0.06	0.96	0.96

Interference measure RT = (Incongruent RT − Congruent RT)/Congruent RT; Interference measure accuracy = Incongruent % accuracy − Congruent % accuracy. Estimates of the interference effect due to exercise were obtained from mixed effects models including trial type (congruent, incongruent) and condition (rest, exercise). Main and interaction fixed effects were included in the model along with random effect intercepts and slopes. An example R mixed-model used for the Stroop accuracy is as follows: lmer(Stroop_Accuracy ~ Rest_Exercise * Congruent_Incongruent + (1 + Rest_Exercise + Congruent_Incongruent | Participant_ID) where Rest_Exercise is a categorical variable for the experimental conditions and Congruent_Incongruent is a categorical variable for the trial type. Interference score accuracy statistics (*t* and *p* values) are based on Rest_Exercise * Congruent_Incongruent interaction effect. Bold indicates significance effects.
Key: RT, reaction time; SEM, standard error of the mean.

important to emphasize that the output from the BMM model is a single, overarching joint posterior distribution in multidimensional parameter space, and thus there is no need for correcting for multiple comparisons. The basics of the BMM algorithm are here, and the code for reproducing the data reported here, as well as additional figures not included due to space limitations, are made available here (https://osf.io/suzfc/).

2.8.1. Exercise versus control Bayesian multilevel modeling analysis

The dependent variable data for the BMMs were the mean Hreg values from each level 1 region of interest (ROI). The Hreg data from each ROI were then set as a dependent variable in BMM aimed to estimate the interaction between the effect of age and exercise versus rest condition. The model formula included the following regressors as fixed effects: (1) Rest_Exercise (whether the observations were recorded after rest or exercise, i.e., the experimental manipulation), (2) age (given that there was varied time between scan sessions, age was adjusted to account for the varied number of days between scan sessions across participants). For example, if the age was 65 years at the first time point, and the second was 2 weeks later, then the age at the second time point would be 65 plus 14 days. (3) Hemisphere (left or right), (4) Condition_Order (whether the observations were the participant's first or second time in the scanner), (5) ROI_Voxel# (the size of the level 1 region in the AAL3 atlas), (6) Time_Point# (the total number of time points), and (7) Whole_Brain_Hreg. The regressors (4–7) were included as nuisance covariates.

Random effects were included both by-participants and by-regions according to the practice of maximally specified structure (e.g., Barr et al., 2013): all regressors were included as random slopes both by-participants and by-regions unless those variables did not vary within units. For example, ROI_Voxel# was not included as a random slope by-regions because the number of voxels was fixed within each region. The full model formula is expressed in R (r-project.org; version 4.2.2) using the brms package (Bürkner, 2017) with both fixed and random effects (Supplementary Text S4).

Although the posterior distributions from all of the main and interaction effects were obtained, only those for the main effect of condition (Rest_Exercise) were of interest. For summarizing the data, the posterior distributions from the ROIs can be separately plotted as marginal distributions, even though they are not actually independent. For this and the following 2 BMM analyses, we obtained the posterior probability distributions for each level 1 and 2 regions, as reported below.

2.8.2. Condition by age interaction Bayesian multilevel modeling analysis

An additional focus of this work was to determine if any of the differences in neural differentiation between exercise and rest conditions were age dependent. We used a similar approach to that discussed in Section 2.8.1 except for the following modification. Instead of using the mean Hreg values from each level 1 ROI as the dependent variable for the BMMs, we used the Hreg values for each ROI extracted from those voxels with the top 20th percentile difference between the exercise and rest condition. This was done because of the hypothesis that only those voxels that showed an effect of exercise would also demonstrate an interaction effect with age. The 20th percentile was chosen based on previous work indicating that summaries obtained from the top 20% of voxels within ROIs provide a reliable and sensitive method for identifying group effects (Mitsis et al., 2008). For completeness, we also carried out the analysis for the Hreg values from the mean values, which are included in the Supplementary materials.

The Hreg data from each ROI were then set as a dependent variable in BMM aimed to estimate the interaction between the effect of age and exercise versus rest condition comparison. The model formula included the same fixed-effects regressors as described in Section 2.8.1.

Random effects were included both by-participants and by-regions according to the practice of maximally specified structure (e.g., Barr et al., 2013): all regressors were included as random slopes both by-participants and by-regions unless those variables did not vary within units. For example, ROI_Voxel# was not included as a random slope by-regions, because the number of voxels was fixed within each region. The full model formula as expressed in R (r-project.org; version 4.2.2) using the brms package (Bürkner, 2017) with both fixed and random effects (see Supplementary Text S4). Although the posterior distributions from all of the main and interaction effects were obtained, only those for the interaction effects involving age and the condition (Rest_Exercise) were of interest.

2.9. Condition by Stroop effect Bayesian multilevel modeling analysis

For this analysis, we examined the interaction between the effects of Stroop accuracy change (stroop_effect_change) and that of the condition (Rest_Exercise). The modeling approach is the same as discussed in Section 2.8.2, except in place of the interaction of age with Rest_Exercise and Hemisphere, we included the interaction with Stroop_Effect_Change (and age was retained only as a covariate). We obtained the posterior probability distributions for each level 1 and 2 regions for these interaction effects, as reported below. Below is the R (r-project.org; version 4.2.2) model using the brms package (Bürkner, 2017) with fixed and full set of random intercepts and slopes by-participants (see Supplementary Text S4). Although the posterior distributions from all of the main and interaction effects were obtained, only those for the interaction effects involving Stroop and the condition (Rest_Exercise) were of interest.

3. Results

3.1. Overview

In Section 3.2, we report that the experimental manipulation of exercise showed high internal validity based on the expected increase in HR and perceived exertion. In Section 3.3, we report better Stroop performance after exercise compared to rest. In Sections 3.4 and 3.5, we report strong evidence for increased neural differentiation in the brain after exercise compared to rest. Whereas in Section 3.6, we report moderate evidence that exercise-related differences in neural differentiation were moderated by age, in Section 3.7, we report weak evidence that exercise-related differences in neural differentiation were moderated by Stroop interference effects.

3.2. Experimental manipulation check

In order to confirm the validity of the exercise manipulation, HR, RPE, SAM valence, and SAM arousal were recorded during the exercise and rest sessions. As expected, there was minimal change in HR by the end of the rest session (decrease of ~4 BPM [standard error of the mean = 1]), and there was a marked increase in HR by the end of the exercise session (increase of ~61 BPM [standard error of the mean = 3.3]). Note that all paired *t*-tests reported in this work use the regression-based approach as described here (Hedberg and Ayers, 2015). A paired *t*-test revealed a significantly greater increase in HR after the exercise condition relative to the rest condition ($t(31) = 19.8$, $p < 0.001$, Cohen's $d = 3.5$). Further, there was a markedly greater increase in RPE by the end of the exercise session relative to the rest session ($t(31) = 31.8$, $p < 0.001$, Cohen's $d = 5.6$). The mean RPE during exercise corresponded to a rating between the verbal

Table 3
General Hreg whole-brain results for the exercise-rest contrast (N = 32; two-tailed corrected for multiple comparisons at an alpha = 0.05 using permutation-based threshold-free cluster enhancement).

