Received: 13 February 2022 | Revised: 26 June 2022 | Accepted: 22 August 2022

DOI: 10.1002/hbm.26070

RESEARCH ARTICLE

WILEY

Cognitive decline and hippocampal functional connectivity within older Black adults

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Funding information
National Institute on Aging, Grant/Award Numbers: P30AG010161, R01AG017917, R01AG055430, R01AG056405, RF1AG022018, UF1NS100599

Abstract

While there has been a proliferation of neuroimaging studies on cognitive decline in older non-Hispanic White adults, there is a dearth of knowledge regarding neuroimaging correlates of cognitive decline in Black adults. Resting-state functional neuroimaging approaches may be particularly sensitive to early cognitive decline, but there are no studies that we know of that apply this approach to examining associations of brain function to cognition in older Black adults. We investigated the association of cognitive decline with whole-brain voxel-wise functional connectivity to the hippocampus, a key brain region functionally implicated in early Alzheimer's dementia, in 132 older Black adults without dementia participating in the Minority Aging Research Study and Rush Memory and Aging Project, two longitudinal studies of aging that include harmonized annual cognitive assessments and magnetic resonance imaging brain imaging. In models adjusted for demographic factors (age, education, sex), global cognitive decline was associated with functional connectivity of the hippocampus to three clusters in the right and left frontal regions of the dorsolateral prefrontal cortex. In domain-specific analyses, decline in semantic memory was associated with functional connectivity of the hippocampus to bilateral clusters in the precentral gyrus, and decline in perceptual speed was inversely associated with connectivity of the hippocampus to the bilateral intracalcarine cortex and the right fusiform gyrus. These

findings elucidate neurobiological mechanisms underlying cognitive decline in older Black adults and may point to specific targets of intervention for Alzheimer's disease.

KEYWORDS
cognition, cognitive decline, functional connectivity, hippocampus, resting-state fMRI

1 | INTRODUCTION

There has been a proliferation of neuroimaging work over the past 30 years which has yielded numerous insights on the neurobiological mechanisms underlying cognitive decline in the context of Alzheimer's disease (AD) (see Johnson et al., 2012 for a review). However, the vast majority of neuroimaging work investigating the neurobiological correlates of cognitive decline in aging has included largely homogenous White samples (Babulal et al., 2019). Underrepresented groups at elevated risk for AD need to be a focus of study for neuroimaging research initiatives. For example, the older Black population is expected to increase rapidly over the next 30–40 years and older Black adults are at greater risk of cognitive impairment and AD dementia compared to their White counterparts. This major public health issue is best addressed by identifying neurobiological mechanisms underlying cognitive decline, yet the neurobiological pathways continue to be understudied in the older Black population, especially using neuroimaging techniques. Further, the lack of representation has the potential to threaten scientific validity as conclusions drawn from homogeneous White samples may not apply to underrepresented groups like older Black adults, due to the differing impacts of social determinants of health and contextual factors on neurobiological processes (Dotson & Duarte, 2020; Gatzke-Kopp, 2016).

Of the many neuroimaging approaches utilized to better understand cognitive decline in aging, resting-state functional magnetic resonance imaging (rsfMRI) holds significant promise. rsfMRI allows for the consideration of functional connectivity between brain regions vis-à-vis correspondence of low frequency blood oxygenation level-dependent signal fluctuations among gray matter regions (Azeez & Biswal, 2017). This approach has been successfully leveraged to better understand brain organizational changes and functional brain disconnections in the context of AD progression (Dennis & Thompson, 2014). Furthermore, functional brain changes may precede neuropathological changes in AD (Sheline et al., 2010), suggesting functional connectivity approaches may be particularly beneficial to understanding cognitive decline in the context of aging prior to dementia diagnosis. However, this approach has rarely been utilized in conjunction with longitudinal comprehensive assessments of cognition, and has suffered from a lack of representation of older Black adults (e.g., Olde Dubbelink et al., 2014; Oren et al., 2019).

