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ORIGINAL ARTICLE

Association of Lifestyle Activities with Functional Brain Connectivity and Relationship to Cognitive Decline among Older Adults

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Abstract

This study examines the relationship of engagement in different lifestyle activities to connectivity in large-scale functional brain networks, and whether network connectivity modifies cognitive decline, independent of brain amyloid levels. Participants ($N = 153$, mean age = 69 years, including $N = 126$ with amyloid imaging) were cognitively normal when they completed resting-state functional magnetic resonance imaging, a lifestyle activity questionnaire, and cognitive testing. They were followed with annual cognitive tests up to 5 years (mean = 3.3 years). Linear regressions showed positive relationships between cognitive activity engagement and connectivity within the dorsal attention network, and between physical activity levels and connectivity within the default-mode, limbic, and frontoparietal control networks, and global within-network connectivity. Additionally, higher cognitive and physical activity levels were independently associated with higher network modularity, a measure of functional network specialization. These associations were largely independent of APOE4 genotype, amyloid burden, global brain atrophy, vascular risk, and level of cognitive reserve. Moreover, higher connectivity in the dorsal attention, default-mode, and limbic networks, and greater global connectivity and modularity were associated with reduced cognitive decline, independent of APOE4 genotype and amyloid burden. These findings suggest that changes in functional brain connectivity may be one mechanism by which lifestyle activity engagement reduces cognitive decline.

Key words: amyloid, cognitive, lifestyle factors, physical activity, resting-state fMRI

Introduction

In light of the understanding that Alzheimer's disease (AD) pathology begins to develop in mid-life, there is an increased focus on identifying modifiable aspects of behavior that confer resilience to AD neuropathology and reduce its effects on cognition. Current evidence suggests that lifestyle factors, above and beyond lifelong intellectual attainment, such as engagement in activities that are cognitively, socially, or physically stimulating are associated with a reduced risk of MCI (Laurin et al. 2001; Wilson et al. 2007; Krell-Roesch et al. 2017) and dementia (Laurin et al. 2001; Verghese et al. 2003; Fratiglioni et al. 2004) and reduced or delayed cognitive decline (Vemuri et al. 2012; Pettigrew et al. 2019). However, little is known about whether there are selective neural mechanisms related to engagement in these specific lifestyle activities that can be identified and if these brain changes reduce cognitive impairment in the presence of pathology.

Prior studies among older individuals without dementia have reported that measures of educational and intellectual attainment are related to functional connectivity in large-scale brain networks, as assessed by resting-state functional magnetic resonance imaging (rsfMRI) (e.g., Arenaza-Urquijo et al. 2013; Bozzali et al. 2015; Perry et al. 2017; Serra et al. 2017; Franzmeier, Caballero, et al. 2017a; Franzmeier, Duering, et al. 2017b; Neitzel et al. 2019). Functional connectivity, as measured by rsfMRI, reflects the intrinsic correlations in the fMRI blood oxygenation level-dependent (BOLD) signal while participants are at rest. However, it remains unclear whether level of engagement in social, cognitive, and physical lifestyle activities is similarly associated with functional connectivity in large-scale networks, after accounting for measures of educational and intellectual achievement. It is also not known if level of engagement in different types of lifestyle activities is associated with differential patterns of functional connectivity since prior studies have exclusively focused on a single type of activity (i.e., physical or social) and no study, to our knowledge, has specifically investigated cognitive lifestyle activity levels in relation to rsfMRI. The current study was designed to address these gaps. Based on the finding that much of the variability in functional brain networks appears to reflect relatively stable individual characteristics, rather than more transient factors, (Gratton et al. 2018), we hypothesized that individual differences in functional connectivity among older adults would be related to the impact of sustained lifestyle factors.

Physical fitness as well as short-term exercise interventions have previously been linked to increased connectivity within brain networks among older participants without dementia, particularly the default-mode network (Voss et al. 2010; Boraxbekk et al. 2016; Voss et al. 2016; Chirles et al. 2017; McGregor et al. 2018). Additionally, one prior study reported that older individuals without dementia with a greater number of social contacts and more high-frequency social contacts had greater connectivity in several large-scale networks, including the frontoparietal, sensorimotor, visual, and insular networks (Pillemer et al. 2017). However, systematic investigations of the relationship between functional connectivity in large-scale brain networks and frequency of engagement in specific lifestyle activities are lacking. It is also not known whether different types of lifestyle activities are associated with functional connectivity in distinct network(s), and if their potential associations are independent of one another. Additionally, it remains unclear whether rsfMRI networks that are associated with measures of lifestyle activities are, in fact, associated with reduced cognitive decline, in the presence of AD pathology.

The overarching goal of the current study was 2-fold: 1) to test the hypothesis that greater engagement in cognitive, social, and physical activities (as measured via self-report) is associated with greater functional connectivity within selective large-scale brain networks and 2) to test whether higher connectivity levels within those networks are associated with reduced cognitive decline, independently of, or in interaction with, levels of brain amyloid (one of the primary proteins that accumulates in AD) and APOE-e4 genotype, the major genetic risk factor for late-onset AD (Farrer et al. 1997). These associations were tested in a cohort of 153 cognitively normal older participants who are part of the ongoing longitudinal BIOCARD study, including 126 with amyloid imaging.

An auxiliary goal was to determine whether lifestyle activity engagement was related to the level of connectivity between functional networks. Whereas connectivity within networks tends to decrease with increasing age, connectivity between large-scale networks tends to increase with aging (Betzel et al. 2014; Chan et al. 2014; Varangis et al. 2019; Chong, Ng, et al. 2019b), suggestive of a decrease in functional specialization with advancing age. To the extent that greater engagement in specific lifestyle activities has beneficial effects on brain connectivity, we hypothesized that it would also be associated with reduced connectivity between large-scale networks, as measured by the graph-theory-based measures of network "segregation" and "modularity" (Rubinov and Sporns 2010; Wig 2017). Furthermore, we hypothesized that greater network segregation and modularity would be associated with decreased cognitive decline.

Materials and Methods

Study Design and Participant Selection

The present study reports on data from the ongoing, longitudinal BIOCARD study, which was started in 1995 at the National Institute of Health (NIH) with the goal of identifying variables among cognitively normal individuals that could predict the subsequent development of symptoms of AD. Approximately 75% of the participants had a first degree relative with a history of dementia of the Alzheimer type, by design. The study was stopped in 2005 for administrative reasons and re-established at Johns Hopkins University (JHU) in 2009. At the NIH, study participants were administered an annual neuropsychological battery and MRI scans; cerebrospinal fluid (CSF) samples and blood specimens were collected every 2 years. Since the study has been at JHU, participants have received annual clinical and cognitive assessments and provided blood specimens. In 2015, the biannual collection of MRI and CSF biomarkers was reinitiated, and amyloid imaging was begun. Details regarding participant recruitment, clinical evaluation, and cognitive assessments have been published previously (Albert et al. 2014). The JHU Institutional Review Board approved this study and all participants provided written informed consent.

