Received: 29 April 2022 | Revised: 20 September 2022 | Accepted: 28 October 2022

DOI: 10.1002/hbm.26148

RESEARCH ARTICLE

WILEY

Connectivity between default mode and frontoparietal networks mediates the association between global amyloid-β and episodic memory

Peter Zhukovsky[1] | Gillian Coughlan[2] | Rachel Buckley[2,3,4] | Cheryl Grady[5] | Aristotle N. Voineskos[1]

[1]Centre for Addiction and Mental Health, Campbell Family Mental Health Research Institute, Toronto, Canada

[2]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[3]Center for Alzheimer Research and Treatment, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

[4]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Victoria, Australia

[5]Rotman Research Institute, Baycrest Health Sciences, Toronto, Ontario, Canada

Correspondence
Peter Zhukovsky and Aristotle N. Voineskos, Centre for Addiction and Mental Health, Kimel Family Translational Imaging Genetics Laboratory, 250 College St, Toronto, ON M5T 1R8, Canada.
Email: peter.zhukovsky@camh.ca

Funding information
Alzheimer's Society, Grant/Award Number: 22-08; Canadian Institutes of Health Research, Grant/Award Number: 143311; National Sciences and Engineering Research Council; CAMH Foundation; University of Toronto; National Institutes of Health, Grant/Award Numbers: P50AG00561, P30NS09857781, P01AG026276, P01AG003991, R01AG043434, UL1TR000448, R01EB009352, R01MH56584, U24RR021382, P50MH071616, R01AG021910, P01AG03991, P50AG05681

Abstract

Beta-amyloid (Aβ) is a neurotoxic protein that deposits early in the pathogenesis of preclinical Alzheimer's disease. We aimed to identify network connectivity that may alter the negative effect of Aβ on cognition. Following assessment of memory performance, resting-state fMRI, and mean cortical PET-Aβ, a total of 364 older adults (286 with clinical dementia rating [CDR-0], 59 with CDR-0.5 and 19 with CDR-1, mean age: 74.0 ± 6.4 years) from the OASIS-3 sample were included in the analysis. Across all participants, a partial least squares regression showed that lower connectivity between posterior medial default mode and frontoparietal networks, higher within-default mode, and higher visual–motor connectivity predict better episodic memory. These connectivities partially mediate the effect of Aβ on episodic memory. These results suggest that connectivity strength between the precuneus cortex and the superior frontal gyri may alter the negative effect of Aβ on episodic memory. In contrast, education was associated with different functional connectivity patterns. In conclusion, functional characteristics of specific brain networks may help identify amyloid-positive individuals with a higher likelihood of memory decline, with implications for AD clinical trials.

Peter Zhukovsky and Gillian Coughlan contributed equally to this study.

1 | INTRODUCTION

Late-onset Alzheimer's disease (AD) manifests with loss of episodic memory (Weston et al., 2018; Zimmermann & Butler, 2018). A defining feature of AD is the "preclinical" phase before the manifestation of clinically significant amnesia, when individuals have elevated cortical amyloid (Dubois et al., 2019; Sperling et al., 2011). The neurotoxic accumulation of amyloid beta (Aβ) appears in preclinical AD (Jack Jr et al., 2016), and later sparks the emergence of other pathologies, such as hyperphosphorylated tau (Jack et al., 2018). Although Aβ is the main target of most treatment trials (Donohue et al., 2014; Papp et al., 2021; Sevigny et al., 2016; Sperling et al., 2020), many Aβ positive individuals do not develop AD or episodic memory impairment (Iacono et al., 2009; Roberts et al., 2018). In other words, not every individual with preclinical AD pathology develops symptomatic AD in late life. Brain function may be one of the factors that distinguish Aβ positive individuals who develop amnestic symptoms, from those who remain cognitively normal.

Large-scale brain systems or intrinsic connectivity networks support diverse cognitive abilities, including episodic memory (Burianova & Grady, 2007; Nyberg et al., 2000; Rugg & Vilberg, 2013). In AD, increased connectivity between frontal brain areas and the posterior subsystem of the default mode network (DMN) may precede the onset of cognitive symptoms (Jones et al., 2016). However, it is unclear whether this change in connectivity facilitates Aβ spread (Palmqvist et al., 2017) or acts as a compensatory change aiming to preserve cognition (resilience hypothesis). In healthy adults, functional connectivity (FC) within the DMN is associated with lower brain age (younger than the actual age), indicative of brain reserve (Ewers, 2020). Moreover, frontal regions that are part of cognitive control and salience networks play a role in brain reserve, despite having high Aβ deposition (Jack et al., 2008; Zhou et al., 2012). In older adults, connectivity hubs within the frontoparietal network (FPN) appear to ameliorate the association between vascular brain lesions and cognitive function (Benson et al., 2018). Thus, connectivity strength, within and between the DMN and FPN, may be an important biological substrate of resilience and susceptibility in preclinical AD (Ewers et al., 2021). However, given the weak brain–behavior associations, replication in additional cohorts with elevated amyloid is desirable.

Network connectivity in preclinical AD may also be shaped by social factors, such as education. For example, greater number of years of education predicts better volumetric integrity of the posterior medial DMN (Coughlan et al., 2021), which is closely linked with overall functional integrity, and appears to delay the onset of cognitive decline (Franzmeier et al., 2017; Mungas et al., 2018; Staekenborg et al., 2020; Wilson et al., 2019). The longitudinal trajectory of an individual's brain network organization is associated with educational attainment (Chan et al., 2021). This suggests that education may mitigate the effect of AD pathology on the brain. Further, education may serve to delay the onset of AD symptoms (Clouston et al., 2020). However, the education effect may act on network subsystems that are independent of cognitive networks affected by Aβ.

Here, we investigated pairwise FC between 21 independent components (ICs) of major brain networks. This fine-grained parcellation of networks allows us to examine subsystems within the brain's large-scale network. FC was estimated in cognitively normal (CDR-0) adults and adults with subtle cognitive impairment (CDR 0.5) who had varying levels of Aβ. Our previous work showed that both the precuneus and superior frontal gyrus are structural features of brain reserve (Coughlan et al., 2021). Therefore, we hypothesized that posterior medial DMN to superior frontal FPN connectivity would be associated with episodic memory (following multiple comparison correction of all other 60 network connections) and would mediate the effect of Aβ on episodic memory. We also tested whether educational attainment was associated with the same network subsystems that mediate the association between Aβ and episodic memory.

2 | METHODS

2.1 | Data

Data used in the preparation of this article were obtained from the Open Access Series of Imaging Studies (OASIS) database (https://www.oasis-brains.org/; accessed: April 4, 2020), collected by the Washington University Knight Alzheimer Disease Research Center over the course of 15 years. Beyond OASIS inclusion criteria, the current study required the availability of 3 T resting-state fMRI, PET scans for Aβ, and episodic memory assessments. All participants gave informed consent, and ethical approval was obtained by the institutional review board of Washington University School of Medicine.

2.2 | Participants

Participants were selected from the OASIS-3 cohort of 1098 subjects. Participants were excluded if they had an active psychiatric or neurological diagnosis, including epilepsy, alcoholism, or head trauma, and/or had a current diagnosis of cardiovascular disease, Parkinson's disease, or Frontotemporal dementia and other active neurological disorders. History of a single stroke or transient ischemic attack was not an exclusion criterion unless it was related to symptomatic onset of cognitive impairment. Following exclusions, 420 participants with quality-controlled fMRI data and amyloid-β data remained (Table 1).