			MNI coordinates				Mean intraclass correlations (Min-Max)		
Hemisphere/Region		Cluster mm^3	x	y	z	Peak Z-value	Exercise mean	Rest mean	Exercise-rest mean
Cerebellum									
R	Vermis 8	196	5	−65	−41	2.71	0.83 (0.79–0.86)	0.75 (0.68–0.84)	0.19 (0.01–0.54)
L	Crus2		−17	−83	−38	2.27	0.71 (0.64–0.79)	0.72 (0.65–0.79)	0.32 (0.22–0.4)
L	Lobule 6	40	−17	−65	−29	2.02	0.73 (0.68–0.82)	0.75 (0.68–0.81)	0.52 (0.43–0.59)
L	Lobule 6		−29	−68	−23	2.15	0.51 (0.40–0.63)	0.60 (0.48–0.74)	0.28 (0.20–0.35)
L	Vermis 4/5	34	−2	−56	−23	2.03	0.72 (0.66–0.77)	0.80 (0.76–0.82)	0.28 (0.05–0.42)
Cerebrum									
L	PHG	142	−26	−32	−26	2.2	0.76 (0.65–0.90)	0.63 (0.56–0.69)	0.40 (0.20–0.53)
L	Hippocampus		−20	−26	−14	2.2	0.71 (0.62–0.78)	0.66 (0.51–0.77)	0.45 (0.27–0.56)
L	Occipital pole	35	−29	−95	−17	2.08	0.69 (0.62–0.75)	0.56 (0.44–0.62)	0.10 (0.01–0.17)
L	Occipital FG	27	−20	−80	−14	2.2	0.27 (0.15–0.43)	0.26 (0.17–0.37)	0 (0–0.002)
			Mean			2.14	0.66	0.64	0.28
			Min			2.02	0.27	0.26	0.00
			Max			2.27	0.83	0.80	0.52

A minimum cluster threshold of 20 voxels was used (each voxel is 3 × 3 × 3 mm); the top 2 peaks from each significant cluster are reported if they are at least 10 mm apart and are in different anatomical structures. Cerebrum regions are defined using the Harvard Oxford atlas, while the cerebellum regions are defined using a standard cerebellum atlas (Diedrichsen et al., 2009); the intraclass correlation coefficient (ICC)vaesof the participant general Hreg values were obtained separately for the exercise minus rest contrast, the exercise minus implicit baseline and the rest minus implicit baseline maps. On average, the ICC values ranged *mostly* from fair to strong in the significant peaks using the following ICC scale (Elliott et al., 2020): [0–0.4] = poor; [0.4–0.6] = fair; [0.6–0.75] = good; [0.75–1] = strong. Peak z-stat = local maximum z statistic; R = Right; L = Left.
Key: PHG, parahippocampal gyrus; FG, fusiform gyrus.

anchors "Somewhat Hard" and "Hard" (RPE Borg 6–20 scale = 13–15) consistent with a moderate-intensity exertion. For the exercise minus rest comparison, while there was a small decrement in SAM valence during exercise ($t(31) = -2.3$, $p = 0.029$, Cohen's $d = -0.41$), there was a small heightening in SAM arousal during exercise ($t(31) = 2.7$, $p = 0.011$, Cohen's $d = 0.36$). These expected effects support the internal validity of the experimental manipulation (exercise and rest) in this study (see summary in Supplementary Table S2).

3.3. Stroop performance

The primary measure of interest is the interference for both the reaction time (RT) and the percent (%) accuracy, which compares the behavior on the congruent trials relative to the incongruent trials. This was obtained as the interaction effect in a mixed effects model with a 2 × 2 design, which included trial type (incongruent or congruent) and condition (exercise or rest). An interaction effect between trial type and condition would suggest that exercise impacts the amount of Stroop interference. As reported in Table 2 (Supplementary Fig. S2), there was a significant interaction effect for the experimental condition and trial type for % accuracy ($t(29) = 2.49$, $p = 0.016$, Cohen's $d = 0.38$). However, there was no significant corresponding interaction effect in RT ($t(29) = -0.13$, $p = .956$, Cohen's $d = -0.13$). This interaction effect for % accuracy indicates that participants were noticeably better at selectively attending to the color-naming task after aerobic exercise relative to seated rest. This finding is particularly notable because the Stroop performance was obtained approximately 90 minutes after the exercise or rest conditions, suggesting a prolonged improvement in executive function due to exercise.

3.4. General Hreg voxel-wise analysis and ICC results

Whole-brain Hreg values were obtained for each participant, followed by a paired *t*-test to compare the values between the rest and exercise conditions. See Table 3 and Fig. 3 for the significant general Hreg clusters within-participant exercise minus rest condition contrasts. The intraclass correlation coefficient (ICC) values are also reported for these results (Supplementary Fig. S3).

There were 6 significant clusters which demonstrated greater neural differentiation following 30 minutes of exercise relative to 30 minutes of rest (two-tailed corrected $p < 0.05$; see Table 3 and Fig. 3). These included both the cerebellum and cerebrum. In the cerebellum, there were 3 clusters that included peaks in both medial and lateral cerebellum regions, including the Vermis, Crus 2, and Lobule 6. In the cerebrum, the most prominent effect was in the parahippocampal gyrus and hippocampus. There was a relatively weaker effect in the occipital pole and association cortices.

Overall, the within-condition reproducibility was primarily good across the local maxima (average for the exercise and rest was 0.66 and 0.64, respectively). Thus, the underlying within-condition reproducibility ranged from good to strong in many of the reported regions. The most reproducible regions with good reproducibility (ICC > 0.6 in both exercise and rest conditions) were in the Vermis, Crus 2, Lobule 6, PHG, and hippocampus. This good reproducibility provides support for using these values in the ROI analyses to examine the relationship between age and the effects of exercise on neural differentiation. Finally, although the within-condition ICC values are the most important metric of reliability, we also report ICC values for the exercise minus rest contrast, some of which had fair reproducibility (ICC > 0.4) such as Lobule 6 and the hippocampal formation; see Table 3 and Supplementary Fig. S3. No clusters were observed which had significantly greater neural differentiation following 30 minutes of rest compared to 30 minutes of exercise.