The present report examines data from 153 cognitively normal participants with rsfMRI, cognitive, and lifestyle activity data collected at the same study visit (i.e., within 2 days of one another). This visit is considered as the "baseline" visit for the purposes of this study. Among these, 126 participants also had a Positron Emission Tomography (PET) scan using Pittsburgh compound B (PiB) to image amyloid beta ($A\beta$) pathology (mean time

between MRI and PET scan acquisition = 3 days, SD = 48). For these 126 participants, up to 5 years of follow-up cognitive data is available (mean follow-up time = 3.3 years, SD = 1.2) and was used to examine the association between the rsfMRI measures, amyloid PET, and cognitive change. Data from an additional 8 participants were excluded due to excessive motion artifacts during the rsfMRI scan (see below for additional details). All data were collected between 2015 and February 2020.

Clinical and Cognitive Assessments

The annual visits at JHU include comprehensive neuropsychological testing and a clinical evaluation consisting of a physical and neurological examination, record of medication use, behavioral and mood assessments, family history of dementia, history of symptom onset, and a Clinical Dementia Rating (CDR) with the participant and a collateral source (Hughes et al. 1982; Morris 1993). Participants included in our analyses were judged to be cognitively normal, based on a consensus diagnostic review by the staff of the JHU BIOCARD Clinical Core, which includes neurologists, neuropsychologists, research nurses, and research assistants. The diagnostic criteria followed the recommendations incorporated in the National Institute on Aging and the Alzheimer's Association working group reports for the diagnosis of MCI (Albert et al. 2011) and dementia due to AD (McKhann et al. 2011). Briefly, this entails the establishment of a syndromic diagnosis (i.e., cognitively normal, MCI, impaired not MCI, or dementia) based on three types of information: 1) clinical data pertaining to the medical, neurological, and psychiatric status of the individual; 2) reports of changes in cognition by the individual and by collateral sources, based on the CDR interview; and 3) decline in cognitive performance, based on review of longitudinal testing from multiple domains (and comparison to published norms). The diagnosis of "Impaired not MCI" was typically given if there was contrasting information from the CDR interview and the cognitive test scores (i.e., the subject or collateral source reported concerns about cognitive changes in daily life, but the cognitive testing did not show changes, or vice versa). Because participants with a diagnosis of impaired not MCI ($N = 28$) do not meet criteria for MCI, they were included among the group of cognitively normal subjects, consistent with prior publications (see Albert et al. 2014 for additional details). Results were the same when these participants were excluded from analysis (data not shown). The diagnoses were made blinded to the MRI and PET biomarker measures.

The main cognitive outcome variable was a global cognitive composite score based on four measures previously identified as the best combination of cognitive predictors of the time to progress from normal cognition to clinical symptom onset of MCI in this cohort (Albert et al. 2014). These measures were 1) Logical Memory delayed recall (Story A) of the Wechsler Memory Scale–Revised (Wechsler 1987), 2) Paired Associates immediate recall of the Wechsler Memory Scale–Revised (Wechsler 1987), 3) Boston Naming (Kaplan et al. 1983), and 4) Digit-Symbol Substitution from the Wechsler Adult Intelligence Scale–Revised (Wechsler 1981). The global cognitive composite score was calculated by z-transforming the individual measures (based on means and SDs from all BIOCARD participants' first visit at JHU), and then summing the z-scores for each visit. If one or more scores were missing for a given visit, the cognitive composite score was coded as missing for that visit. All participants had global cognitive composite scores at the time of their rsfMRI and PET scans and only 21 scores (3.6%) were missing for subsequent visits.

Lifestyle Activities Assessment

Engagement in physical, cognitive, and social activities was assessed using the CHAMPS activity questionnaire (Stewart et al. 2001). The CHAMPS measures self-reported frequency and duration of engagement in 40 activities "during a typical week in the past month." It primarily assesses physical activities (28 items) but also includes some cognitive ($N = 6$) and social ($N = 6$) activity items. The designated physical activity items include both high-intensity (e.g., jog or run; aerobics; moderate or fast swimming) and low-intensity activities (e.g., play golf; do light gardening; walking leisurely for pleasure or exercise), as determined by the estimated energy expenditure. These were combined into a single physical activity measure to capture both exercise and low-intensity physical activities related to daily life. The remaining non-physical activities were categorized as either cognitive or social activities based on previous literature (Aartsen et al. 2002; Jopp and Hertzog 2010; Carlson et al. 2012; Parisi et al. 2015; Pettigrew et al. 2019); see Supplementary Materials for additional details). Physical, cognitive, and social activities were each quantified based on frequency of engagement (times/week), reflecting the sum of all relevant item frequencies within an activity category, to result in three continuous variables. Frequency rather than duration of activity engagement was used as the primary measure because prior work by our group found a relationship between the frequency measures and cognitive trajectories (Pettigrew et al. 2019). Additionally, the frequency of physical activity engagement was strongly correlated with the estimated weekly caloric expenditure from physical activities [$r(151) = 0.69$, $P < 0.0001$], calculated as the product of self-reported duration, intensity (using metabolic equivalent of task values adjusted for older adults), and participant body weight, as described in Stewart et al. (2001). This suggests that the frequency of physical activity engagement measure also encapsulates information about the intensity and duration of physical activities.

The CHAMPS has been given to participants in BIOCARD since 2015 (Pettigrew et al. 2019). A square-root transformation was applied to the three CHAMPS variables to correct for skewness.

Cognitive Reserve Composite Score

A cognitive reserve (CR) composite score was calculated to determine whether associations between specific lifestyle activities and functional brain connectivity are independent of lifelong intellectual attainment, measured by a composite proxy score. The CR composite score was calculated based on three measures collected at study entry (between 1995 and 2005): 1) scores from the National Adult Reading Test (Nelson 1982); 2) scores on the vocabulary subtest of the WAIS-R (Wechsler 1981); and 3) years of education. These measures were z-scored and then averaged. As previously reported, the individual measures were strongly correlated and loaded on a single factor in factor analysis (Soldan et al. 2013).

Vascular Risk Summary Score

A previously validated vascular risk score (Gottesman et al. 2017) was computed by summing five dichotomous vascular

risk factors (coded as 0 = absent or 1 = recent/remote) obtained during a medical history interview conducted at the same visit as the MRI scan: hypertension, hypercholesterolemia, diabetes, current smoking (i.e., within the last 30 days), and obesity (i.e., measured body mass index ≥ 30 kg/m^2).

Physical Function Summary Score

Three objective measures of physical function were collected at the same visit as the MRI scan: 1) time (in s) to complete a 5-m walk (average of two trials); 2) time (in s) to complete five repeated chair stands; and 3) grip strength (in kg, average of left and right hands), measured using a standard hydraulic hand dynamometer (Baseline® 12-0240). These three measures were each converted to z-scores and then averaged to generate a physical function summary score. Two participants used a walking aid to complete the gait speed test, while all others walked unassisted.

APOE Genetic Analysis

APOE alleles were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). APOE $\varepsilon 4$ carrier status was dichotomized (1 if an individual had at least one $\varepsilon 4$ allele; 0 otherwise).

Magnetic Resonance Imaging Acquisition and Preprocessing

MRI scans were obtained on a 3 T Phillips Achieva system. Resting state BOLD data were collected using an echo-planar imaging sequence with the following parameters: number of slices = 48; field of view (FOV) = 212×212 mm^2; voxel size = $3.3 \times 3.3 \times 3.3$ mm^3; time repetition (TR)/time echo (TE) = 3000/30 ms; flip angle = 75. The duration of each scan session was 420 s and comprised of 140 functional volumes. Participants were instructed not to move, to close their eyes, and to relax while in the scanner.