2.3 | Aβ PET and fMRI acquisition

Aβ values were acquired via PET scanning with the use of one of two tracers: Pittsburgh compound B (PIB) or (18F) AV-45 florbetapir. Values are reported as standard-uptake-value-ratio (SUVR), and partial volume correction was applied via the regional spread function (RSF) in the PET Unified Pipeline (PUP) (Su et al., 2015), using the Desikan–Killiany atlas (Desikan et al., 2006; https://github.com/ysu001/PUP). The majority of participants' amyloid scans used PIB ($n = 354$), as only

TABLE 1 Overview of sample demographics used in the PLS analyses

	CDR-0		CDR-0.5		CDR-1		*F*-statistic/X^2 (*p* value)
N	**286**		**59**		**19**		
M/F	125	161	35	24	10	9	5.1 (.08)
Age	73.3	(6.0)	75.8	(7.0)	77.8	(7.3)	7.6 (<.001)
Education (Y)	15.8	(2.7)	15.1	(3.0)	13.6	(3.5)	6.4 (.002)
MMSE	28.9	(1.3)	26.9	(2.6)	23.7	(2.6)	114.1 ($4^{*}10^{-39}$)
Mean relative RMS before denoising	0.15	(0.06)	0.16	(0.06)	0.15	(0.07)	0.66 (.52)
Mean FD after denoising	0.03	(0.01)	0.03	(0.01)	0.03	(0.01)	2.0 (.13)
Delayed recall	12.9	(4.35)	7.3	(5.68)	1.8	(2.66)	70.9 (10^{-26})

Note: Clinical Dementia Rating group differences were assessed using one-way ANOVAs for continuous data and Chi-square tests for categorical data. Delayed recall was measured using Wechsler Memory Scale.

Abbreviations: FD, framewise displacement; M/F, male/female; MMSE, Mini-Mental State Examination; PLS, partial least squares; RMS, root mean square realignment.

66 participants had an AV-45 scan. To correct the effects of tracer, we used the residuals of a linear model with mean cortical Aβ levels and tracer. Cerebellum was used as the reference region. Cutoffs were defined based on OASIS-3 guidelines (LaMontagne et al., 2019). More details on data acquisition, timing, and processing are available in LaMontagne et al. (2019). Siemens 3 T scanners were used to obtain blood oxygenation level-dependent (BOLD) signaling data. Data were preprocessed using the Freesurfer image analysis suite as described in LaMontagne et al., 2019 and downloaded from XNAT central. The most common parameter combination of the resting-state fMRI data was: voxel size $= 4 \times 4 \times 4$ mm^3, TE $= 0.027$ s, TR $= 2.2$ s, and scan duration $= 6$ min. In our baseline analyses, only one participant had an fMRI sequence with TR $= 2.5$ s and one fMRI sequence comprised 163 instead of 164 volumes. In the follow-up analyses, only one fMRI sequence comprised 163 instead of 164 volumes and 30 sequences had a TR $= 2.5$ s.

2.4 | fMRI processing

We used the FSL processing pipeline (Alfaro-Almagro et al., 2018). Specifically, we downloaded fMRI data in BIDS format from OASIS and applied FSL FEAT (v3.15) for fMRI preprocessing (removing the first three volumes, linear detrending of 100 s, and smoothing with a kernel of 5 mm). We then used MELODIC (Beckmann and Smith, FMRIB Technical Report TR02CB1) to estimate subject-level ICs and applied in-house developed software, Alternative Labeling Tool, ALT (Zhukovsky, Coughlan, et al., 2022), to label these components as signal or noise. ALT reduces motion artifacts and performs similarly to hand classification. We regressed out the noise components (with *fsl_regfilt*), thus obtaining denoised data. All the above preprocessing occurred in subject space. We used Freesurfer structural image segmentations (downloaded from OASIS3) to leverage the high-quality, nonlinear registration to MNI152 space. Freesurfer *reg-feat2anat* command was used to complete the registrations. We mapped each participant's denoised data to the MNI152 space and assessed the registration quality using *slicesidir*. Participants with mean relative RMS of more than 0.3 were excluded from the analyses to ensure high data quality (Parkes et al., 2018).

2.5 | Network connectivity estimation

In constructing functional connectomes, a data-driven parcellation was obtained from a group-level ICA in 4000 healthy older participants from the UK Biobank. The original ICA analysis was set at 25 ICs, four of which were considered noise. The 21 signal ICs yielded 210 (i.e., ([21*21] − 21)/2) unique pairwise connections, each of which was examined separately. ICs are discrete constellations of fMRI voxels that represent resting-state subnets whose activity is independent from each other. Timeseries data was extracted for the 21 components using *fslmeants*. We used *FSLNets* (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets) to generate connectivity matrices using ridge-regularized partial connectivity that were subsequently analyzed. We previously mapped these 21 ICs onto the Yeo 7-network parcellation (Yeo et al., 2011) in MNI152 space (Zhukovsky, Wainberg, et al., 2022), to contextualize the spatial locations of the ICs within the brain's largest networks (Visual, Somatomotor, Dorsal/Ventral Attention, Limbic, Frontoparietal, and DMNs). We favored a data-driven parcellation as it captures large-scale aspects of brain networks and allows us to directly compare our results to findings from a large-scale UK Biobank data set.

2.6 | Cognitive status and episodic memory

Cognitive status and neuropsychological assessment included The Clinical Dementia Rating (CDR) scale, a Dementia Staging Instrument, which was used to characterize participants with normal cognition (CDR-0) or subtle cognitive impairment (CDR-0.5). This is a commonly used clinical outcome measure in clinical trials (Morris, 1993; Sevigny et al., 2016). The Mini-Mental State Examination (MMSE) indicated participants' global cognitive function in the domains of orientation,

registration, attention and calculation, recall, and language (Arevalo-Rodriguez et al., 2015). Immediate and delayed recall of episodic information were tested using the recall of story passages from the Logical Memory II subtest of the Wechsler Memory Scale (WMS; story units recall version) (Elwood, 1991).

2.7 | Statistical analysis

2.7.1 | Relations between global Aβ, connectivity networks, and delayed episodic memory

Partial least squares (PLS) regression (Chong & Jun, 2005; De Jong, 1993) was used to assess the relation between FC and episodic memory. For models featuring memory as the outcome, and for the multivariate brain–memory relationships, only the MRI scan within a year of the cognitive assessment was included, leading to a moderate reduction in the sample size ($n = 364$). We regressed out age, sex, and mean relative RMS from the FC data, while regressing out age, sex, and the absolute time differences between the fMRI scan and memory assessment from episodic memory data. As a result, the predictor matrix X included 210 partial pairwise connectivities (364×210), while the outcome matrix Y included delayed memory recall scores (number of logical units remembered from a story; 364×1). Following previous PLS applications (Morgan et al., 2019; Zhukovsky, Wainberg, et al., 2022), we used permutation testing ($n = 5000$) to assess whether PLS latent variables explained a significant amount of variance in memory. During each permutation, memory scores were shuffled randomly and the PLS was repeated, whereby we recorded the amount of variance in the permuted outcome explained by the PLS model. For significance testing, we calculated p values as the proportion of permutations on which the percentage of variance explained in the memory outcome was greater than in the PLS with nonpermuted data. If, in more than 5% of permutations, the "random" PLS explained more variance in the outcome than in the nonpermuted model, then the model was deemed nonsignificant. We used bootstrapping ($n = 5000$) to generate Z-regression weights for each of the predictors, indicating which network connectivity predictors robustly contributed to the latent PLS variable. A threshold of $|Z| > 3$ was used to determine the predictors that were robustly associated with episodic memory performance.