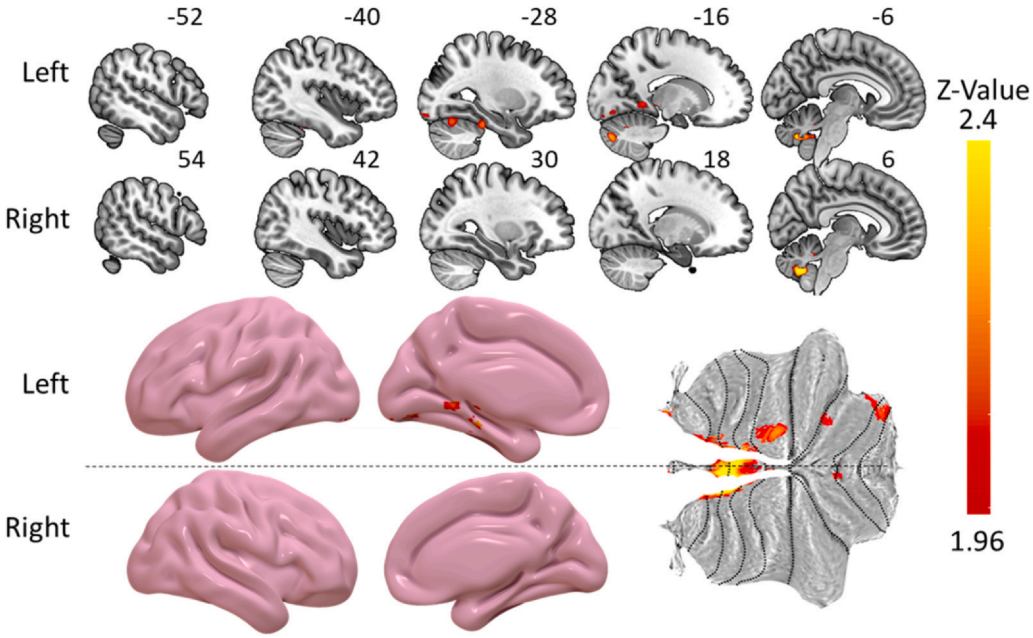

Fig. 3. Group-level paired *t*-test comparing the general Hreg after 30 minutes of exercise compared to 30 minutes of seated rest (exercise-rest). A permutation-based threshold-free cluster enhancement approach was used to correct for multiple comparisons; the color scale depicts the z-value from the minimum (z = 1.96 which is equivalent a two-tailed alpha level = 0.05) to a maximum of 4. As reported in detail in Table 3, the most prominent regions which show a significant difference are in the cerebellum and left hippocampus. Top are sagittal slices with MNI slice #, and bottom are surface projections for the cortex and a flattened map of the cerebellar surface.

3.5. Exercise versus control Bayesian multilevel modeling ROI results

We obtained marginal posterior distributions from all level 1 and 2 regions for the main effect of exercise across the entire parcellated brain. In Fig. 4, we report the posterior distributions for each level 1 region and provide the P+ of this interaction effect relative to 0. In interpreting the results, we followed a quantitative and qualitative assessment of the posterior distribution effects. That is, we defined thresholds for discussing the data as either having strong, medium, or weak evidence and further interpreted those areas that also had previous theoretical relevance (Limbachia et al., 2021). The following P+ evidence strength scale will be used: weak = 0.85–0.899 or 0.15–0.101, medium = 0.9–0.949 or 0.1–0.051, strong = 0.95–1.0 or 0.05–0.

Across the entire brain, there was evidence that neural differentiation increased due to exercise in the back of the brain, and then when proceeding anteriorly, there was a decrease in differentiation due to exercise. This is depicted by the orange/red to green to blue color schemes in the posterior distributions and brain plots in Fig. 4. Specifically, the cerebellum showed strong evidence of an effect in increased differentiation due to exercise. There was also medium evidence of increased differentiation in the ventral occipital temporal cortex, and weak evidence in ventral occipitotemporal and occipital cortex regions, including the fusiform, lateral occipital cortex, and lingual gyrus. In the frontal cortex, there was decreased differentiation; whereas there was medium evidence in the MFG, IFG, SMA, OFC, and SFG, there was weak evidence in the ACC.

3.6. Condition by age interaction Bayesian multilevel modeling ROI results

We obtained marginal posterior distributions from all level 1 and 2 regions for the age by condition interaction effect. We report the posterior distributions for each level 1 region in Fig. 5 and interpret them using the same criteria as discussed in Section 3.5. There were 10 brain regions with medium evidence for a positive age by condition interaction, and 6 regions showing weak evidence. Broadly speaking, the regions most associated with this interaction were in the temporal lobe, cerebellum, and parietal lobe. It is worth noting that many of the plots from the regions demonstrating significant interactions show a pattern such that the effect of exercise was greater for relatively older adults. The prevailing pattern specifically is a more negative association with age at rest (downward sloping lines in blue) compared to after exercise (less-downward sloping lines in red). This is most prominent in the cerebellum and parietal region plots reported in Fig. 5.

3.7. Condition by Stroop interaction Bayesian multilevel modeling ROI results

We obtained marginal posterior distributions from all level 1 and 2 regions for the age by condition interaction. We report the posterior distributions for each level 1 region in Fig. 6 and interpret them using the same criteria, as discussed in Section 3.5. There were 4 brain regions with weak evidence for a positive Stroop by condition interaction effect. Generally, these effects were reported in the temporal lobe, with the most prominent effect in the MTL. The prevailing pattern revealed that individuals who most improved on the Stroop task (after exercise relative to rest) tended to also show the greatest increase in Hreg due to exercise.

4. Discussion

First, behaviorally, participants were better at suppressing Stroop interference after the exercise condition, which confirms previous reports of improved executive function after aerobic exercise. Second, differences in neural differentiation due to exercise present as an anterior-posterior spatial gradient across the entire brain with posterior regions having pronounced *increased* neural differentiation and anterior regions having pronounced *decreased* neural differentiation. Third, the increases in neural differentiation in temporal lobe and cerebellum were greater as age increased, suggesting that