The BOLD data underwent standard preprocessing steps (using SPM and in-house MATLAB scripts), including slice timing correction, realignment, normalization to Montreal Neurologic Institute (MNI) 152 volumetric space via magnetization-prepared rapid gradient echo (MPRAGE) image, spatial smoothing using a Gaussian filter with a full-width half-maximum of 4 mm (Hou et al. 2019). The BOLD image series were detrended and bandpass-filtered to 0.01–0.1 Hz to retain the low-frequency fluctuation components.

To reduce the motion effect on functional connectivity, the filtered BOLD data underwent a modified form of the motion scrubbing procedure proposed by Power and colleagues (Power et al. 2012; Power et al. 2014). Motion scrubbing was performed after temporal filtering (Chan et al. 2014; Yeo et al. 2015; Hou et al. 2019). Specifically, temporal masks were created to flag motion-contaminated frames so that they could be ignored during subsequent correlation matrix calculations. Motion-contamination volumes were identified by frame-by-frame displacement (FD, calculated as the sum of absolute values of the differentials of the 6 rigid-body head motion parameters). Volumes with FD ≥ 0.5 mm were flagged (Power et al. 2012; Power et al. 2014). In addition, the frames acquired immediately prior and immediately after flagged frames were discarded to account for temporal spread of artifactual signal resulting from the temporal filtering during preprocessing (Chan et al. 2014). After motion scrubbing, there were 8 participants with <70 frames of remaining data, who were excluded from analysis. The mean number of volumes per subject after motion scrubbing was 126.4 (SD = 15.0). The mean FD per subject was 0.18 mm (SD = 0.07). To further ensure that motion during scanning did not influence the results, we ran sensitivity analyses including mean FD values (i.e., subject-level motion) as covariates in primary analyses.

MPRAGE scans were also obtained and used for anatomical reference, image registration, and brain volume quantification (TR = 6.8 ms, TE = 3.1 ms, shot interval 3000 ms, flip angle = 8, FOV = 240×256 mm^2, 170 slices with $1 \times 1 \times 1.2$ mm^3 voxels, and scan duration = 5 min 59 s). Brain volumes were computed using MRICloud, an automatic processing tool (Mori et al. 2016; www.MRICloud.org). Total cerebral cortex volume, corrected for total intracranial volume (using the ratio method), was used as a covariate, as described below, to account for potential atrophy.

Construction of Functional Connectivity Networks

The motion scrubbed preprocessed BOLD data were further processed to regress out nuisance signals, including global, white matter, and CSF signals, as well as 6 rigid-body head motion parameters (which were not temporally filtered (Filippi et al. 2017; Chong, Ng, et al. 2019b; Millar et al. 2020). T_1-weighted MPRAGE images were segmented using SPM, yielding white matter and CSF masks. The white matter signal and CSF signal were averaged over the masks. Following nuisance regression, the BOLD data were parcellated into 114 region-of-interests (ROIs) estimated in MNI 152 volumetric space, based on the parcellation by Yeo et al. (2011), which was derived by clustering regions with similar connectivity profiles using data from 1000 subjects (Yeo et al. 2011). Cross-correlation coefficients were calculated between each pair of ROIs and converted to z-scores using a Fisher-z transform, yielding a 114×114 matrix of z-transformed values. To quantify network-wise functional connectivity, the connectivity matrix was reduced from 114×114 to 7×7 by averaging the z-transformed values belonging to the same network, as described by Yeo et al. (2011), which resulted in the following seven networks: frontoparietal control, default mode, dorsal attention, salience/ventral attention, limbic, visual, and somatomotor. Additionally, global connectivity within networks was calculated as mean connectivity across all seven networks.

Graph-Theory Measures of Functional Connectivity: Modularity and Segregation

Using graph theory implemented in the Brain Connectivity Toolbox (Rubinov and Sporns 2010) and in-house MATLAB scripts, two measures were computed reflective of the degree of network distinctiveness (or network separation) for each subject: "modularity" and "segregation." Both measures were computed based on the predefined subnetworks from the Yeo parcellation (e.g., Betzel et al. 2014).

"Modularity" quantifies the degree to which a network can be decomposed into mutually separate subnetworks (or modules) that are internally integrated, yet segregated from one another (Newman 2006; Betzel et al. 2014). Modularity was computed using the algorithm by Rubinov and Sporns (2011), which is based on both positively and negatively weighted connections

of the unthresholded correlation matrix. In this algorithm, positively weighted connections represent similar activation patterns between pairs of nodes in the same module, while negatively weighted connections represent activation patterns of nodes in distinct modules, or antiphase coupling. It has been argued that one advantage of this algorithm over others that are based on thresholded connection weights is that it is not associated with loss of information that accompanies thresholding or binarization of correlation matrices, which is often done arbitrarily and may require the examination of different thresholds. This algorithm takes into account the fact that negative correlations have a different role in network organziation than positive correlations and incorporates neurophysiological anticorrelations (Chang and Glover 2009; Betzel et al. 2014), although the interpretation of negative correlations remains controversial (Murphy et al. 2009; Chai et al. 2012). Of note, the modularity index primarily depends on the relative difference between weight magnitudes and secondarily on the sign of the weights (Rubinov and Sporns 2011).

"Segregation" was computed as the difference between within-network connections and between-network connections, relative to the within-network connections (Wig 2017). Higher modularity and segregation values indicate greater network separation. Preliminary analyses indicated that network modularity and segregation were highly correlated in this sample ($r(151) = 0.98$, $P < 0.0001$); therefore, results below are only reported for modularity but were highly similar for segregation.

PiB PET Image Acquisition and Processing

A subset of 126 participants underwent dynamic PET imaging using the ^{11}C-labeled Pittsburgh compound B (PiB) tracer on an Advance PET scanner (GE Healthcare) to assess cortical amyloid burden. Data were acquired immediately following the IV bolus injection. Distribution volume ratio images were calculated in the native space of each PET image using a simplified reference tissue model with cerebellar gray matter as the reference region (Zhou et al. 2003). Anatomical regions were defined on the structural MRI of each participant using MRICloud and mapped to the native space of each PET image. Mean cortical DVR (cDVR) was calculated by averaging cDVR values across cortical regions, as described previously (Bilgel et al. 2018; Walker et al. 2020). Participants with a mean cDVR value of >1.06 were considered as PiB positive. This threshold was derived in a previous study using a 2-class Gaussian mixture model fitted to cDVR data (Bilgel et al. 2016).

Statistical Analysis

Group differences in demographic variables at the time of the MRI scan were assessed by t-test or Wilcoxon rank sum test for continuous variables, as appropriate, or chi-square tests for dichotomous variables.