Finally, we then created two mediation models to test whether FC mediates the relationship between Aβ and memory. While the mediator in the first model was the latent variable from the PLS summarizing 19 connectivities, the mediator in the second model was the connectivity between the posteromedial DMN-20 and FPN-6. Significance was assessed using 5000 bias-corrected bootstrap estimates of their 95% confidence intervals (CIs).

2.7.2 | Effects of education

We assessed the relationship between years of education and within- and between-network connectivity ($n = 420$), controlling for Aβ levels and CDR status. The general linear models testing for the main effects of education are summarized below:

$$FC \sim Education + A\beta\ SUVR + CDR + \%\ signal + mean\ relative\ RMS + \Delta time + age * sex$$

Outliers (>3 standard deviations from the mean) were removed (Anderson et al., 2020).

2.8 | Repeating PLS and mediation analyses in a partially overlapping sample with data collection at different time points

Memory performance, resting-state fMRI, and PET-Aβ scans were collected as part of different visits in OASIS3. For the main analysis, we used only baseline data, with data matching keeping the MRI scan within a year of the Aβ scan for linear models with FC as the outcome.

To extend our findings, we used a different data alignment approach, conducting the cross-sectional PLS and mediation analyses in an OASIS sample that partially overlapped with the original sample ($n = 361$). In this analysis, we used all available time points to find the assessments that were as close together as possible (Supporting Information). fMRI scan times were matched as close as possible to the time of the PET scan. While 90% of the participants in this sample (Figure S1) were also part of the main analysis of the baseline sample, this additional cross-sectional analysis included different time points. As a result, only 47% of scans overlapped between the main analysis and the additional analysis. The sample used in this additional analysis was on average 1 year older than the baseline sample (75.2 vs. 74.0 years of age). As before, the PLS predictor matrix X (361×210) included 210 connectivities, and the outcome matrix included delayed memory recall (361×1). Finally, we used the beta-weights obtained in our main PLS to predict memory performance from FC data obtained primarily in the same participants with unique time points ($n = 191$). We use a correlation between observed and predicted memory scores to assess "out-of-sample" performance of our PLS model.

We next attempted to extend the mediation findings using this partially overlapping sample. The mediator in the first model was the latent variable from the PLS summarizing 19 connectivities, the mediator in the second model was the connectivity between the posteromedial DMN-20 and FPN-6.

2.9 | Data availability statement

Data used in the preparation of this article were obtained from the OASIS-3 database (https://www.oasis-brains.org/) and are freely available after registration. All code is made available on the following GitHub account (https://github.com/peterzhukovsky/resilience).

3 | RESULTS

3.1 | Participants

An overview of sample demographics is shown in Table 1. The OASIS-3 sample was predominantly Caucasian (60 African-Americans, 3 Asians, 357 Caucasians, 418 Non-Hispanic, and 2 Hispanic participants). As expected, the CDR-1 and CDR-0.5 groups were older than the CDR-0 group. We also found significant main effects of CDR on the MMSE. Relative RMS displacement of the fMRI images was relatively low, with <10% of participants being excluded since they showed mean RMS > 0.3. Mean framewise displacement (FD) measured after fMRI preprocessing was minimal across all groups, with no significant differences between CDR groups.

3.2 | FC associated with delayed episodic memory recall

We tested whether network connectivity was related to memory. Our PLS model featuring three latent variables explained 45.63% of the variance in delayed memory recall ($P_{PERMUTATION} = 0.032$, Figure 1a). We focus on the PLS1 variable, which explained 18% of the variance in memory recall (Figure 1b). Ten connectivities with normalized PLS1 weights $Z < -3$ (highlighted in blue Figure 1c), and 9 connectivities with $Z > 3$ (highlighted in red in Figure 1c) were identified. Importantly, lower connectivity between the posterior medial DMN and lateral frontal proportion of the FPN (IC-20 with IC-6 or IC-1 with IC-16), was associated with better delayed recall of episodic information. On the other hand, higher visuo-motor and within-DMN connectivity were associated with better delayed recall.