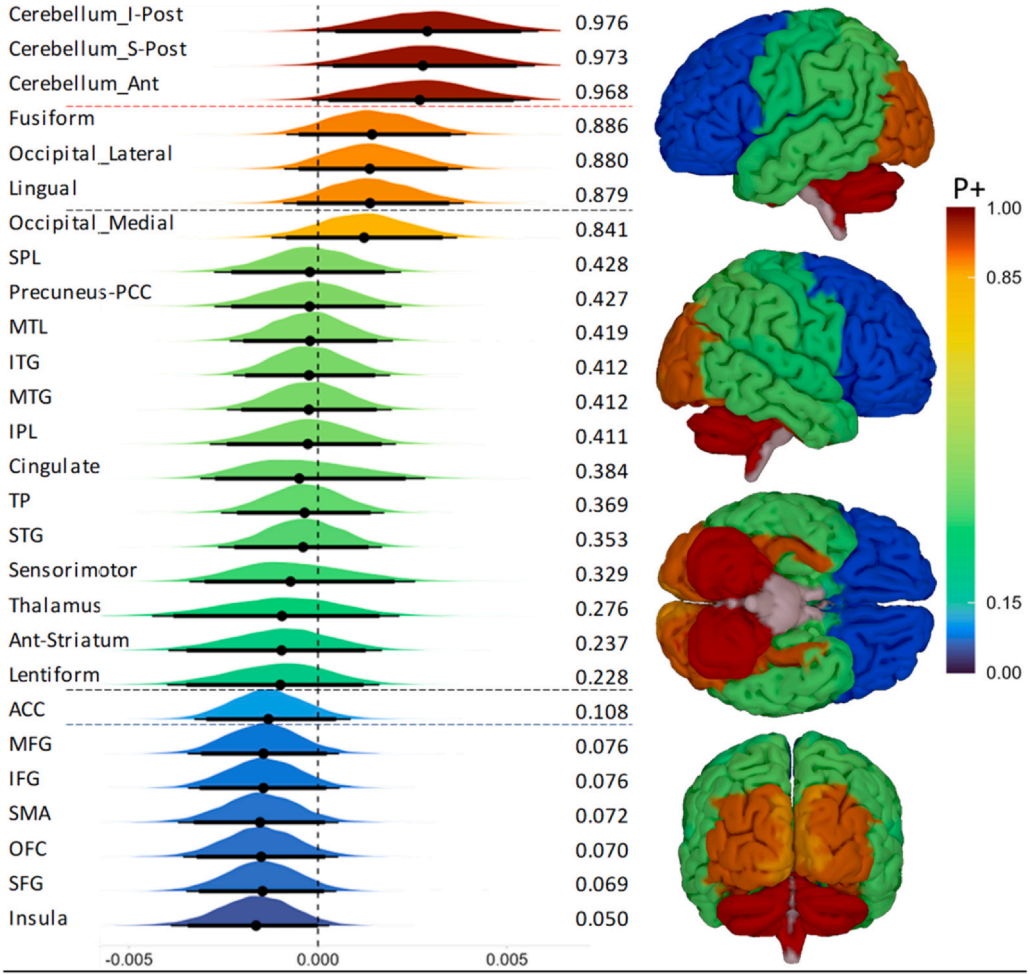

Fig. 4. Neural differentiation differences due to exercise or rest. These results use the average heterogeneity regression (Hreg) values across all of the voxels in each region of interest (ROI). Marginal posterior distributions from each level 1 ROI; see Supplementary S4 for the level 2 ROI results. The area under the curve greater than 0 (a null effect; vertical dotted line) indicates the P+ of the effect of exercise. For each parcel, high P+ (red/orange colors) indicates greater mean Hreg (neural differentiation) due to exercise minus rest. Low P+ (blue colors) indicate lower mean Hreg due to exercise minus rest. There is no traditional thresholding, and all of the effect posterior distributions are plotted. Horizontal dotted lines depict thresholds for reportable ROI effects as follows: weak = 0.85–0.899 or 0.15–0.101, medium = 0.9–0.949 or 0.1–0.051, strong = 0.95–1.0 or 0.05–0. On the right are brain renderings of the colors of the posterior distributions with the associated P+ color scale. Note: see Supplementary Fig. S5 for complementary results that do not collapse across hemisphere; they are not qualitatively different from those reported here. Abbreviations: Ant, anterior; A/PCC, anterior/posterior cingulate cortex; I/M/SFG, inferior/middle/superior frontal gyrus; I/M/STG, inferior/middle/superior temporal gyrus; MTL, medial temporal lobe; S/IPL, superior/inferior parietal lobule; S/I-post, superior/inferior posterior; SMA, supplementary motor area; TP, temporal pole.

these local neural responses may be functionally "redifferentiated" in the older participants. Finally, the magnitude of decreased Stroop interference after exercise was weakly associated with the magnitude of neural differentiation differences in the temporal lobe, suggesting a functional correspondence between the exercise-related neural differentiation and Stroop performance effects. Together, these results suggest that a single session of aerobic exercise leads to increased executive function and neural differentiation that is both more pronounced in older ages and related to improvements in executive function.

4.1. Acute exercise and executive function

There was a significant reduction in the Stroop interference effect in accuracy and thus improved inhibition or selective attention after a 30-minute exercise session. It is worth emphasizing that performance was measured after an fMRI session that immediately followed the exercise (or seated rest) conditions, and thus indicates that these effects may persist at least 90 minutes after exercise. This finding is supported by work reporting that improved executive function (i.e., a composite score of multiple tasks including the Stroop task performance) lasted up to 2 hours after aerobic exercise (Basso et al., 2015). These findings support the idea that the specific executive function associated with inhibiting prepotent responses is improved up to 90 minutes following 30 minutes of exercise.

Although this finding is also broadly in line with previous literature reporting improvements in Stroop performance immediately after aerobic exercise, there are inconsistencies in the previous literature worth considering (Barella et al., 2010; Chang et al., 2019; Hogervorst et al., 1996; Lichtman and Poser, 1983; Sibley et al., 2006). For instance, some of these studies only observed effects of decreased RT (but not increased accuracy) on the congruent, incongruent, and/or neutral reading conditions after exercise, but not specifically the Stroop interference effects (Barella et al., 2010; Chang et al., 2019). Still for those studies that did demonstrate an improvement specifically on Stroop interference effects, they were reported either only with RT (not accuracy) (Hogervorst et al., 1996; Sibley et al., 2006), or simply with the number of words read within a fixed amount of time (Lichtman and Poser, 1983). In this study, we do not replicate these RT or number of responses of Stroop