Cross-Sectional Analyses of Baseline Lifestyle Activity Engagement and Resting-State Functional Connectivity

Linear regressions were performed to test if frequency of engagement in lifestyle activities was associated with 1) functional connectivity within five of the networks most relevant to cognitive function: default-mode, control, dorsal attention, salience, and limbic networks, 2) global connectivity within networks, and 3) the graph theory measure of modularity. Separate models were run for each of the seven rsfMRI measures, which served as the outcome variables. The three activity variables were simultaneously entered in each model to assess their independent associations with the rsfMRI measures. The *P*-values for the activity measures were corrected for multiple comparisons using the false discovery rate (FDR, seven tests, using a threshold of $P = 0.05$) (Benjamini and Hochberg 1995), and adjusted *P*-values are shown, unless otherwise indicated. All models covaried baseline age, sex, and years of education.

A series of sensitivity analyses were also run. First, to account for the potentially confounding effect of brain atrophy on functional connectivity, total cerebral cortex volume was included as an additional covariate in each model. Second, to determine if associations between the lifestyle activity variables and rsfMRI measures were independent of level of CR, models were rerun with the CR-composite score as a predictor instead of years of education (which is part of the CR-composite score). Third, given that functional connectivity has also been associated with vascular risk factors (Spielberg et al. 2017; Rashid et al. 2019; Carnevale et al. 2020; Donofry et al. 2020) and physical fitness (Voss et al. 2016; Talukdar et al. 2018), we examined whether associations between functional connectivity and frequency of engagement in lifestyle activities are independent of vascular risk factors and of physical function.

Functional Connectivity and Longitudinal Change in Cognition: Relationship to APOE4 Genetic Status and PET Amyloid

For those rsMRI measures that showed statistically significant associations with one or more lifestyle activity measures, we tested if the rsfMRI measures were also associated with the prospective rate of change in cognitive performance over time and whether this association was independent of APOE4 genotype and level of brain amyloid (measured by PET). To do so, we used general mixed regression models with linear effect of time and a random intercept for each participant. For these models, all continuous variables, except for time, were standardized to have a mean = 0 and SD = 1; binary variables were not transformed. The longitudinal global cognitive composite score was the outcome variable, using scores obtained at the baseline MRI scan and all subsequent scores. In Longitudinal Model 1, the predictors were age at baseline MRI, sex, years of education, the rsfMRI measure, the APOE4 genotype indicator, the rsfMRI × APOE4 interaction, time, and all interactions (i.e., elementwise products) of each predictor with time. In these models, the rsfMRI × time interaction tests whether the rsfMRI variable modifies the rate of change in the cognitive composite score over time. Additionally, the three-way interaction between the rsfMRI measure, APOE4 genotype, and time was included to examine if the association between functional connectivity and cognitive trajectories differs for APOE4 carriers and noncarriers. If the three-way interaction was not significant, models were rerun excluding this term, as well as the rsfMRI × APOE4 interaction term. Longitudinal Model 2 was identical to Model 1, except that the PiB-positive indicator was included instead of the APOE4 indicator.

Results

Table 1 shows participants' characteristics at baseline rsfMRI scan, separately for all participants in the analysis and for the subgroup with PiB PET scans. The functional connectivity

Table 1 Participant characteristics at baseline MRI scan

Variable	Participants in analysis ($N = 153$)	Participants in analysis with PiB PET scan ($N = 126$)
Age in years, mean (SD)	69.3 (8.2)	68.5 (8.5)
Sex, females (%)	63.4%	63.5%
Race, White (%)	98.4%	97.6%
APOE $\varepsilon 4$ carriers (%)	32.0%	32.5%
Education, mean years (SD)	17.3 (2.2)	17.4 (2.3)
MMSE, mean (SD)	29.3 (0.9)	29.2 (1.0)
Cognitive Composite, mean (SD)	2.0 (2.1)	2.1 (2.4)
Paired Associates Immediate, mean (SD)	20.8 (2.4)	20.8 (2.8)
Logical Memory Delayed, mean (SD)	16.8 (3.4)	17.3 (3.5)
Boston Naming, mean (SD)	29.1 (1.2)	29.1 (1.3)
Digit Symbol Substitution, mean (SD)	57.2 (11.8)	56.8 (13.4)
CR Composite, mean (SD)	0.2 (0.7)	0.2 (0.7)
Vascular Risk Summary Score, mean (SD)	1.3 (1.1)	1.2 (1.0)
Vascular Risk Summary Score ≥ 1 (%)	72.8%	72.1%
Vascular Risk Summary Score ≥ 2 (%)	39.1%	35.2%
Physical Function Composite, mean (SD)	0.1 (0.7)	0.1 (0.7)

measures did not differ by APOE4 genetic status (all $P > 0.09$, unadjusted, covarying age, sex, and education).

Cross-Sectional Results: Lifestyle Activity Engagement and Functional Connectivity

Results from the linear regression analyses demonstrated that the frequency of engagement in cognitive activities was associated with greater connectivity in the dorsal attention network (estimate = 0.017, $SE = 0.005$, $P = 0.006$) and greater modularity (estimate = 0.007, $SE = 0.003$, $P = 0.038$). Additionally, higher frequency of engagement in physical activities was associated with greater connectivity within the default mode (estimate = 0.013, $SE = 0.005$, $P = 0.013$), limbic (estimate = 0.038, $SE = 0.014$, $P = 0.015$), and control networks (estimate = 0.010, $SE = 0.004$, $P = 0.020$), as well as with greater global within-network connectivity (estimate = 0.018, SE = 0.004, $P < 0.0005$), and greater modularity (estimate = 0.007, $SE = 0.003$, $P = 0.043$). There were no significant associations between social activity engagement for any of the functional connectivity measures (all $P > 0.18$ unadjusted). In these models, older participants had lower connectivity and modularity (all $P < 0.05$ unadjusted), except for the limbic network, which showed no age-associations ($P = 0.9$, data not shown). Years of education were not associated with any connectivity measure. The pattern of results was the same when only one lifestyle activity variable was entered in each model (data not shown).

Sensitivity analyses showed that the results were also the same when total cerebral cortex volume, the CR composite score, or APOE4 genetic status were included as additional covariates in separate models. There were no interactions between any of the activity variables and APOE4 genotype or the PiB-positive indicator (all $P > 0.1$), suggesting that associations between activity variables and the rsfMRI measures were not modulated by APOE4 genetic status or amyloid positivity. The results from fully adjusted models (i.e., simultaneously including age, sex, the CR composite score, APOE4-status, and total cerebral cortex volume) are shown in Table 2 and Figure 1 and were also the same. The CR composite score was not associated with connectivity in any network (all $P > 0.2$). Results were the same in the subsample with PiB PET imaging (see Supplementary Table 1). Overall, the amount of variance in the rsfMRI measures explained by the individual lifestyle variables ranged from 4% to 12%, after accounting for covariates.

With the addition of the physical function and vascular risk summary scores to the fully adjusted models (see Table 2), associations continued to be significant between most of the activity variables and the connectivity measures. The association between cognitive activity engagement and connectivity in the dorsal attention network remained significant, as did the relationships between physical activity engagement and connectivity in the default-mode, limbic, control networks, and global connectivity and modularity (all $P < 0.05$); however, the association between cognitive activity and modularity was attenuated ($P = 0.08$ unadjusted). To further explore the potential impact of physical function and vascular risk on the rsfMRI measures, the fully adjusted models were rerun, including only the significant lifestyle activity variables. Higher vascular risk scores were associated with lower connectivity in the default-mode network and lower modularity (both $P < 0.05$ unadjusted) and higher connectivity in the limbic network ($P = 0.015$ unadjusted), while greater physical function scores were associated with greater global within-network connectivity and greater modularity (P's < 0.05 unadjusted), see Supplementary Table 2 for full model results. The pattern of results remained the same when subject-level motion (mean FD values) was included as an additional covariate (data not shown).