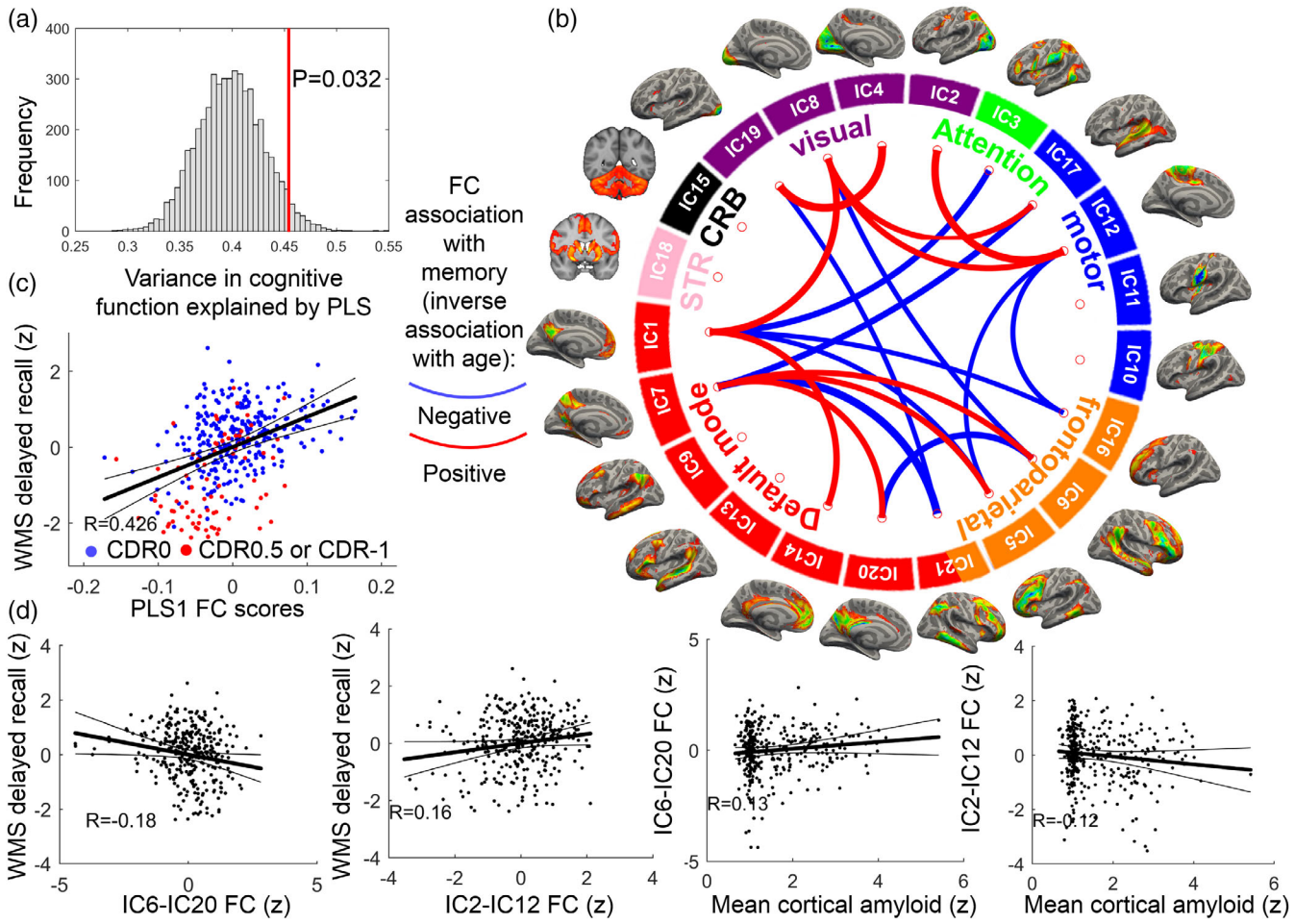

FIGURE 1 Brain–cognition relationship between partial functional connectivity (FC) and delayed memory recall. The loadings of these components on PLS1 and their respective association with memory are shown in (a). These relationships are tested in a multivariate partial least squares (PLS) regression, which generates a latent variable PLS1 (a), whose scores were found to predict worse memory recall ($R_{364} = 0.426$, $p < .001$). PLS1 scores were significantly lower in participants with CDR-1 and CDR-0.5 compared to CDR-0 ($F_{1,361} = 15.3$, $p = 4e{-}7$). PLS1 weights with |Z| > 3 weights are shown in (b). Higher connectivity of the frontoparietal and default mode independent components (ICs) predicted worse memory recall (e.g., DMN-20 to FPN-6 and FP/DMN-21 to FPN-5, and FPN-6 to DMN-9). Higher visuo-motor and visuo-DMN connectivity were associated with better memory recall. Correlations of key connectivities, Aβ, and memory are shown in (c). 95% confidence intervals are shown; more information on the individual FC weights can be found in the Supporting Information. Brain images in (b) show the spatial maps of each IC. Aβ, mean cortical Aβ SUVR-resting state functional levels; WMS, Wechsler memory scales.

In Figure 1c, connectivities highlighted in blue loaded positively on PLS1, with higher connectivity resulting in higher PLS1 scores, and worse memory. Conversely, connectivities highlighted in red loaded negatively on PLS1, with higher connectivity resulting in lower PLS scores and better memory. Participants with CDRs of 0.5 and 1 showed worse memory performance (see Table 1) and lower FC brain scores on PLS1 ($F_{1,361} = 15.3$, $p = 4e{-}7$) than those with CDR-0.

3.3 | Posterior medial DMN connectivity with the frontal FPN mediates the association between global Aβ and episodic memory

Finally, we tested whether the partial connectivities identified by PLS mediated the relationship between Aβ and delayed recall of episodic information. Two mediation analyses confirmed first, a significant indirect effect of the latent FC variable, reflecting the connectivity pattern seen in Figure 2b. and second, a significant indirect effect of connectivity between posterior medial DMN (IC-20) and lateral frontal FPN (IC-6) on the relationship between Aβ and memory (−0.02, 95% CI = −0.04 to 0.0004; bootstrapped $p < .05$) (Supporting Information for direct effect).

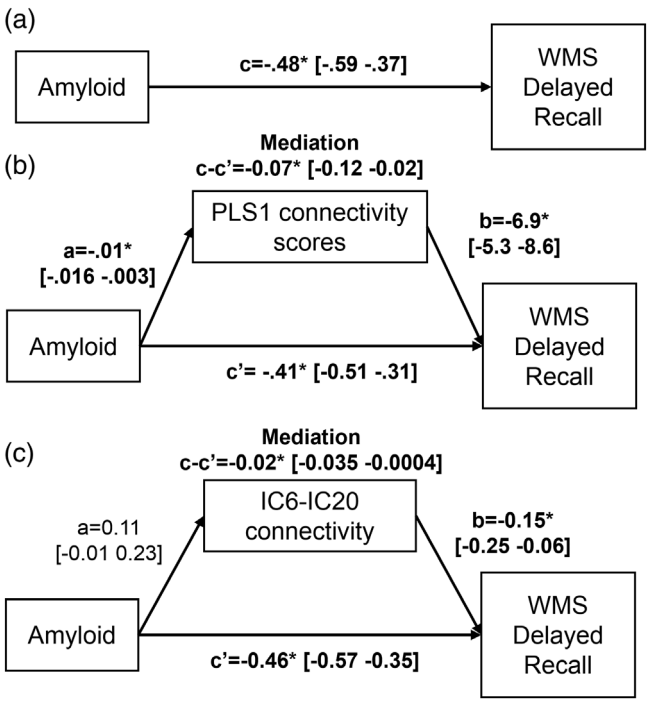

FIGURE 2 Mediation analyses of the main sample showed a significant indirect effect of the latent PLS1 variable summarizing functional connectivities (FCs) on relationship between Aβ and memory. While we found strong direct effects of amyloid on memory (a), our mediation model showed that higher Aβ levels were associated with lower PLS1 scores (b) and higher DMN-20 to FPN-6 connectivity (c), which were linked to worse memory recall.

3.4 | Additional analyses in an overlapping sample at unique timepoints

In the overlapping sample, with a majority of unique time points not included in the original analysis, we found many of the same relationships as shown in Figure S2. A PLS model featuring four latent variables explained a significant amount of variance in memory ($p = .038$, Figure S2b). PLS1 explained 20.2% of the variance in memory recall (Figure S2b). PLS1 implicated many of the connectivities identified in the main analysis, such as DMN-20 to FPN-6 and DMN-20 to DMN-7 (Figure S2b). Our mediation analysis also returned consistent results, showing a significant indirect effect of the latent FC variable and of connectivity between posterior medial DMN (IC-20) and lateral frontal FPN (IC-6) on the relationship between Aβ and memory (bootstrapped $p < 0.05$, Table S3).

We were able to achieve moderate out-of-sample performance using the PLS model trained on the main sample to predict memory recall in the sample including unique time points, with predicted versus observed Pearson's correlation of $r_{189} = .17$, $p = .018$ (Figure S3).

3.5 | Effects of educational attainment on function connectivity

Next, we tested whether the connectivities associated with education overlap with the connectivities that emerged in our previous analysis. Controlling for global Aβ, CDR, age, and sex, weaker connectivity between the IC-20 and IC-11, and increased connectivity between IC-16 and IC-14 were associated with more education (Figure 3a). Most pairwise connectivities associated with education (Figure 3b) did not overlap with connectivities identified in our PLS analysis (Figure 1), although connectivity between components of the default mode, motor, and visual networks were involved in both.

4 | DISCUSSION

In older adults who are on the AD trajectory, we examined large-scale brain networks that influence the association between elevated Aβ burden and episodic memory. Consistent with the hypothesis that connectivity between the default mode and FPN mediates this Aβ-memory association, our structural equation model analyses showed that posterior medial DMN-FPN connectivity partially mediates the Aβ-memory association. Education was associated with connectivities including DMN and motor components, after accounting for Aβ and CDR status. Interestingly, education was not associated with Aβ levels. Taken together, these findings suggest educational attainment does not act on network subsystems that mediate the association between preclinical Aβ burden and episodic memory.