Previous neuroimaging efforts have established the hippocampus as an important brain structure for cognitive decline in the context of AD (Jaroudi et al., 2017; Kantarci & Jack, 2003) in primarily White samples. Cortical reductions in the hippocampus have been associated with age-associated cognitive decline above and beyond total gray matter volume change, and the hippocampus is particularly susceptible to AD neuropathology accumulation (Blanken et al., 2017; Fjell et al., 2014; Fletcher et al., 2018). In prior work, we found cognitive decline prior to scan was associated with hippocampal morphology in nondemented older adults (Fleischman et al., 2013). However, all of this prior work was done in primarily White participant samples, and little is known about the association of neuroimaging characteristics of the hippocampus with measures of cognitive decline in older Black adults.

In this study, we extend prior work by examining the association of cognitive decline with bilateral hippocampal functional connectivity in 132 older Black adults without dementia from the Minority Aging Research Study (MARS) and the Rush Memory and Aging Project (MAP). We hypothesized that cognitive decline would be directly associated with functional connectivity of the hippocampus with frontal brain regions consistent with prior literature suggesting these links to be central to cognitive function and the progression of AD (Allen et al., 2007; Beason-Held et al., 2021; Fjell et al., 2014; Nyberg et al., 2019; Sigurdsson & Duvarci, 2016; Wang et al., 2006). Specifically, we expect that stronger functional connectivity between the hippocampus and frontal regions will be associated with slower decline, and weaker functional connectivity will be associated with faster decline. Since our measure of global cognition is a composite measure comprised of tests of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability, all of which have been linked in previous work to hippocampal functional connectivity (e.g., Eichenbaum, 2017; Horowitz-Kraus et al., 2017; Liu et al., 2021; Schwab et al., 2020; Yao et al., 2016), we also explored associations by cognitive domain. Older Black adults were a focus of this study given the dearth of functional neuroimaging work in this population, a group known to be more susceptible to AD (Mayeda et al., 2016).

2 | METHODS

2.1 | Participants

Older Black participants of the MARS (Barnes, Lewis, et al., 2012; Barnes, Shah, et al., 2012) and the Rush MAP (Bennett et al., 2012) completed annual clinical evaluations which included cognitive testing. A subset of participants completed an MRI brain scan which included structural and resting-state functional acquisitions. MARS and MAP are epidemiologic cohort studies of aging based in the greater Chicago area and are harmonized in recruitment procedures, data collection and data management through the Rush AD Center. On August 10, 2020, all 904 Black participants from MARS and MAP were identified, of whom 169 had completed a 3 T brain MRI scan at the same

study scanner resulting in an fMRI acquisition that passed internal quality control. Of these 169, 2 were excluded due to having dementia (diagnosed as described in Barnes, Lewis, et al. (2012), Barnes, Shah, et al. (2012) and Bennett et al. (2012)), yielding 167 participants. Of these 167 participants, 35 participants did not have enough data to compute cognitive slopes, leaving 132 nondemented older Black participant data sets for the current analysis.

2.2 | Cognition

Global cognition and cognitive domains were determined using a well-established battery of 18 cognitive tests measuring a broad array of abilities (Bennett et al., 2012; Wilson et al., 2003; Wilson et al., 2015). The battery included two semantic memory measures (Verbal Fluency and Boston Naming), seven episodic memory measures (Word List Memory, Word List Recall, and Word List Recognition from the procedures established by the CERAD; immediate and delayed recall of Logical Memory Story A; and immediate and delayed recall of the East Boston Story), three working memory measures (Digit Span subtests forward and backward of the Wechsler Memory Scale-Revised and Digit Ordering), 4 perceptual speed measures (oral version of the Symbol Digit Modalities Test, Number Comparison, Stroop Color Naming, Stroop Word Reading), and 2 visuospatial ability measures (Judgment of Line Orientation and Standard Progressive Matrices). As previously described (Wilson et al., 2015), scores on the tests were transformed into individual z-scores according to the mean and standard deviation of the baseline cognitive evaluation of the parent study sample. For cognitive domain scores, z-scores were averaged across all tests within a domain. For global cognition, z-scores were averaged across all tests. The slope of cognitive decline for each participant was estimated by fitting a linear mixed model to available longitudinal cognitive testing data up to the neuroimaging date, adjusted for age, sex, and years of education. The Mini-Mental Status Examination (MMSE) was also collected as a cognitive screening measure.