Longitudinal Results: Functional Connectivity, APOE4 Genetic Status, Amyloid Positivity, and Cognitive Change

The results from Longitudinal Models 1 and 2 are shown in Table 3. The main effect of time was not significant in any model (all $P > 0.2$), suggesting that, on average, cognitive trajectories were flat for the group as a whole, over the follow-up period of ~3 years. However, significant rsfMRI × time interactions indicated that cognitive trajectories exhibited increases over this time period for individuals with high global connectivity and modularity, and high connectivity in the default-mode, dorsal attention, and limbic networks ($P \leq 0.05$ for all rsfMRI × time

Table 2 Linear regression results for associations between lifestyle activity variables and functional connectivity measures in the full sample ($N = 153$)

Functional connectivity variable	Cognitive Activities Estimate (SE)	Social Activities Estimate (SE)	Physical Activities Estimate (SE)
Default-Mode	0.010 (0.006)	0.002 (0.007)	**0.016 (0.006)**$*$
Limbic	0.000 (0.017)	−0.006 (0.018)	**0.034 (0.017)**$*$
Dorsal Attention	**0.021 (0.007)**$**$	0.006 (0.007)	0.006 (0.007)
Salience	0.003 (0.006)	−0.004 (0.006)	0.003 (0.006)
Control	0.004 (0.005)	0.012 (0.005)	**0.011 (0.005)**$*$
Global Connectivity	0.003 (0.005)	0.004 (0.005)	**0.019 (0.004)**$***$
Modularity	**0.010 (0.004)**$*$	0.002 (0.005)	**0.008 (0.003)** $^{\#}$

Note: Cognitive, social, and physical activity variables were simultaneously entered in each model, which was also adjusted for age, sex, CR-composite score, total cerebral cortex volume, and APOE4 genotype. FDR-corrected P-values (7 tests) are reported as follows: $^{\#}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$.

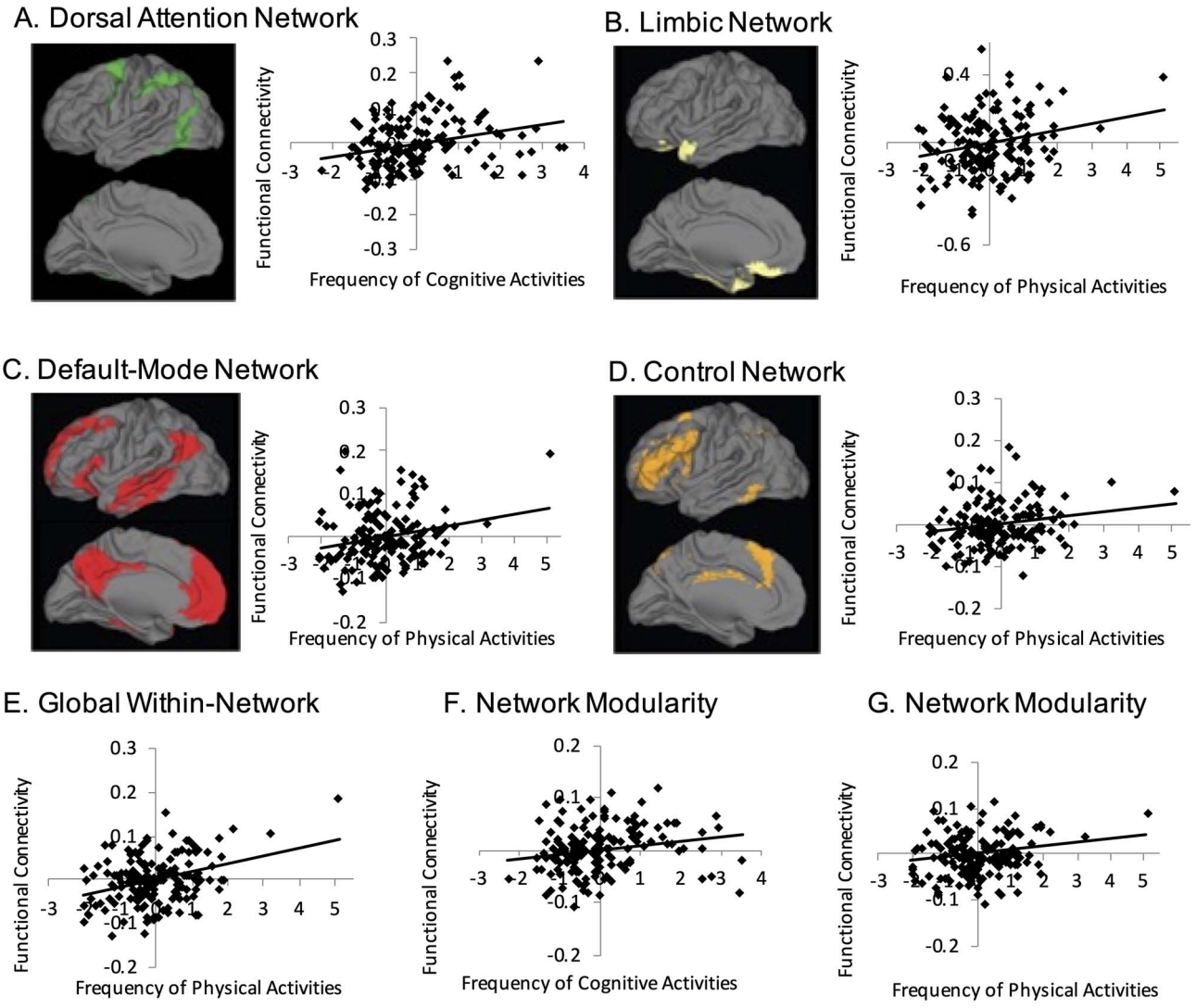

Figure 1. Brain regions within the dorsal attention network (*A*), limbic network (*B*), default-mode network (*C*), and frontoparietal control network (*D*) are shown in the left panel. The right panel shows scatterplots of the partial correlation between residual functional connectivity within each network (*y*-axis) and frequency of engagement in cognitive (*A*) or physical (*B*, *C*, and *D*) activities (*x*-axis). A scatterplot of the partial correlation between residual global connectivity within networks and frequency of engagement in physical activities is shown in (*E*). Also shown are scatterplots of the partial correlation between network modularity and frequency of engagement in cognitive (*F*) and physical activities (*G*). All scatterplots are adjusted for age, sex, CR-composite score, APOE-e4 genetic status, and total cerebral cortex volume.