The posterior DMN and the FPN emerged as the key predictors of episodic memory. The PLS analyses confirmed connectivity between these network subsystems mediates the association between Aβ and memory impairment. This finding is consistent with

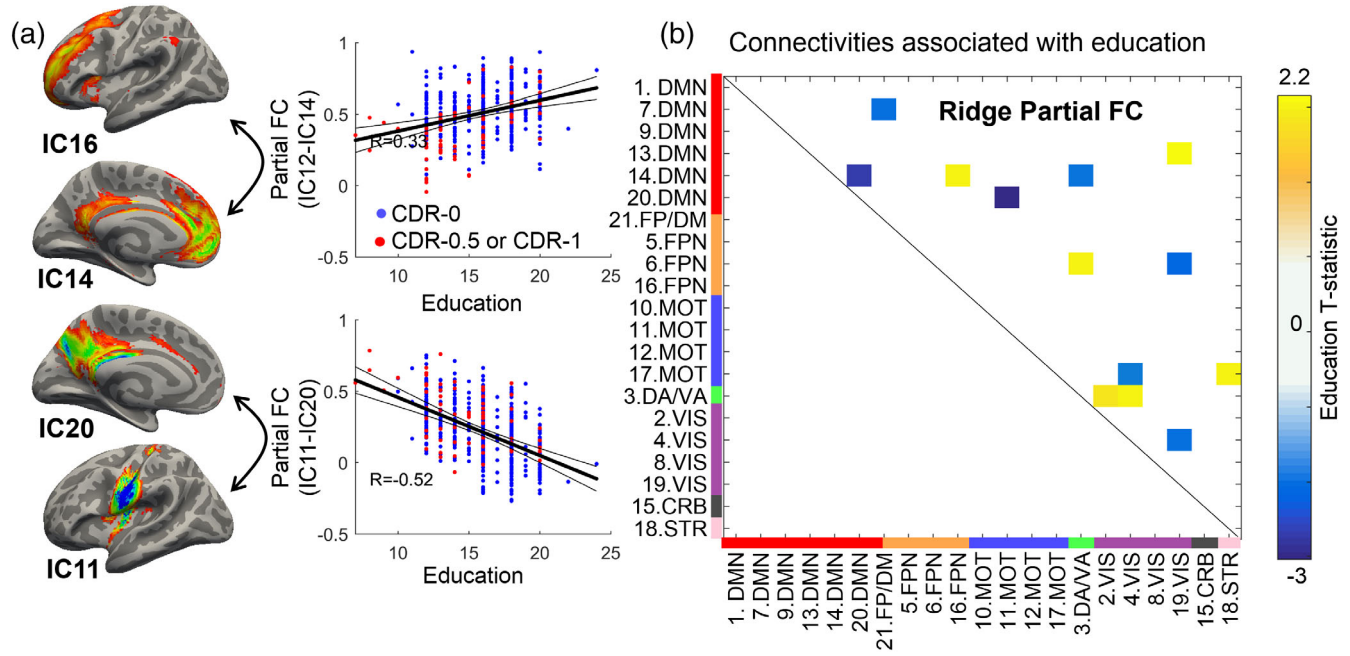

FIGURE 3 Functional connectivity (FC) correlates the education. Education was positively and negatively associated with FC of DMN to motor components, as shown by example associations in (a; $n = 484$). Blue dots represent CDR-0 and red dots represent CDR-0.5 and CDR-1 participants. All significant (permutation $p < .05$) associations between education and FC are shown in (b). Positive associations between education and FC are shown in orange/yellow while negative associations are shown in blue.

previous reports that higher connectivity of the precuneus with superior frontal regions is associated with poorer cognition (Bagarinao et al., 2019). Neuroimaging studies also show that FC of hubs in the FPN and DMN (Ewers, 2020; Hedden et al., 2009; Zhou et al., 2012) are associated with AD. Indeed, the posterior DMN regions (including the posterior cingulate and precuneus cortices) in particular have been shown to underpin spatial disorientation and amnesia in the earliest stages of AD (Coughlan et al., 2018, 2020).

While these findings provide valuable insight into brain regions contributing to disease susceptibility, the role of these regions in preserving cognition has been under-explored, particularly when considering how life experience, such as education, may act on connectivities associated with resilience. In our analyses, higher connectivity between the posterior DMN (precuneus cortex, posterior cingulate cortex) and FPN (including superior frontal gyrus) emerged as a key signature of susceptibility to Aβ burden, leading to memory impairment. Our prior work also shows that these brain areas play a key role in structural brain reserve among genetically vulnerable adults, and the structural integrity of these regions is significantly associated with episodic memory (Coughlan et al., 2021). Combined with our earlier work, the current findings thus add support to the theory that these select brain regions may mitigate the risk of memory impairment conferred by the Aβ.

Nevertheless, an important question concerning the interpretation of the increased DMN-FPN connectivity remains: is the increase in DMN-FPN connectivity a sign of a resilience mechanism (Spreng & Turner, 2019), or connectivity "overload" that is later associated with spread of Aβ (Jones et al., 2016). Increased FC between lateral prefrontal FPN regions (implicated in cognitive control) and DMN regions (implicated in self-referential and memory processes) is at the core of the default-executive coupling hypothesis of aging (Spreng & Turner, 2019; Uddin, 2021). Task-based fMRI evidence suggests that in healthy aging, lateral FPN regions become less efficient, and compensate for age-related decline in executive function by enhancing their connectivity with anterior and posterior DMN (Adnan et al., 2019; Spreng & Turner, 2019). However, high connectivity between the posterior DMN and frontal hub regions also predicts Aβ accumulation (Jones et al., 2016), and the connectivity pattern is later reduced in MCI (Lee et al., 2016). Increased FC may be a general compensatory mechanism in aging; however, increased connectivity in those who also have Aβ accumulation may increase the spread of Aβ. Higher connectivity with the DMN-FPN suggests that individuals may have a higher probability of showing detectable memory impairment. Treatment targets that reduce hyperconnectivity in the posterior DMN-FPN circuit could potentially alter the course of Aβ deposition and cognitive decline.

In addition to DMN-FPN connectivity, our PLS analysis also implicated visual and motor networks as correlates of episodic memory. Specifically, hypoconnectivity between the visual and motor network components predicted worse memory outcomes in response to higher Aβ. Although less evidence on the role of visual–visual and visual–motor connectivity in preclinical AD is available compared to the DMN-FPN connectivity discussed above, activation likelihood estimation meta-analysis results found diminished primary visual cortex connectivity in MCI and AD (Badhwar et al., 2017). Moreover, a large cohort study of healthy older adults found that resting-state

correlates of visuospatial memory included parietal–motor networks (Suri et al., 2017). Older adults show task-based activation of visual areas during memory encoding and recall (Simon-Vermot et al., 2018), while younger adults show task-based visual activation during episodic memory retrieval (Bone & Buchsbaum, 2021), especially when the stimuli are presented in the visual domain (Bonnici et al., 2016). Our findings that unique patterns of both hyper and hypoconnectivity connectivity influence memory impairment in response to Aβ are thus consistent with a role for visuo-motor connectivity in memory recall. However, future studies are needed to understand the role played by visual–motor network connectivity and to test whether these circuits have therapeutic potential.

Lifestyle factors subserve network function and include education (Staekenborg et al., 2020), verbal intelligence (Boyle et al., 2021), physical activity, and sleep (Willetts et al., 2018). Interestingly, the network connectivity patterns that mediated the relationship between Aβ and episodic memory were not the same as those associated with education. This suggests that the neural reserve conferred by education does not involve the same network subsystems that are vulnerable to Aβ (i.e., preclinical disease).

Our study has limitations. In healthy participants, previous studies have shown that robust and reproducible brain cognition relationships require thousands of individuals (Marek et al., 2022) and a high sample-per-feature ratio (Helmer et al., 2021). The effect size of our brain–behavior association is moderate, with multivariate correlations of ∼0.42 and univariate correlations of 0.1–0.2. These effect sizes are larger than recent large-scale brain-wide association studies in healthy participants (Helmer et al., 2021; Marek et al., 2022). In the OASIS-3 sample, participants showed a wide range of memory performance, some showing early signs of cognitive impairment measured using the CDR. It is possible that such impairments may contribute to larger effects of brain-cognition associations than in more normative population datasets such as UK Biobank or the Adolescent Brain Cognitive Development study. We argue that the comparatively smaller sample size in our analyses can still yield reproducible findings due to potentially larger effects in clinical populations (Gratton et al., 2022). Although longitudinal designs optimally address the features underlying the concept of cognitive resilience, rich information can be gained from cross-sectional studies because they provide insight into neurobiological mechanisms and developing research approaches. Further, it is important to consider that age influences the functional organization of the human brain (Setton et al., 2022). As both UK Biobank and OASIS-3 data sets include older adults, our group ICA generated a similar pattern of findings, however. Moreover, it is important to establish whether DMN-FPN connectivity mediates the relationship between Aβ and other cognitive processes, such as executive function or information processing.