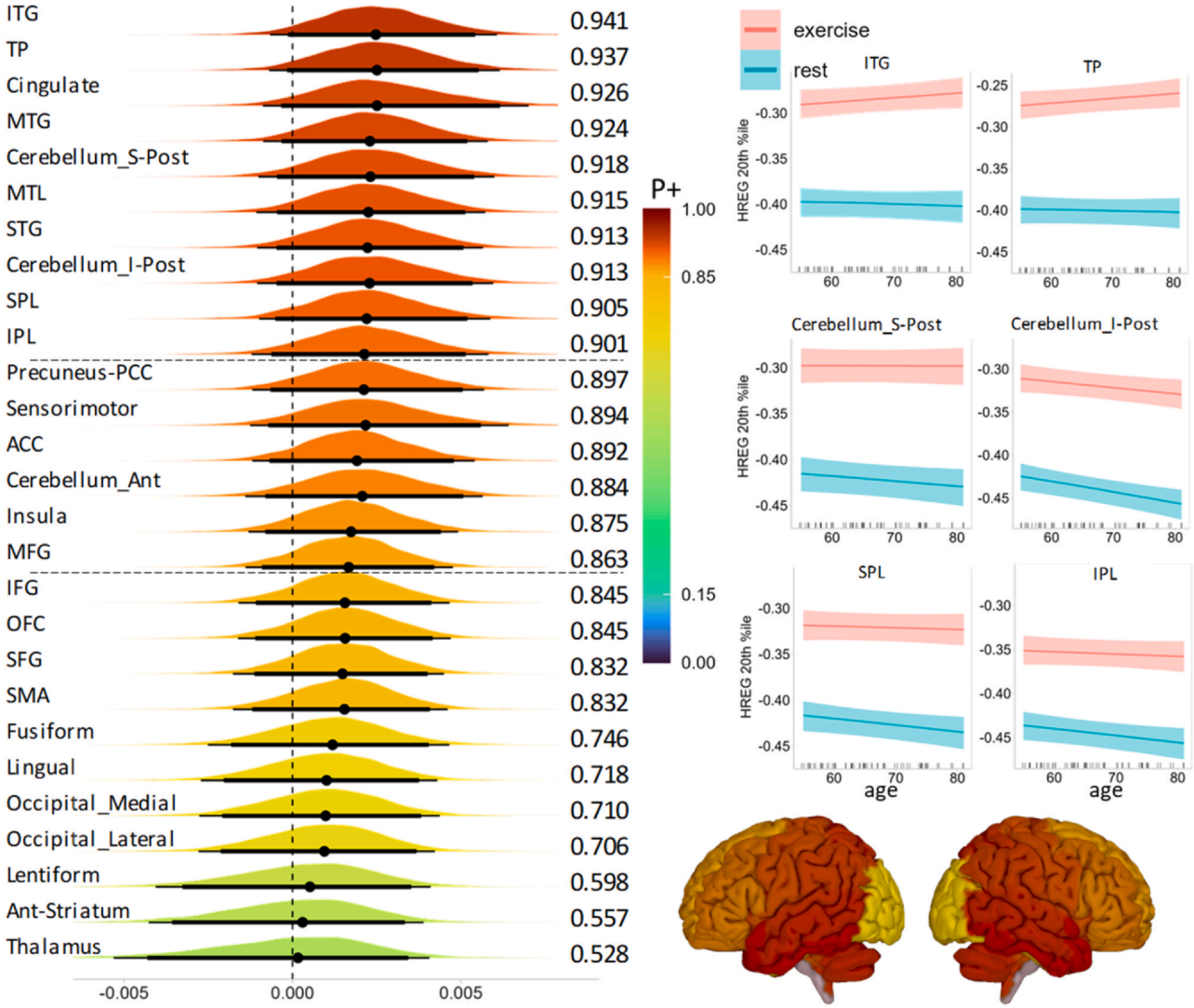

Fig. 5. Neural differentiation interacts with age and the experimental conditions (exercise and rest). These results use the average heterogeneity regression (Hreg) values for those voxels with the top 20 percentile greatest difference in condition were included for each participant and parcel (HREG 20th %ile). For completeness, see Supplementary Fig. S6 for the results using the total average Hreg values in each parcel. Marginal posterior distributions from each level 1 region of interest; see Supplementary Fig. S7 for the level 2 region of interest results. The area under the curve greater than 0 (a null effect; vertical dotted line) indicates the P+ of the effect of the interaction between age and condition. For each parcel, high P+ (red/orange colors) indicates greater Hreg (neural differentiation) due to exercise minus rest. Low P+ (blue colors) indicates lower mean Hreg due to exercise minus rest. Horizontal dotted lines depict thresholds for reportable parcel for weak (0.85–0.899) and medium (0.9–0.949) effects. On the right top are effect plots with confidence intervals showing the direction of interaction effects from a subset of the medium-strength interaction effects reported on the left. See Supplementary Fig. S8 for all of the medium and weak effect plots. On the right bottom are brain renderings of the colors of the posterior distributions with the associated P+ color scale. Note see Supplementary Fig. S9 for complementary results not collapsed across hemisphere; they are not qualitatively different from those reported here. Abbreviations: Ant, anterior; A/PCC, anterior/posterior cingulate cortex; I/M/SFG, inferior/middle/superior frontal gyrus; I/M/STG, inferior/middle/superior temporal gyrus; MTL, medial temporal lobe; S/IPL, superior/inferior parietal lobule; S/I-post, superior/inferior posterior; SMA, supplementary motor area; TP, temporal pole.

interaction exercise effects, but instead present a novel Stroop accuracy interference effect in the absence of a RT effect after exercise. One possibility is that much of the previous literature reported Stroop effects for RT based on measurements taken soon after exercise (e.g., Hogervorst et al., 1996; Sibley et al., 2006), and it may be the case that these effects for RT are not present after more than 60 minutes delay after exercise (e.g., Barella et al., 2010). Given that the effects reported here are 90 minutes after exercise, it may reflect a novel finding for the persistence of Stroop accuracy effects that has not been extensively examined yet. Another point to consider is that our instructions did not clearly state an emphasis on speed and accuracy per se, and thus it is possible that participants may have inadvertently tended to focus on RT over accuracy, which is known to lead to relatively more robust Stroop interference effects in accuracy (Chen and Johnson, 1991). Thus, it is possible that a tendency to focus more on RT led to a more readily detectable exercise Stroop interference accuracy effect in this study. Further work is necessary to clarify the robustness of these Stroop effects given different experimental manipulations. Finally, it should be noted that this finding is also broadly in line with findings that flanker task performance is better after a single session of exercise in young (Coleman et al., 2018) and older adults (Kamijo et al., 2009).

When looking at the brain-behavior relationships, it was also observed that there was at least weak evidence that Stroop task performance was related to temporal lobe regions, including the medial temporal lobe, inferior temporal gyrus, temporal pole, and middle temporal gyrus. One interpretation is that relatively low neural differentiation in these temporal lobe regions is associated