Table 3 Results from linear mixed regression models assessing rsfMRI connectivity metrics in relationship to longitudinal cognitive change

	Longitudinal Model 1: rsfMRI connectivity and APOE4 status				Longitudinal Model 2: rsfMRI connectivity and PiB positive status		
	Estimate	SE	P-value		Estimate	SE	P-value
Default-mode network							
time	0.006	0.029	0.847	time	−0.005	0.029	0.876
rsfMRI	−0.043	0.061	0.477	rsfMRI	−0.037	0.060	0.535
rsfMRI × time	0.057	0.019	0.003	rsfMRI × time	0.058	0.019	0.003
APOE4	0.121	0.168	0.475	Amyloid	0.012	0.176	0.945
APOE4 × time	−0.094	0.033	0.006	Amyloid × time	−0.053	0.036	0.147
Limbic network							
time	0.005	0.030	0.861	time	0.002	0.030	0.957
rsfMRI	−0.015	0.071	0.833	rsfMRI	−0.025	0.070	0.724
rsfMRI × time	0.039	0.018	0.031	rsfMRI × time	0.042	0.018	0.019
APOE4	0.109	0.171	0.525	Amyloid	0.019	0.178	0.913
APOE4 × time	−0.071	0.035	0.044	Amyloid × time	−0.062	0.037	0.102
Dorsal Attention Network							
time	−0.002	0.030	0.949	time	−0.010	0.030	0.731
rsfMRI	0.084	0.061	0.167	rsfMRI	0.098	0.060	0.103
rsfMRI × time	0.042	0.019	0.032	rsfMRI × time	0.038	0.020	0.054
APOE4	0.105	0.168	0.532	Amyloid	−0.012	0.175	0.946
APOE4 × time	−0.091	0.034	0.01	Amyloid × time	−0.065	0.038	0.09
Control Network							
time	0.002	0.030	0.952	time	−0.006	0.030	0.837
rsfMRI	0.039	0.073	0.594	rsfMRI	−0.006	0.066	0.930
rsfMRI × time	0.017	0.018	0.337	rsfMRI × time	0.022	0.019	0.237
APOE4	0.126	0.167	0.453	Amyloid	0.015	0.177	0.932
APOE4 × time	−0.085	0.035	0.016	Amyloid × time	−0.053	0.038	0.164
Network Modularity							
time	0.010	0.029	0.736	time	0.003	0.029	0.910
rsfMRI	0.084	0.083	0.315	rsfMRI	0.124	0.083	0.137
rsfMRI × time	0.054	0.017	0.002	rsfMRI × time	0.056	0.017	0.002
APOE4	0.090	0.170	0.599	Amyloid	−0.033	0.178	0.855
APOE4 × time	−0.098	0.033	0.004	Amyloid × time	−0.071	0.037	0.054
Global Network Connectivity							
time	−0.004	0.027	0.897	time	−0.002	0.028	0.944
rsfMRI × APOE × time	0.095	0.038	0.014	—	—	—	—
rsfMRI × APOE	−0.148	0.175	0.397	rsfMRI	0.013	0.060	0.830
rsfMRI	0.015	0.064	0.819	rsfMRI	0.013	0.060	0.830
rsfMRI × time	0.041	0.023	0.075	rsfMRI × time	0.075	0.020	<0.0001
APOE4	0.115	0.169	0.499	Amyloid	0.010	0.176	0.954
APOE4 × time	−0.075	0.032	0.020	Amyloid × time	−0.074	0.036	0.043

Note. All models are adjusted for age, sex, education, and their interactions with time. All continuous variables, except time, are standardized with mean = 0, SD = 1.

interactions) and decreases among those with low connectivity values. Connectivity metrics were not related to baseline level of performance. There was no association between connectivity in the control network and level or change in cognitive performance.

Additionally, Longitudinal Model 1 showed that there was a greater decline in the cognitive composite score over time among APOE4 carriers compared with noncarriers ($P < 0.05$ for all APOE4 × time interactions). APOE4 was not associated with baseline level of cognitive performance (all $P > 0.4$). With the exception of global connectivity, the three-way interactions between the rsfMRI measures, APOE4 genotype, and time were not significant (all $P > 0.11$), suggesting that APOE4 genotype and the rsfMRI measures were independently associated with change in the cognitive composite score. These results are illustrated in Figure 2 (for global connectivity and modularity) and Supplementary Figure 1 (for the individual networks). For the global connectivity measure, the three-way interaction was significant (estimate = 0.01, $SE = 0.04$, $P = 0.014$), suggesting that the negative association between APOE4 genotype and cognitive change was attenuated among individuals with greater global connectivity (see Fig. 2).

In Longitudinal Model 2, there were no significant three-way interactions between any rsfMRI measure, PiB-positivity, and time (all $P > 0.1$), suggesting that the rsfMRI measures are associated with cognitive change independent of amyloid burden. PiB-positive status tended to be associated with greater declines in cognitive trajectories (see Fig. 2, though the PiB × time interaction did not reach significance in all models, see Table 3). Results were similar when continuous cDVR values were used instead of the dichotomous PiB-positive indicator (data not shown).