In conclusion, our results support existing evidence that functional brain properties partially mediate the association between amyloid-β and episodic memory. We show that connectivity of the posterior DMN (predominately the precuneus cortex) with the FPN (predominately superior frontal gyri) mediates this association—a finding which is supported by previous work (Cassady et al., 2021; Hedden et al., 2009). This has clear implications for clinical trials that aim to enroll individuals with elevated amyloid, who have the highest likelihood of suffering cognitive decline during the trial. Future research should examine if connectivity of this circuit may facilitate interventions (Koch et al., 2022) and provide a biomarker for outcomes in cognitive remediation trials (Rajji et al., 2020).

ACKNOWLEDGMENTS

The authors thank all the participants of the OASIS-3 sample for their contribution to this incredibly valuable study and the OASIS-3 investigators for sharing and organizing the data. The authors also thank Brennan DeSouza for his critical feedback and his help with proofreading the manuscript. The authors acknowledge the funding grants that supported OASIS data including P50 AG05681, P01 AG03991, R01 AG021910, P50 MH071616, U24 RR021382, and R01 MH56584. Data were provided by OASIS-3: Principal Investigators: T. Benzinger, D. Marcus, J. Morris; NIH P50AG00561, P30NS09857781, P01AG026276, P01AG003991, R01AG043434, UL1TR000448, and R01EB009352. AV-45 doses were provided by Avid Radiopharmaceuticals, a wholly owned subsidiary of Eli Lilly. PZ was funded by the Postdoctoral Fellowship Award from Canadian Institutes of Health Research. GC was funded by Postdoctoral Fellowship Award from the Alzheimer's Society of Canada (award number 22-08). GC received funding from a Foundation Grant from Canadian Institutes of Health Research (Grant number 143311). RB received funding from an R00 Pathway to Independence Award from the National Institute of Health (Grant number AG061238). ANV currently receives funding from CIHR, the NIH, the National Sciences and Engineering Research Council (NSERC), the CAMH Foundation, and the University of Toronto.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data used in the preparation of this article were obtained from the OASIS-3 database (https://www.oasis-brains.org/) and are freely available after registration. All code is made available on the following github account (https://github.com/peterzhukovsky/resilience).

ORCID

Peter Zhukovsky https://orcid.org/0000-0002-7181-2095
Gillian Coughlan https://orcid.org/0000-0003-1806-702X
Cheryl Grady https://orcid.org/0000-0001-9533-8802

REFERENCES

Adnan, A., Beaty, R., Lam, J., Spreng, R. N., & Turner, G. R. (2019). Intrinsic default—Executive coupling of the creative aging brain. *Social Cognitive and Affective Neuroscience*, *14*, 291–303.

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., Sotiropoulos, S. N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D. C., Zhang, H., Dragonu, I., Matthews, P. M., … Smith, S. M. (2018). Image processing and quality

control for the first 10,000 brain imaging datasets from UK biobank. *NeuroImage*, *166*, 400–424. https://doi.org/10.1016/j.neuroimage.2017.10.034

Anderson, K. M., Collins, M. A., Kong, R., Fang, K., Li, J., He, T., Chekroud, A. M., Yeo, B. T. T., & Holmes, A. J. (2020). Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. *Proceedings of the National Academy of Sciences of the United States of America*, *117*, 25138–25149.

Arevalo-Rodriguez, I., Smailagic, N., Roquéi Figuls, M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O. L., & Bonfill Cosp, X. (2015). Cullum S (2015): Mini-mental state examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database of Systematic Reviews*, CD010783.

Badhwar, A. P., Tam, A., Dansereau, C., Orban, P., Hoffstaedter, F., & Bellec, P. (2017). Resting-state network dysfunction in Alzheimer's disease: A systematic review and meta-analysis. *Alzheimer's & Dementia*, *8*, 73–85.

Bagarinao, E., Watanabe, H., Maesawa, S., Mori, D., Hara, K., Kawabata, K., Yoneyama, N., Ohdake, R., Imai, K., Masuda, M., Yokoi, T., Ogura, A., Taoka, T., Koyama, S., Tanabe, H. C., Katsuno, M., Wakabayashi, T., Kuzuya, M., Ozaki, N., … Sobue, G. (2019). Reorganization of brain networks and its association with general cognitive performance over the adult lifespan. *Scientific Reports*, *9*, 1–15. https://doi.org/10.1038/s41598-019-47922-x

Benson, G., Hildebrandt, A., Lange, C., Schwarz, C., Köbe, T., Sommer, W., Flöel, A., & Wirth, M. (2018). Functional connectivity in cognitive control networks mitigates the impact of white matter lesions in the elderly. *Alzheimer's Research & Therapy*, *10*, 1–13.

Bone, M. B., & Buchsbaum, B. R. (2021). Detailed episodic memory depends on concurrent reactivation of basic visual features within the posterior hippocampus and early visual cortex. *Cerebral Cortex Communications*, *2*, 1–15.

Bonnici, H. M., Richter, F. R., Yazar, Y., & Simons, J. S. (2016). Multimodal feature integration in the angular gyrus during episodic and semantic retrieval. *The Journal of Neuroscience*, *36*, 5462–5471.

Boyle, R., Jollans, L., Rueda-Delgado, L. M., Rizzo, R., Yener, G. G., McMorrow, J. P., Knight, S. P., Carey, D., Robertson, I. H., Emek-Savaş, D. D., Stern, Y., Kenny, R. A., & Whelan, R. (2021). Brain-predicted age difference score is related to specific cognitive functions: A multi-site replication analysis. *Brain Imaging and Behavior*, *15*, 327–345.

Burianova, H., & Grady, C. L. (2007). Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *Journal of Cognitive Neuroscience*, *19*, 1520–1534.

Cassady, K. E., Adams, J. N., Chen, X., Maass, A., Harrison, T. M., Landau, S., Baker, S., & Jagust, W. (2021). Alzheimer's pathology is associated with dedifferentiation of intrinsic functional memory networks in aging. *Cerebral Cortex*, *31*, 4781–4793.

Chan, M. Y., Han, L., Carreno, C. A., Zhang, Z., Rodriguez, R. M., LaRose, M., Hassenstab, J., & Wig, G. S. (2021). Long-term prognosis and educational determinants of brain network decline in older adult individuals. *Nature Aging*, *1*(11), 1053–1067.

Chong, I. G., & Jun, C. H. (2005). Performance of some variable selection methods when multicollinearity is present. *Chemometrics and Intelligent Laboratory Systems*, *78*, 103–112.

Clouston, S. A. P., Smith, D. M., Mukherjee, S., Zhang, Y., Hou, W., Link, B. G., & Richards, M. (2020). Education and cognitive decline: An integrative analysis of global longitudinal studies of cognitive aging. *Journals of Gerontology – Series B Psychological Sciences and Social Sciences*, *75*, E151–E160.

Coughlan, G., Laczó, J., Hort, J., Minihane, A. M., & Hornberger, M. (2018). Spatial navigation deficits—Overlooked cognitive marker for preclinical Alzheimer disease? *Nature Reviews. Neurology*, *14*, 496–506. https://doi.org/10.1038/s41582-018-0031-x

Coughlan, G., Zhukovsky, P., Puthusseryppady, V., Gillings, R., Minihane, M., Cameron, D., & Hornberger, M. (2020). Functional connectivity between the entorhinal and posterior cingulate cortices associated with navigation impairment following path integration in at-genetic-risk Alzheimer's disease. *Neurobiology of Aging*, *90*, 110–118.