2.3 | Neuroimaging

MRI scans of the brain were conducted on all participants with a 3 Tesla MRI scanner. A 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence was leveraged to collect high-resolution T1-weighted anatomical data. MPRAGE scan parameters included: time to echo (TE) = 3.7 ms, time to repetition (TR) = 8 s, preparation time = 955 ms, flip-angle = 8°, field-of-view (FOV) = 24.0 cm × 22.8 cm, 181 sagittal slices, slice thickness = 1 mm, no gap, 240 × 228 acquisition matrix, parallel imaging acceleration factor of 2 along the phase encoding direction, scan time = 5 min 57.5 s. Resting-state MRI data were collected using a 2D gradient echo echo-planar imaging (EPI) sequence with the parameters: TR = 3000 ms; TE = 30 ms; flip angle = 80°; 45 axial slices; 3.3 mm slice thickness; acquisition/reconstruction matrix 64 × 59; FOV = 21.2 cm × 19.9 cm; 160 time-points/volumes; scan time = 8 min 17.9 s. Participants were instructed to keep their eyes open during the EPI scan.

Preprocessing and quality assurance of functional and structural MRI data were performed in accordance with the default pipeline implemented in the CONN Toolbox version 19.a (https://web.conn-toolbox.org/home; Whitfield-Gabrieli & Nieto-Castanon, 2012). Briefly, this included functional scan realignment, slice-timing correction, coregistration to MPRAGE, spatial normalization and smoothing according to a full-width at half-maximum isotropic Gaussian kernel filter of 8 mm. Anatomical images were segmented according to gray matter, white matter, and cerebrospinal fluid maps, and functional and structural images were normalized to Montreal Neurological Institute (MNI) space (MNI152). These steps were conducted using Statistical Parametric Mapping version 12 (SPM12) software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). As a general quality assurance procedure in our research group prior to any preprocessing, functional scans were assessed according to a head movement exclusion of more than 1.9 mm translation in any axis and less than 1.9° angular rotation around any axis over any 10-s interval. In preprocessing, functional scans were submitted to artifact and motion outlier identification using the Artifact Detection Toolbox (https://www.nitrc.org/projects/artifact_detect/) according to conservative settings (95th percentile of normative sample). These settings identified time points as outliers if the global mean signal intensity exceeded three standard deviations or if movement from a preceding image exceeded a 0.5 mm deviation. These time points were included as regressors along with principal components delineated from anatomical noise regions (five components for white matter, five components for cerebrospinal fluid) and realignment parameters with derivatives during a denoising step in the CONN toolbox pipeline. Finally, a band-pass filter of 0.008–0.09 Hz was fitted to the functional MRI data.

2.4 | Statistical analysis

As implemented in the CONN Toolbox, anatomically derived regions of interest (ROIs) were defined according to the Harvard-Oxford Brain Atlas (Whitfield-Gabrieli & Nieto-Castanon, 2012). In the present study, these included the left and right hippocampus (two ROIs total), which were then averaged (hereto forward referred to as "averaged ROI") to maintain consistency with the approach utilized in prior work (Fleischman et al., 2013). A mean signal time course for the averaged ROI was calculated, and analyses were conducted by examining the correlations between the averaged ROI signal time course and the time series of every other voxel in the brain. The voxels showing significant functional connectivity to the averaged ROI were identified as those whose correlation differed significantly from 0 based on Fisher's z-transformation of the correlation. In order to delineate clusters of voxels significantly connected to the averaged ROI, Gaussian random field theory was implemented and two thresholds were consecutively applied. The first threshold was on individual voxels (p-value < .001), and the next threshold was on individual clusters (corrected for multiple comparisons according to a false discovery rate p-value < .05). A two-tailed test was selected as we a priori believed cognitive level and rates of cognitive decline could be associated with differences in functional connectivity of the ROIs in either direction

TABLE 1 Demographic and cognitive descriptive data

Sample ($n = 132$)	Mean or percent (standard deviation)	Baseline z-score at scan (standard deviation)	Slope rate of change (standard deviation)
Age (years)	75.92 (6.23)		
Education (years)	15.61 (3.77)		
Sex (% female)	81.1%		
MMSE	28.20 (1.75)		
Global cognition		0.136 (0.525)	−0.020 (0.048)
Semantic memory		0.119 (0.645)	−0.059 (0.061)
Episodic memory		0.277 (0.602)	−0.007 (0.028)
Working memory		−0.003 (0.738)	0.015 (0.023)
Perceptual speed		0.109 (0.732)	−0.055 (0.038)
Visuospatial ability		−0.075 (0.815)	−0.008 (0.009)

Abbreviation: MMSE, Mini-Mental Status Examination.