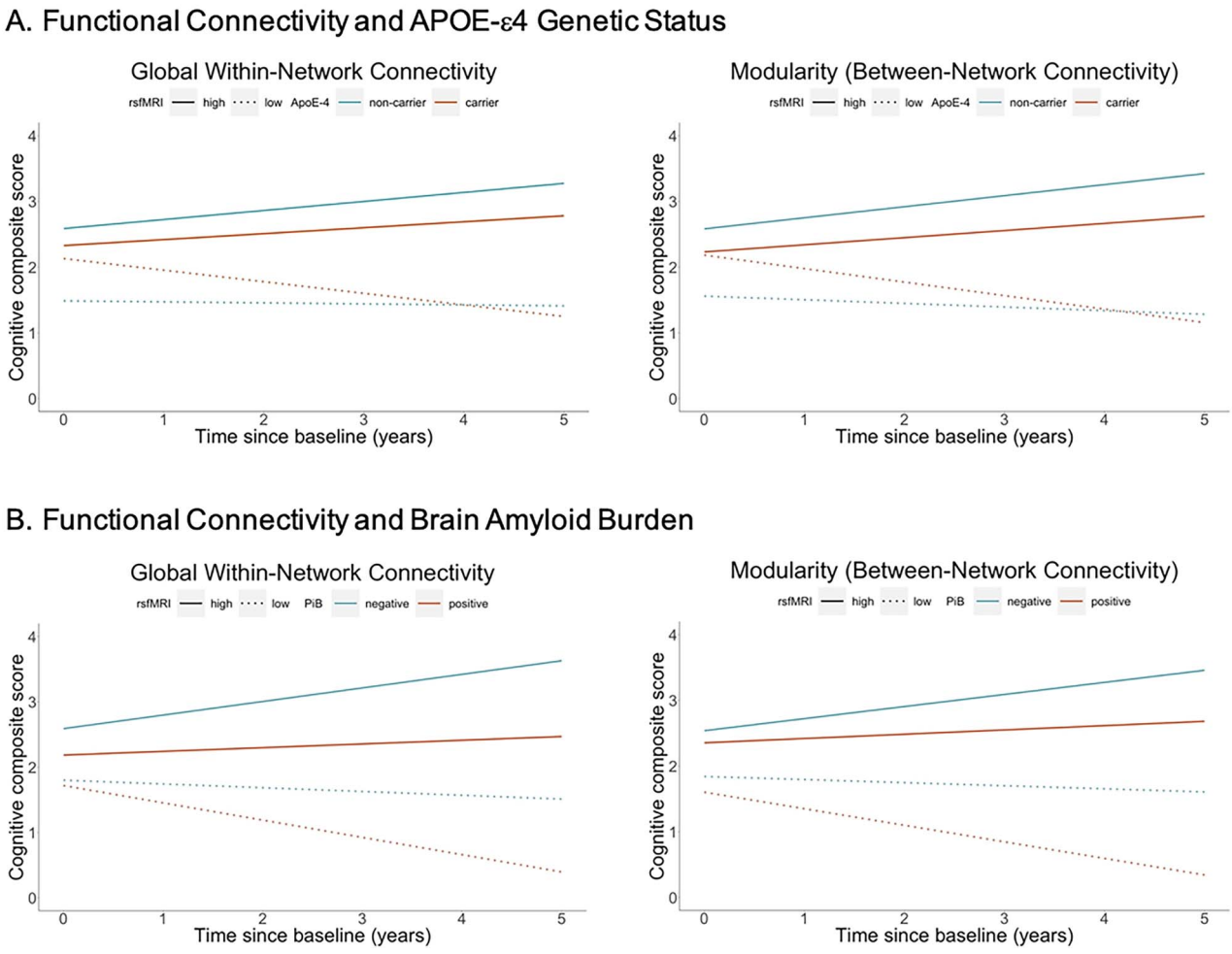

Figure 2. Shown are estimates from linear mixed-effects models predicting longitudinal cognitive composite scores over time among individuals classified into four groups, based on their rsfMRI connectivity at baseline and APOE-e4 genetic status (*A*) or PiB-positive status (*B*). The estimates are adjusted for baseline age, sex, education, and their interactions with time. Individuals with high rsfMRI values (i.e., above the median, solid lines) showed practice effects over time, on average, while individuals with low rsfMRI values (i.e., below the median, dotted lines) showed a decline in cognitive composite scores, on average. APOE-e4 carriers and PiB-positive individuals (red lines) tended trajectories with steeper declines than APOE-e4 non-carriers and PiB-negative individuals (blue lines), respectively. See Table 3 for results.

Discussion

The current study provides the first comprehensive examination of lifestyle activity engagement and rsfMRI connectivity. There are several notable findings. First, we found that greater self-reported engagement in cognitive and physical activities was associated with greater functional connectivity in distinct large-scale brain networks. Specifically, cognitive activities were related to the dorsal attention network, and physical activities were related to the default-mode, limbic, and frontoparietal control networks, as well as to greater global within-network connectivity. Additionally, both greater cognitive and physical activity engagement were independently associated with greater network modularity. These associations were independent of APOE4 genotype and amyloid burden, and were largely independent of global brain atrophy, vascular risk, physical function, and level of CR. Second, higher connectivity in the dorsal attention, default-mode, and limbic networks, as well as greater global within-network connectivity and network modularity were associated with reduced cognitive decline, independent of APOE4 genotype and brain amyloid load.

Taken together with prior evidence that older individuals have reduced connectivity within networks and a decrease in network modularity, these findings suggest that greater frequency of engagement in cognitively and physically stimulating activities may counteract the negative impact of age on functional connectivity within and between large-scale brain networks. Furthermore, the beneficial effects of cognitive and physical activity levels on brain function and cognitive performance appeared to be largely independent of amyloid pathology and the main genetic risk factor for late onset AD. Though future studies are needed to confirm that greater engagement in cognitive or physical activities are indeed associated with smaller longitudinal declines in within-network connectivity and network modularity, these findings support the view that changes in functional brain connectivity may be one mechanism by which lifestyle activity engagement influences cognitive impairment and decline. Studies using mediation modeling will be critical for evaluating this hypothesis, as well as potential mechanisms that link lifestyle activities to functional connectivity and cognitive change.

The view that lifestyle variables may exert their protective effects on cognitive decline by influencing functional connectivity is consistent with prior cross-sectional studies that have linked proxy measures of CR (including years of education, occupational attainment, and verbal intelligence) to measures of rsfMRI connectivity among older adults. For example, among individuals with and without dementia, more years of education have been associated with greater functional connectivity in frontoparietal control regions (Perry et al. 2017; Serra et al. 2017; Franzmeier, Caballero, et al. 2017a; Franzmeier,Duering, et al. 2017b; Neitzel et al. 2019), as well as in regions that are part of the default-mode network (Bozzali et al. 2015; Perry et al. 2017), dorsal attention and somatomotor networks (Perry et al. 2017), and limbic regions (Arenaza-Urquijo et al. 2013). However, the specific regions or networks involved have varied across studies, likely reflecting differences in the regions examined across studies, variability in analytic approaches and network parcellation, and differences in levels of neuropathology or neurodegeneration among study participants. Additionally, the diagnostic status of participants (e.g., cognitively normal vs. MCI vs. dementia) may influence the results, as suggested by some studies (Bozzali et al. 2015; Serra et al. 2017). To our knowledge, there are no longitudinal studies that have examined whether those rsfMRI variables linked to measures of CR are also associated with cognitive decline or risk of clinical progression.

There are several potential mechanisms by which physical and cognitive activity engagement may influence functional connectivity. For example, studies in both animals and humans have shown that voluntary exercise enhances neurotrophic factors that decline with age and are important for synaptic plasticity, synaptogenesis, neurogenesis, and angiogenesis, including brain-derived neurotrophic factor (BDNF), insulin-derived growth factor-1 (IGF-1), and vascular endothelial growth factor (for a review, see Voss, Vivar, et al. 2013b). A few studies have suggested links between these growth factors and measures of functional connectivity (Voss, Erickson, et al. 2013a; Mueller et al. 2016; Woelfer et al. 2020). Thus, physical activity may attenuate age-related declines in neurotrophic factors, which may strengthen synaptic connections within existing networks and protect against disconnection and dedifferentiation. Additionally, physical activities may strengthen processes related to neurovascular coupling that influence the BOLD response (Liu 2013), such as cerebral blood flow and cerebrovascular reactivity (Gauthier et al. 2015; Kleinloog et al. 2019; Zlatar et al. 2019; Kaufman et al. 2021).

Frequent engagement in cognitive activities may strengthen connectivity within functional brain networks by increasing synchronization of brain regions that are frequently co-engaged during cognitive task performance via improved long-term synapse potentiation and synaptic plasticity. In support of this possibility and consistent with our results, a recent systematic review concluded that cognitive training among older adults consistently increases functional connectivity within brain networks and appears to increase segregation between networks (van Balkom et al. 2020). Additionally, results from small-scale cognitive training studies suggest that cognitive activity may enhance cerebral blood flow (Chapman et al. 2016) and increase levels of BDNF (Pressler et al. 2015; Rahe et al. 2015; Ledreux et al. 2019), similarly to what has been observed for physical activities.