Coughlan, G., Zhukovsky, P., Voineskos, A., & Grady, C. (2021). A profile of brain reserve in adults at genetic risk of alzheimer's disease. *Alzheimer's & Dementia*, *13*, 1–11.

De Jong, S. (1993). SIMPLS: An alternative approach to partial least squares regression. *Chemometrics and Intelligent Laboratory Systems*, *18*, 251–263.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*, 968–980.

Donohue, M. C., Sperling, R. A., Salmon, D. P., Rentz, D. M., Raman, R., Thomas, R. G., Weiner, M., & Aisen, P. S. (2014). The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. *JAMA Neurology*, *71*, 961–970.

Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Broich, K., Cavedo, E., Crutch, S., Duyckaerts, C., Frisoni, G. B., Gauthier, S., Gouw, A. A., Habert, M., Holtzman, D. M., Kivipelto, M., Lista, S., … Devices, M. (2019). Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*, *12*(3), 292–323.

Elwood, R. W. (1991). The Wechsler Memory Scale-Revised: Psychometric characteristics and clinical application. *Neuropsychology Review*, *2*, 179–201.

Ewers, M. (2020). Reserve in Alzheimer's disease: Update on the concept, functional mechanisms and sex differences. *Current Opinion in Psychiatry*, *33*, 178–184.

Ewers, M., Luan, Y., Frontzkowski, L., Neitzel, J., Rubinski, A., Dichgans, M., Hassenstab, J., Gordon, B. A., Chhatwal, J. P., Levin, J., Schofield, P., Benzinger, T. L. S., Morris, J. C., Goate, A., Karch, C. M., Fagan, A. M., McDade, E., Allegri, R., Berman, S., … Alzheimer's Disease Neuroimaging Initiative and the Dominantly Inherited Alzheimer Network. (2021). Segregation of functional networks is associated with cognitive resilience in Alzheimer's disease. *Brain*, *144*, 2176–2185.

Franzmeier, N., Duering, M., Weiner, M., Dichgans, M., & Ewers, M. (2017). Left frontal cortex connectivity underlies cognitive reserve in prodromal Alzheimer disease. *Neurology*, *88*, 1054–1061.

Gratton, C., Nelson, S. M., & Gordon, E. M. (2022). Brain-behavior correlations: Two paths toward reliability. *Neuron*, *110*, 1446–1449.

Hedden, T., Van Dijk, K. R. A., Becker, J. A., Mehta, A., Sperling, R. A., Johnson, K. A., & Buckner, R. L. (2009). Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *The Journal of Neuroscience*, *29*, 12686–12694.

Helmer, M., Warrington, S., Mohammadi-Nejad, A.-R., Lisa, J., Howell, A., Rosand, B., Anticevic, A., Sotiropoulos, S. N., & Murray, J. D. (2021). On stability of canonical correlation analysis and partial least squares with application to brain-behavior associations Markus. *bioRxiv*.

Iacono, D., Markesbery, W. R., Gross, M., Pletnikova, O., Rudow, G., Zandi, P., & Troncoso, J. C. (2009). The Nun Study: Clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology*, *73*, 665–673.

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., … Silverberg, N. (2018). NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*, 535–562.

Jack, C. R., Lowe, V. J., Senjem, M. L., Weigand, S. D., Kemp, B. J., Shiung, M. M., Knopman, D. S., Boeve, B. F., Klunk, W. E., Mathis, C. A., & Petersen, R. C. (2008). 11C PiB and structural MRI

provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. *Brain*, *131*, 665–680.

Jack, C. R., Jr., Therneau, T. M., Wiste, H. J., Weigand, S. D., Knopman, D. S., Lowe, V. J., Mielke, M. M., Vemuri, P., Roberts, R. O., Machulda, M. M., Senjem, M. L., Gunter, J. L., Rocca, W. A., & Petersen, R. C. (2016). Rates of transition between amyloid and neurodegeneration biomarker states and to dementia among non-demented individuals: A population-based cohort study. *Lancet Neurology*, *15*, 56–64.

Jones, D. T., Knopman, D. S., Gunter, J. L., Graff-Radford, J., Vemuri, P., Boeve, B. F., Petersen, R. C., Weiner, M. W., & Jack, C. R. (2016). Cascading network failure across the Alzheimer's disease spectrum. *Brain*, *139*, 547–562.

Koch, G., Casula, E. P., Bonnì, S., Borghi, I., Assogna, M., Minei, M., Pellicciari, M. C., Motta, C., Acunto, A. D., Porrazzini, F., Maiella, M., Ferrari, C., Caltagirone, C., Santarnecchi, E., Bozzali, M., & Martorana, A. (2022). Precuneus magnetic stimulation for Alzheimer's disease: A randomized, sham-controlled trial. *Brain*, awac285.

LaMontagne PJ, Benzinger TL, Morris JC, Keefe S, Hornbeck R, Xiong C, Grant E, Hassenstab J, Moulder K, Vlassenko AG, Raichle ME, Cruchaga C, Marcus D (2019): OASIS-3: Longitudinal neuroimaging, clinical, and cognitive dataset for normal aging and Alzheimer disease, medRxiv.

Lee, E.-S., Yoo, K., Lee, Y.-B., Chung, J., Lim, J.-E., Yoon, B., Jeong, Y., & Alzheimer's Disease Neuroimaging Initiative. (2016). Default mode network functional connectivity in early and late mild cognitive impairment. *Alzheimer Disease and Associated Disorders*, *30*, 289–296.

Marek, S., Tervo-Clemmens, B., Calabro, F. J., Montez, D. F., Kay, B. P., Hatoum, A. S., Donohue, M. R., Foran, W., Miller, R. L., Hendrickson, T. J., Malone, S. M., Kandala, S., Feczko, E., Miranda-Dominguez, O., Graham, A. M., Earl, E. A., Perrone, A. J., Cordova, M., Doyle, O., … Dosenbach, N. U. F. (2022). Reproducible brain-wide association studies require thousands of individuals. *Nature*, *603*, 654–660.

Morgan, S. E., Seidlitz, J., Whitaker, K. J., Romero-Garcia, R., Clifton, N. E., Scarpazza, C., van Amelsvoort, T., Marcelis, M., van Os, J., Donohoe, G., Mothersill, D., Corvin, A., Pocklington, A., Raznahan, A., McGuire, P., Vértes, P. E., & Bullmore, E. T. (2019). Cortical patterning of abnormal morphometric similarity in psychosis is associated with brain expression of schizophrenia-related genes. *Proceedings of the National Academy of Sciences of the United States of America*, *116*, 9604–9609.

Morris, J. C. (1993). The clinical dementia rating (CDR): Current version and scoring rules. *Neurology*, *43*, 2412–2414.

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: Implications for cognitive reserve. *Neurobiology of Aging*, *68*, 142–150.

Nyberg, L., Persson, J., Habib, R., Tulving, E., McIntosh, A. R., Cabeza, R., & Houle, S. (2000). Large scale neurocognitive networks underlying episodic memory. *Journal of Cognitive Neuroscience*, *12*, 163–173.

Palmqvist, S., Schöll, M., Strandberg, O., Mattsson, N., Stomrud, E., Zetterberg, H., Blennow, K., Landau, S., Jagust, W., & Hansson, O. (2017). Earliest accumulation of β-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nature Communications*, *8*, 1214.