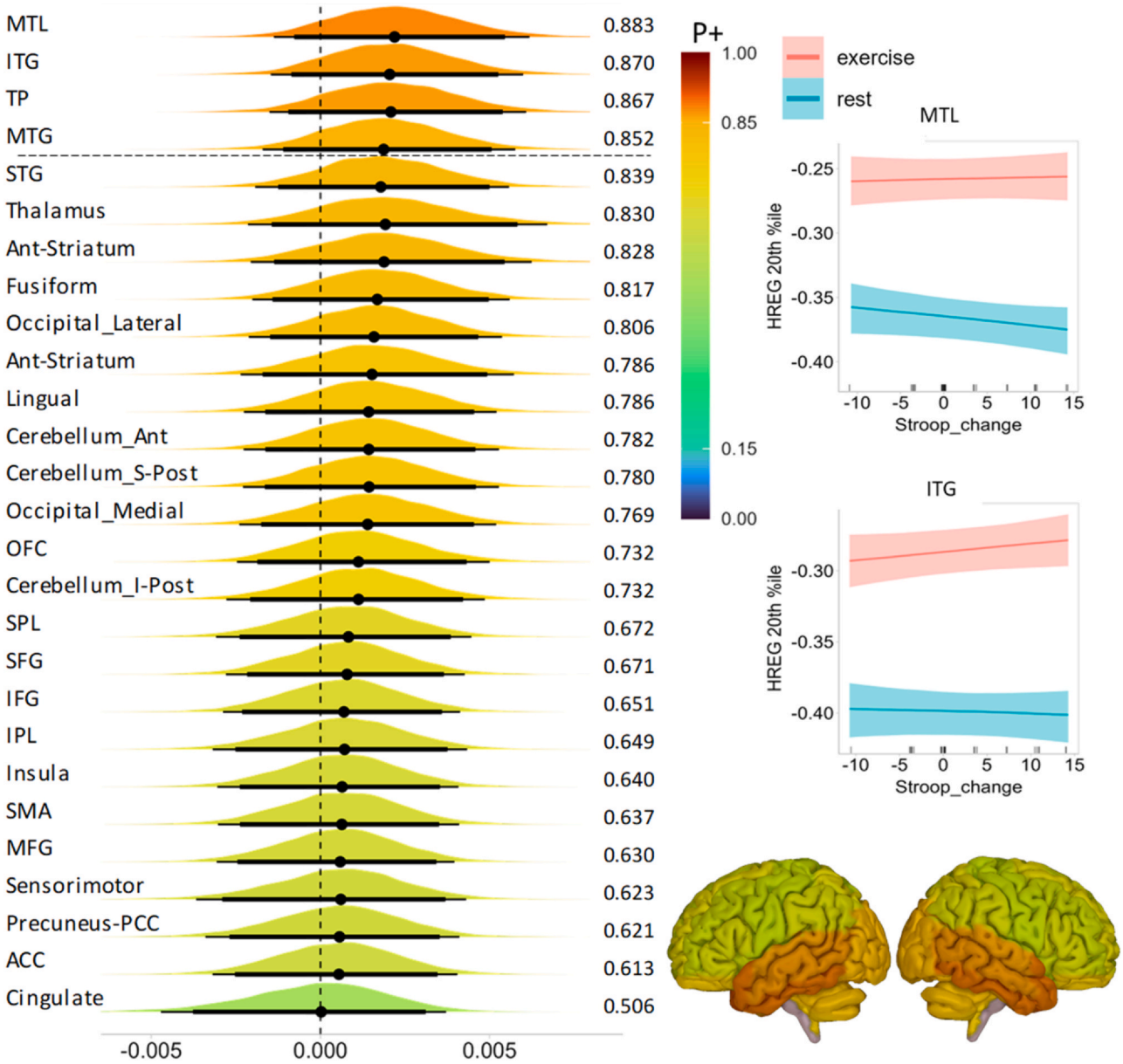

Fig. 6. Neural differentiation interacts with Stroop and the experimental conditions (exercise and rest). These results use the average heterogeneity regression (Hreg) values for those voxels with the top 20 percentile greatest difference in condition were included for each participant and parcel (HREG 20th percentile). For completeness, see Supplementary Fig. S10 for the results using the total average Hreg values in each parcel. Marginal posterior distributions from each level 1 region of interest; see Supplementary Fig. S11 for the level 2 region of interest results. The area under the curve greater than 0 (a null effect; vertical dotted line) indicates the P+ of the effect of the interaction between age and condition. For each parcel, high P+ (red/orange colors) indicates greater Hreg (neural differentiation) due to exercise minus rest. Low P+ (blue colors) indicates lower mean Hreg due to exercise minus rest. The horizontal dotted line depicts a threshold for weak effects (0.85–0.899). On the right top are effect plots with confidence intervals showing the direction of interaction effects from a subset of the weak interaction effects reported on the left. See Supplementary Fig. S12 for all weak effect plots. On the right bottom are brain renderings of the colors of the posterior distributions with the associated P+ color scale. Note see Supplementary Fig. S13 for complementary results not collapsed across hemisphere; they are not qualitatively different from those reported here. Abbreviations: Ant, anterior; A/PCC, anterior/posterior cingulate cortex; I/M/SFG, inferior/middle/superior frontal gyrus; I/M/STG, inferior/middle/superior temporal gyrus; MTL, medial temporal lobe; S/IPL, superior/inferior parietal lobule; S/I-post, superior/inferior posterior; SMA, supplementary motor area; TP, temporal pole.

with less suppression of the prepotent, task-irrelevant information (i.e., ignore the word and focus on the color), and that exercise leads to a heightened neural differentiation that facilitates better ability to access the task-relevant information. This interpretation fits with previous work with adolescents (Banich et al., 2007) and older adults (Milham et al., 2002). The observation of a weak effect for a relationship between Stroop accuracy (measured 90 minutes after exercise) and neural differentiation (measured between 10 and 90 minutes after exercise) suggests that we may be underestimating the effects of acute exercise on executive function here, and that the effects of executive function may be present in an interesting, time-dependent manner postexercise for at least 1–2 hours. after exercise. Here, we provide just one aspect of the alignment of neural and behavioral measures obtained at different parts of this potentially dynamic residual improvement in executive function. Future work is required to explore more detailed measures of executive function improvements after exercise across multiple time scales in order to better understand the nature of the magnitude of these.

4.2. Changes in neural differentiation after exercise

The overarching novel finding is that a single session of exercise leads to a striking anterior-posterior spatial gradient of neural differentiation across the entire brain. This led to greater neural differentiation in the cerebellum, occipital and temporal cortex, and lower neural differentiation in the frontal cortex. Given the panoply of proposed neural and molecular factors associated with acute exercise (Basso and Suzuki, 2017; Stillman et al., 2020), there may be multiple, concurrent contributing underlying mechanisms, as discussed below.

4.2.1. Increased neural differentiation in posterior regions after exercise

As predicted, in more posterior brain regions, including the temporal lobe and cerebellum, there was evidence for an increase in neural differentiation after a single session of exercise. More focally, the effects of increased neural differentiation from the whole-brain voxel-level analysis were observed within the medial cerebellum (vermis), lateral cerebellum (Crus 2 and lobule 6), and hippocampal formation. Generally, these findings of improved local differentiation are associated with better differentiated local neural signals, and thus considered a beneficial functional outcome of aerobic exercise. This is of particular importance to the older population studied here, which is considered to undergo age-related dedifferentiation in multiple neural systems (Carp et al., 2011; Dennis and Cabeza, 2011; Park et al., 2004). At least one other study provides direct support for these findings, as they examined the local neural differentiation via a neural distinctiveness measure and found that 6 months of aerobic exercise training led to greater visual system neural distinctness in older adults (Kleemeyer et al., 2017). Thus, our findings fit with previous works indicating that higher fitness or exercise training is associated with better differentiation (redifferentiation) of neural networks and local neural signals in older adults.

One possible underlying neural mechanism of these effects is exercise-induced stimulation of GABAergic signaling. It is first important to consider that a core feature of local neural differentiation is that it is considered to be associated with relatively efficient sparse neural codes; the more sparse the neural code, the fewer neurons or synapses required to code the same information (Chalk et al., 2018). This coding model fits well with the selective neural tuning properties in sensory regions (Beyeler et al., 2019). Critically, GABAergic lateral inhibition is important for maintaining these sparse population codes (Paiton et al., 2020), and consequently, these codes can be thought of as resulting from a coordination of excitatory and inhibitory local signaling. For instance, one study observed increased neural selectivity (i.e., neural differentiation) after administration of GABA to the monkey visual cortex (Leventhal et al., 2003). Other work has directly found that GABA, but not glutamate levels, are directly correlated with declines in neural selectivity within the human visual cortex (Bang et al., 2023). Thus, an increase in GABA signaling may be a mechanism underlying increased local neural differentiation after exercise. In support of this idea is work reporting increases in both glutamate and GABA in the visual cortex after vigorous aerobic exercise—with GABA having a twice the percent increase relative to glutamate 20 minutes after exercise (Maddock et al., 2016). One contributing mechanism may be increased astrocyte activation, which has been shown to have increased activation after exercise (Li et al., 2021) and is known to modulate local GABAergic neurotransmission (Losi et al., 2014; Mederos and Perea, 2019). It is important to note that the regions most associated with sparse coding in the literature are primarily in sensory areas (i.e., occipital/temporal) and the cerebellum—that is, the posterior brain regions associated with the greatest increase in local neural differentiation after exercise in this study—and not within the more frontal prefrontal or motor cortices (Beyeler et al., 2019; Cayco-Gajic and Silver, 2019). Thus, the GABAergic system modulation of local sparse coding systems in the occipital, temporal, and cerebellar regions may help to explain this more posterior increase in neural differentiation after exercise.