Interestingly, the current study did not find any relationships between years of education or the CR composite score with functional connectivity, as has been reported in a number of earlier studies. This finding may be related to the fact that many prior studies focused on connectivity between specific regions (e.g., Arenaza-Urquijo et al. 2013; Bozzali et al. 2015; Franzmeier,Caballero, et al. 2017a; Franzmeier,Duering, et al. 2017b; Neitzel et al. 2019) rather than examining large-scale brain networks, as was done in this study. It is also possible that associations with CR are more evident among participants with cognitive impairment, as many prior studies included participants with MCI, along with cognitively normal participants, or did not specifically screen for MCI at study entry (e.g., Bozzali et al. 2015; Marques et al. 2016; Perry et al. 2017; Serra et al. 2017; Franzmeier, Caballero, et al. 2017a; Franzmeier,Duering, et al. 2017b; Weiler et al. 2018; Lee et al. 2019; Neitzel et al. 2019). Notably, in this study, the associations between lifestyle activities and rsfMRI connectivity were independent of the CR composite score, suggesting that variables reflective of intellectual achievement and engagement in lifestyle activities may have independent, and possibly additive, effects on functional connectivity.

We did not find any associations between the frequency of engagement in social activities and measures of functional brain network connectivity. Research on this topic is very sparse, though one prior report suggested that a higher quality and quantity of social networks (measured by number of social contacts) was related to greater functional connectivity in left frontoparietal and other regions (Pillemer et al. 2017). Given that the assessment of social activity engagement in the present study was relatively limited, it is possible that findings would differ when using more comprehensive assessments of social activities.

It is noteworthy, as illustrated in Figure 2, that among individuals with high within-network connectivity values and high network modularity (i.e., above the median, as indicated by the solid lines), cognitive performance tended to improve over time, potentially reflecting practice effects that are commonly observed with repeated cognitive assessments. By comparison, among participants with low connectivity values (i.e., dotted lines), cognitive performance tended to decline. This suggests that these types of connectivity measures may be useful in identifying cognitively normal older individuals at risk of cognitive decline, particularly if used in combination with measures of amyloid or AD genetic risk.

Our results are consistent with, and expand on, the limited number of prior studies that have examined the relationship between rsfMRI connectivity and longitudinal clinical and cognitive outcomes. For example, Buckley et al. (2017) reported that older individuals with normal cognition and higher functional connectivity in the default-mode, salience, and control networks at baseline demonstrated reduced decline of the preclinical Alzheimer cognitive composite score (Buckley et al. 2017). Similarly, higher baseline connectivity within the default-mode network has been associated with reduced risk of progression to MCI, independent of PET amyloid levels (Rabin et al. 2020). Furthermore, a study with longitudinal rsfMRI demonstrated that participants who progressed to MCI had a greater decrease in global within-network connectivity compared with individuals who remained cognitively normal over time (Wisch et al. 2020). The specific networks or network properties associated with cognitive trajectories may be dependent on the cognitive domains assessed. For example, exploratory analyses of the present data using domain-specific cognitive composite scores suggested that episodic memory performance is more strongly

linked to the default-mode and limbic networks, whereas executive functions were related to the salience/ventral attention network (see Supplementary Materials). These results are consistent with a longitudinal study specifically linking change in connectivity within the default-mode network to episodic memory change, but not executive function change (Staffaroni et al. 2018).

To our knowledge, the association between whole-brain network modularity or segregation and longitudinal changes in cognitive performance has not been evaluated previously. However, a recent study reported that a greater decrease in segregation of the frontoparietal control network was weakly associated with a greater decrease in processing speed among older adults without dementia over the course of 4 years (Malagurski et al. 2020). Additionally, cross-sectional studies have provided evidence that higher network segregation and modularity (i.e., high connectivity within networks and low connectivity between networks) are associated with better cognitive performance. For example, studies among older adults without dementia reported associations between higher network segregation and better episodic memory performance (Chan et al. 2014; Varangis et al. 2019). Similarly, studies across the spectrum of AD found that higher modularity was related to lower AD symptom severity, as measured by the CDR scale (Brier et al. 2014) and to higher global cognitive scores in the presence of amyloid and tau pathology (Ewers et al. 2021). More broadly, results using neural network modeling suggest that across the adult age span, greater brain modularity is associated with better cognitive performance across a variety of tasks because a more modular network structure facilitates processing within local, specialized networks that are integrated by so-called "connector hubs," that is, brain regions that connect specialized networks to one another (Bertolero et al. 2018). Additional longitudinal biomarker studies are needed to more clearly delineate how functional connectivity both within and between networks changes in relationship to AD biomarkers and how these connectivity changes relate to cognitive performance.

An interesting secondary finding in the current study is the association between higher vascular risk summary scores and lower connectivity in the default-mode network, lower network modularity, and higher connectivity in the limbic network (Supplementary Table 2). Consistent with the present results, decreases in default-mode network connectivity have previously been reported among individuals with higher vascular risk burden, including total cholesterol, diastolic blood pressure, Type 2 diabetes, and obesity (Musen et al. 2012; Macpherson et al. 2017; Syan et al. 2019; Ding et al. 2020; Kobe et al. 2021), and decreased network modularity has been linked to obesity (Chao et al. 2018). Other studies among middle-aged and older participants without dementia have found both positive and negative associations between vascular risk factors and functional connectivity in different brain regions (Li et al. 2015; Chao et al. 2018; Rashid et al. 2019; Zonneveld et al. 2019; Carnevale et al. 2020; Ding et al. 2020). The relationship between vascular risk factors and functional connectivity can likely be attributed to the fact that the BOLD signal reflects the hemodynamic response to neural activity (Bright et al. 2020) and is dependent on vascular (e.g., blood flow, blood volume, cerebrovascular reactivity) and metabolic processes (e.g., cerebral oxygen consumption) that are altered among individuals with a greater burden of vascular risk (e.g., Dai et al. 2008; Hajjar et al. 2010; King et al. 2018; Chau et al. 2020; Clark et al. 2020; Jiang et al. 2020; Kepes et al. 2021). However, it remains unclear whether specific vascular risk factors are preferentially associated with specific networks or network parameters and how these associations change with age or in the presence of AD pathology (Chong, Jang, et al. 2019a).

The current findings should be considered within the context of several limitations. First, study participants were highly educated, primarily White, and have a strong family history of AD-dementia, which limits generalizability of the findings. Second, the lifestyle activities were measured using self-report. Therefore, future studies using more objective measures of activity engagement, such as actigraphy or real-time tracking via electronic apps, are needed to replicate and extend the present finding. Of note, greater lifestyle activity engagement, as measured by the CHAMPS questionnaire, was shown to be associated with less cognitive decline prior to the onset of MCI (Pettigrew et al. 2019), suggesting that the questionnaire is sensitive to clinically meaningful individual differences. Third, many lifestyle activities, including those assessed by the CHAMPS questionnaire, are not purely cognitive, social, or physical but tap into at least two of these domains (e.g., dancing, or playing cards with other people). Consequently, the impact of engagement in these activities on measures of rsfMRI connectivity may at least partially reflect the combined effect of two or more activity domains. Studies using other questionnaires and methods of activity assessment are, therefore, needed to confirm the present pattern of results. Fourth, although the associations between functional connectivity and the rate of change in cognition were very robust, the amount of variance in functional connectivity explained by the lifestyle activity variables was relatively small, suggesting a limited impact of lifestyle activity engagement. As suggested by the exploratory findings in this study, other modifiable lifestyle factors, including those related to vascular risk and physical function, may also modify aspects of functional connectivity, independently of activity engagement. Thus, the combined effects of various modifiable lifestyle factors may have a more substantial impact on brain functional connectivity and ultimately on cognitive change across the adult lifespan.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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