Papp, K. V., Rentz, D. M., Maruff, P., Sun, C. K., Raman, R., Donohue, M. C., Schembri, A., Stark, C., Yassa, M. A., Wessels, A. M., Yaari, R., Holdridge, K. C., Aisen, P. S., & Sperling, R. A. (2021). The computerized cognitive composite (C3) in A4, an Alzheimer's disease secondary prevention trial. *Journal of Prevention of Alzheimer'Disease*, *8*, 59–67.

Parkes, L., Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *NeuroImage*, *171*, 415–436. https://doi.org/10.1016/j.neuroimage.2017.12.073

Rajji, T. K., Bowie, C. R., Herrmann, N., Pollock, B. G., Bikson, M., Blumberger, D. M., Butters, M. A., Daskalakis, Z. J., Fischer, C. E., Flint, A. J., Golas, A. C., Graff-Guerrero, A., Kumar, S., Lourenco, L., Mah, L., Ovaysikia, S., Thorpe, K. E., Voineskos, A. N., & Mulsant, B. H. (2020). Design and rationale of the PACt-MD randomized clinical trial: Prevention of Alzheimer's dementia with cognitive remediation plus transcranial direct current stimulation in mild cognitive impairment and depression. *Journal of Alzheimer's Disease*, *76*, 733–751.

Roberts, R. O., Aakre, J. A., Kremers, W. K., Vassilaki, M., Knopman, D. S., Mielke, M. M., Alhurani, R., Geda, Y. E., Machulda, M. M., Coloma, P., Schauble, B., Lowe, V. J., Jack, C. R., & Petersen, R. C. (2018). Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurology*, *75*, 970–979.

Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology*, *23*, 255–260.

Setton, R., Mwilambwe-Tshilobo, L., Girn, M., Lockrow, A. W., Baracchini, G., Hughes, C., Lowe, A. J., Cassidy, B. N., Li, J., Luh, W.-M., Bzdok, D., Leahy, R. M., Ge, T., Margulies, D. S., Misic, B., Bernhardt, B. C., Stevens, W. D., De Brigard, F., Kundu, P., … Spreng, R. N. (2022). Age differences in the functional architecture of the human brain. *Cerebral Cortex*, 1–21.

Sevigny, J., Chiao, P., Bussière, T., Weinreb Paul, H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., O Gorman, J., Qian, F., Arastu, M., Li, M., Chollate, S., Brennan, M. S., Quintero-Monzon, O., Scannevin, R. H., Arnold, H. M., … Sandrock, A. (2016). The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. *Nature*, *537*, 50–56.

Simon-Vermot, L., Taylor, A. N. W., Araque Caballero, M., Franzmeier, N., Buerger, K., Catak, C., Janowitz, D., Kambeitz-Ilankovic, L. M., Ertl-Wagner, B., Duering, M., & Ewers, M. (2018). Correspondence between resting-state and episodic memory-task related networks in elderly subjects. *Frontiers in Aging Neuroscience*, *10*, 1–10.

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., Iwatsubo, T., Jack, C. R. J., Kaye, J., Montine, T. J., Park, D. C., Reiman, E. M., Rowe, C. C., Siemers, E., Stern, Y., Yaffe, K., Carrillo, M. C., Thies, B., Morrison-Bogorad, M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, *7*, 280–292.

Sperling, R. A., Donohue, M. C., Raman, R., Sun, C., Yaari, R., Holdridge, K., Siemers, E., Johnson, K. A., Aisen, P. S., & Study, A. (2020). Association of factors with elevated amyloid burden in clinically normal older individuals. *JAMA Neurology*, *77*, 735–745.

Spreng, R. N., & Turner, G. R. (2019). The shifting architecture of cognition and brain function in older adulthood. *Perspectives on Psychological Science*, *14*, 523–542.

Staekenborg, S. S., Kelly, N., Schuur, J., Koster, P., Scherder, E., Tielkes, C. E. M., Scheltens, P., & Claus, J. J. (2020). Education as proxy for cognitive reserve in a large elderly memory clinic: "Window of benefit". *Journal of Alzheimer's Disease*, *76*, 671–679.

Su, Y., Blazey, T. M., Snyder, A. Z., Raichle, M. E., Marcus, D. S., Ances, B. M., Bateman, R. J., Cairns, N. J., Aldea, P., Cash, L., Christensen, J. J., Friedrichsen, K., Hornbeck, R. C., Farrar, A. M., Owen, C. J., Mayeux, R., Brickman, A. M., Klunk, W., Price, J. C., … Benzinger, T. L. S. (2015). Partial volume correction in quantitative amyloid imaging. *NeuroImage*, *107*, 55–64.

Suri, S., Topiwala, A., Filippini, N., Zsoldos, E., Mahmood, A., Sexton, C. E., Singh-Manoux, A., Kivimäki, M., Mackay, C. E., Smith, S., & Ebmeier, K. P. (2017). Distinct resting-state functional connections associated with episodic and visuospatial memory in older adults. *NeuroImage*, *159*, 122–130. https://doi.org/10.1016/j.neuroimage.2017.07.049

Uddin, L. Q. (2021). Cognitive and behavioural flexibility: Neural mechanisms and clinical considerations. *Nature Reviews. Neuroscience*, *22*, 167–179. https://doi.org/10.1038/s41583-021-00428-w

Weston, P. S. J., Nicholas, J. M., Henley, S. M. D., Liang, Y., Macpherson, K., Donnachie, E., Schott, J. M., Rossor, M. N., Crutch, S. J., Butler, C. R., Zeman, A. Z., & Fox, N. C. (2018). Accelerated long-term forgetting in presymptomatic autosomal dominant Alzheimer's disease: A cross-sectional study. *Lancet Neurology*, *17*, 117–132.

Willetts, M., Hollowell, S., Aslett, L., Holmes, C., & Doherty, A. (2018). Statistical machine learning of sleep and physical activity phenotypes from sensor data in 96,220 UK Biobank participants. *Scientific Reports*, *8*, 1–10.

Wilson, R. S., Yu, L., Lamar, M., Schneider, J. A., Boyle, P. A., & Bennett, D. A. (2019). Education and cognitive reserve in old age. *Neurology*, *92*, E1041–E1050.

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fisch, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*, 1125–1165.

Zhou, J., Gennatas, E. D., Kramer, J. H., Miller, B. L., & Seeley, W. W. (2012). Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron*, *73*, 1216–1227.

Zhukovsky, P., Coughlan, G., Dickie, E. W., & Hawco, C. (2022). Alternative labeling tool: A minimal algorithm for denoising single-subject resting-state fMRI data with ICA-MELODIC. *Brain Imaging and Behavior*, *16*, 1823–1831. https://doi.org/10.1007/s11682-022-00650-9

Zhukovsky, P., Wainberg, M., Milic, M., Tripathy, S. J., Mulsant, B. H., Felsky, D., & Voineskos, A. N. (2022). Multiscale neural signatures of major depressive, anxiety, and stress-related disorders. *Proceedings of the National Academy of Sciences of the United States of America*, *119*, 1–10.

Zimmermann, J. F., & Butler, C. R. (2018). Accelerated long-term forgetting in asymptomatic APOE ε4 carriers. *Lancet Neurology*, *17*, 394–395.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhukovsky, P., Coughlan, G., Buckley, R., Grady, C., & Voineskos, A. N. (2023). Connectivity between default mode and frontoparietal networks mediates the association between global amyloid-β and episodic memory. *Human Brain Mapping*, *44*(3), 1147–1157. https://doi.org/10.1002/hbm.26148