Looking at the more detailed voxel-wise analysis, we only identified significant increases in neural differentiation for the exercise relative to rest condition. The largest cluster in the cerebrum, and the region with the highest reproducibility, was the left hippocampus. These findings fit with previous literature indicating that the hippocampus is responsive to exercise in the aging brain (Bettio et al., 2017; Erickson et al., 2011; Voss et al., 2019). Specifically, the function of the hippocampus and surrounding parahippocampal and entorhinal cortices has been shown to improve after a single aerobic exercise session as measured with an fMRI pattern separation task (Suwabe et al., 2018), a working memory fMRI task (Li et al., 2019), semantic memory task (Won et al., 2019b; previous study using a subset of the data reported here), and flanker task (Won et al., 2019a). These findings also fit with studies finding microstructural changes in the hippocampus in older adults after a single session of aerobic exercise (Callow et al., 2021; previous study using a subset of the data reported here), which may be associated with exercise-induced changes in the extracellular space and glial, synaptic, and dendritic processes within the hippocampus. Additionally, one study in younger adults indicated that hippocampal cerebral blood flow selectively improves after a single session of exercise (Steventon et al., 2019). One mechanism that may contribute to these localized acute effects of exercise is mild inflammation (Cerqueira et al., 2020), which—although damaging in high and chronic amounts—has been associated with positive neuroinflammatory impacts such as the promotion of neurogenesis in the hippocampus (Sung et al., 2020). Beyond promoting neurogenesis in the longer term, mild neuroinflammation is also thought to stimulate local hippocampal glial function and neural signaling soon after exercise (Callow et al., 2021, 2023; DiSabato et al., 2016; Whitney et al., 2009). It is possible that heightened glial function after exercise can contribute to the modulation of local neural signaling processing (e.g., Araque and Navarrete, 2010), which is required for changes in neural differentiation. Overall, these results align with both structural and functional neuroimaging data indicating exercise-induced changes in the hippocampal formation after a single session of aerobic exercise.

Next, the largest cluster for the voxel-wise analysis was in the cerebellum. Although differences in task-based fMRI (i.e., working memory task) immediately after exercise have been reported in the cerebellum for both prepubescent children (Chen et al., 2016) and young adults (Li et al., 2019), here we report these effects in the cerebellum of late middle age to older adults. The cerebellum is known to be associated with both sensory and motor processing as well as higher cognitive function (Koziol et al., 2014), and thought to act as a coprocessor with specific cerebrum centers to which it is connected (D'Angelo and Casali, 2013). The more medial regions, including the Vermis, are thought to be associated with the more automatic sensory and motor functions, while the more lateral regions are associated with higher-level cognition functions (Klein et al., 2016). Previous work has reported that increased functional connectivity between the cerebellum and the precuneus and inferior parietal lobule after 12-weeks of exercise training in mild cognitive impairment patients was associated with improved verbal fluency performance (Won et al., 2021). Although we did not detect any brain-behavior relationship in the cerebellum, we anticipate that more extensive cognitive-behavioral testing including verbal fluency may relate to differences in cerebellar neural differentiation after a single exercise session.

Notably, the predominance of significantly greater neural differentiation effects was observed in brain regions associated with the separation of neural signals (i.e., pattern separation). As described by Cayco-Gajic and Silver (2019), both the hippocampus (i.e., the

dentate gyrus) and the cerebellar cortex contain pattern separation-specific circuitry, and both regions were observed to show significant differences in this study. The critical computation performed by this circuitry relates to separating overlapping input neural signals. Whereas for the hippocampus this computation is critical for encoding distinct memory representations, for the cerebellum this is critical for sensory discrimination, associative learning (Cayco-Gajic and Silver, 2019), and cognitive control (Abrahamse et al., 2016). This leads to an interesting hypothesis that exercise particularly affects those circuits which are suited for neural pattern separation, a key mechanism of which is divergent excitatory projections with feedback inhibition.

4.2.2. Decreased neural differentiation in frontal regions after exercise

Interestingly, in multiple frontal cortical regions, there was a medium effect for decreased neural differentiation after a single session of exercise.

One possible underlying mechanism to explain these frontal results is that of an acute increase in catecholamine signaling, which is thought to contribute to heightened neural signal gain (i.e., improved signal-to-noise ratios) (Breton-Provencher et al., 2021; Li and Rieckmann, 2014; Li and Sikström, 2002; Mather and Harley, 2016). One specific catecholamine system that may play a key role is that of norepinephrine (NE) release from the locus coeruleus (LC), a nucleus that is known to be active by the sympathetic nervous system by way of the nucleus of the solitary tract after exercise (Arbat-Plana et al., 2019; Critchley and Harrison, 2013; Yamazaki et al., 2023). One consequence of the LC-NE activation after exercise has been put forward by the "network reset" theory, which posits that its central role is to facilitate the interruption and reorganization of task networks (Bouret and Sara, 2005). From this vantage point, a function of the LC-NE system may be to prime task networks for being reorganized for carrying out a particular task, and that this state of network resetting may be associated with more synchronized, less differentiated signals. This interpretation is supported by findings indicating an increased neural synchrony in several neural networks in older adults after acute exercise (Weng et al., 2017). Thus, the LC-NE system modulation of neural signals within more frontal task-dependent brain regions may help to partially explain this more anterior brain region decrease in differentiation after exercise.

From an information processing perspective, these frontal findings further align with the age-related frontal over-recruitment hypothesis (Grady, 2008; Maillet and Rajah, 2014), which posits that age induces reduced function in posterior brain regions such as those associated with memory processing. This is associated with compensatory over recruitment of task-specific frontal cortical regions. This hypothesis has been supported primarily by memory research (e.g., Cabeza et al., 1997; Madden et al., 1999), but has been put forward as a general principle of task-specific frontal circuitry in the aging brain (Cabeza and Dennis, 2013). Within this framework, an interpretation is that a single session of exercise leads to increased neural differentiation in posterior brain regions. This, in turn, is in concert with a lack of necessary frontal compensation. Thus, the frontal cortex is associated with a decreased neural differentiation due to exercise-induced reprieve from a basal heightened compensatory state. Further work is required to determine if these frontal differentiation decreases really do occur in concert with these posterior differentiation increases, and whether they are associated with direct beneficial effects on cognitive function.

4.2.3. Summary interpretation of changes in neural differentiation after exercise

Taken together, the above-mentioned findings and mechanisms help to explain both the more differentiated increases in more posterior regions, while also leading to a less differentiated state in more frontal neural systems. These mechanistic interpretations align with the bigger picture view that a key consequence of exercise on the brain is that it helps to prime multiple cognitive systems for sensory, attention, memory, and executive tasks (Moriarty et al., 2019). Both the anterior-posterior spatial gradient of neural differentiation changes and the more focal voxel-wise analysis result in pattern separation regions (i.e., hippocampal formation and cerebellum) that may show a general neural signature reflecting an increased capacity to engage in a wide array of cognitive tasks.

4.3. Age interacts with the effects of exercise on neural differentiation

The third main finding is that there is moderate evidence of an interaction effect between age and the effect of exercise within the temporal lobes, cerebellum, and parietal lobe. It is worth noting that the preponderance of evidence for neural dedifferentiation effects is in these more posterior regions based on sensory and memory-based fMRI experiments (Koen and Rugg, 2019). These findings fit with the idea that there is an exercise-induced neural redifferentiation in more posterior brain regions, which are also most consistently observed to be associated with age-dependent neural dedifferentiation.

This "exercise-induced neural redifferentiation" hypothesis posits that exercise leads to an increase in neural differentiation at older ages such that the older brain regions become functionally younger, that is, redifferentiated. The interaction effect pattern that best supports this hypothesis is when the relationship between age and neural differentiation has a negative slope during rest, but the relationship between age and neural differentiation has a horizontal or positive slope during exercise. That is, the effects of exercise bring the neural differentiation levels in the *older* participants closer to that of the levels observed in the *relatively* younger, late middle-aged participants. This is observed in Fig. 5 effect plots on the right, and most clearly in the cerebellum and parietal lobe. Overall, these findings suggest a redifferentiation of local fMRI signals in older age after a single session of exercise in temporal lobe, cerebellar, and parietal regions.

It is interesting to note that previous work has demonstrated that older adults with higher fitness levels had long-range neural network connectivity profiles closer to those of the young adult sample (Voss et al., 2016). Although our work does not have separate young and old samples, our sample does span late middle age (55–64 years old) to old age (65–81 years old). The findings reported in this section essentially indicate that the neural profile—at the level of local neural differentiation—in the older age participants tended to correspond more to the (*relatively* younger) late middle age neural profile immediately after exercise. Further work is necessary to clarify the ways in which the neural profiles of older adults may better match that of younger adults, and the manner by which these effects immediately after exercise may contribute to long-term benefits of fitness in older adults on the brain.

4.4. Limitations and future directions

Although there are a number of limitations in this study, these findings provide a solid foundation for future work to explore new directions. One major limitation is the sample. First, it included only 32 participants and so limits the generalizability of the findings that may be revealed by a larger sample. Second, although it does include late middle-aged adults and older adults, it does not include younger adults for comparison. The rationale for this was to focus on those older ages for which exercise is known to be most impactful on cognitive and neural health. We acknowledge that it would be valuable to incorporate a younger sample in future studies. Another possible limitation is that, whereas the exercise condition was fairly

engaging, the rest control condition involved sitting quietly without any typical stimulation (e.g., phone use, music, movies, social media), and it could induce states of boredom that could impact neural function (Danckert and Merrifield, 2018). We argue that our control task did not necessarily lead to a state of boredom in our participants. Boredom has been argued to be associated with low valence states (Eastwood et al., 2012), and in our study, the valence was actually significantly higher during the seated rest period relative to the exercise. This said, there may be aspects of boredom not correlated with valence level that could be present. Future studies would benefit from considering a more stimulating rest period (e.g., listening to music both during exercise and seated rest). Another limitation is that we did not acquire extensive cognitive tests in order to better pair the cognitive improvements that may be related to the brain-wide neural differentiation differences reported here. It is predicted that performance on cognitive tasks which utilize hippocampal formation such as associative memory, source memory, and recollection tasks (Davachi et al., 2003; Diana et al., 2010) would be associated with the magnitude of neural differentiation changes in the medial temporal lobe. It would be beneficial for future studies to have extensive cognitive testing, including episodic memory, to better understand these brain-behavior relationships.

Another limitation is that the spatial resolution of our work did not allow for fine-grained analyses of the hippocampus subfields. Previous work has suggested that the hippocampus is not only impacted by pattern separation processes—sourced in the dentate gyrus—but also by pattern completion levels—sourced in CA 2/3 (Knierim and Neunuebel, 2016; Lee et al., 2015; Riphagen et al., 2020; Rolls, 2013). Thus, a mixture of effects driven by pattern separation and pattern completion neural circuitry may obscure any age interaction effects reported here for the hippocampus. This interpretation follows our findings in that, although we found effects in the medial part of the left hippocampus, these were not clearly specific to the dentate gyrus, nor did we observe these in the coarse-grain ROI analysis. Thus, the hippocampus proper may require a more detailed investigation (i.e., that separates the dentate gyrus from the CA 3) in order to better pry apart the interaction effects of exercise and age.

Finally, the serendipitous finding of an anterior-posterior gradient of neural differentiation across the whole-brain sets up further work to explore what this means. For instance, it may be that exercise stimulates changes in connectivity across multiple neural networks, such that while there is greater neural differentiation in more posterior regions (associated with improved sensory and motor processing), there is a concurrent decrease in frontal neural differentiation (associated with a decreased demand on frontal compensatory mechanisms). If so, then this would suggest that a connectivity-based analysis may reveal specific concordance between different brain regions as impacted by exercise, and that decreased frontal neural differentiation may be associated with behavior in an inverse manner from more posterior regions.

4.5. Conclusion

Overall, these findings support the hypothesis that, after just a single session of moderate-intensity aerobic exercise, there are executive function improvements as well as differences in local neural signal differentiation across the brain. Notably, there was increased neural differentiation in posterior brain regions, which are reported to play a role in the separation of neural signals, which include the hippocampal formation and the cerebellar cortex (Cayco-Gajic and Silver, 2019). There were also decreases in neural differentiation in frontal cortices that may indicate a reprieve from age-dependent frontal compensatory processing and/or a heightened capacity for the resetting of the frontal network as they shift between task states. Finally, these effects interact with age in a manner that suggests that one mechanism of functional improvement due to exercise is a "neural redifferentiation" of local neural signals in the hippocampal formation and cerebellum.

Submission declaration and verification

We verify that this work has not been published previously, that it is not under consideration for publication elsewhere, and that its publication is approved by all authors. If published it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Disclosure statement

Alfonso Alfini, PhD, National Heart, Lung, and Blood Institute, NIH (Dr Alfini contributed to this article as an employee of Johns Hopkins University). The views expressed are his own and do not necessarily represent the views of the National Institutes of Health or the United States Government). No other authors have competing interests.

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Author contributions

JP performed the analysis and wrote the initial draft of the paper. JW and LW contributed to data collection. RW and YW contributed to the analyses. DC, JW, RW, and JCS contributed to manuscript writing and revisions. JCS, AA, and LW designed the study.

Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.08.008.

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