(strengthening or weakening). Next, baseline cognition and rates of cognitive decline were regressed upon results separately, while controlling for age, education, and sex. Since a different field mapping technique was utilized on some of the scans, field mapping technique was coded and also included as a fourth covariate in functional connectivity regression models. Functional connectivity regression models were conducted using the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012).

3 | RESULTS

3.1 | Descriptive data

Descriptive data are presented in Table 1. The mean age of the participants was approximately 76 years old with a standard deviation of 6.23. The mean number of years of education was more than 15, indicating the participants had achieved, on average, a schooling education beyond high school. The standard deviation of years of education was 3.77. Participants were predominantly female (81%). As would be expected for participants without dementia, the average MMSE score was 28.

3.2 | Functional connectivity of the averaged hippocampus

Results of the voxel-wise whole-brain functional connectivity analyses to the averaged hippocampus for global cognition and cognitive domains at baseline are shown in Figure 1. Results for the slopes of global cognition and cognitive domains are shown in Figure 2. Details on significant clusters for both the cognitive baseline and slope variables are presented together in Table 2.

We first examined associations with cognitive variables at time of scan, or analytic baseline of this study. When considering cognitive variables at baseline and adjusting for covariates, whole-brain functional connectivity analyses to the averaged hippocampus revealed one significant cluster for global cognition primarily in the left frontal pole/middle frontal gyrus (963 voxels in cluster, $t = 4.88$, $p < .001$, peak voxel $x = -34$, $y = 30$, $z = 52$). When considering semantic memory at time of scan, two clusters were significant. One was in the left frontal pole/middle frontal gyrus (1339 voxels in cluster, $t = 5.09$, $p < .001$, peak voxel $x = -40$, $y = 12$, $z = 48$) and the other was in the right frontal pole (246 voxels in cluster, $t = 4.52$, $p = .048$, peak voxel $x = 22$, $y = 24$, $z = 32$). When considering episodic memory at baseline, one cluster was significant in the left frontal pole/middle frontal gyrus (1578 voxels in cluster, $t = 5.01$, $p < .001$, peak voxel $x = -34$, $y = 28$, $z = 50$). All clusters can be interpreted as within the dorsolateral prefrontal regions and were positively correlated with the averaged hippocampus. To be more specific, greater functional connectivity was associated with higher cognitive scores. No significant clusters were observed for working memory, perceptual speed, or visuospatial ability at baseline.

When considering the slope of cognitive variables (cognitive decline) and adjusting for covariates, whole-brain functional connectivity to the averaged hippocampus revealed three significant clusters for global cognition. The first cluster was in the right frontal pole/middle frontal gyrus (652 voxels in cluster, $t = 4.54$, $p < .001$, peak voxel $x = 22$, $y = 38$, $z = 48$), the second cluster was in the left middle frontal gyrus (384 voxels in cluster, $t = 4.73$, $p = .009$, peak voxel $x = -28$, $y = 24$, $z = 38$), and the third was in the left frontal pole (276 voxels in cluster, $t = 4.19$, $p = .026$, peak voxel $x = -10$, $y = 42$, $z = 30$). These three clusters can be interpreted as within the dorsolateral prefrontal regions. When considering semantic memory slope, two clusters were significant. One cluster was in the left precentral gyrus (430 voxels in cluster, $t = 4.45$, $p = .005$, peak voxel $x = -12$, $y = -16$, $z = 54$) and the second cluster was in the right precentral gyrus (389 voxels in cluster, $t = 4.35$, $p = .005$, peak voxel $x = 16$, $y = -30$, $z = 62$). When considering perceptual speed slope, two clusters were significant. One cluster was in the bilateral intracalcarine cortex (593 voxels in cluster, $t = -4.28$, $p < .001$, peak voxel $x = 6$, $y = -82$, $z = 8$) and the second was in the right fusiform gyrus (271 voxels in cluster, $t = -4.29$, $p = .021$, peak voxel $x = 22$, $y = -72$, $z = -14$). The clusters for global cognition and semantic

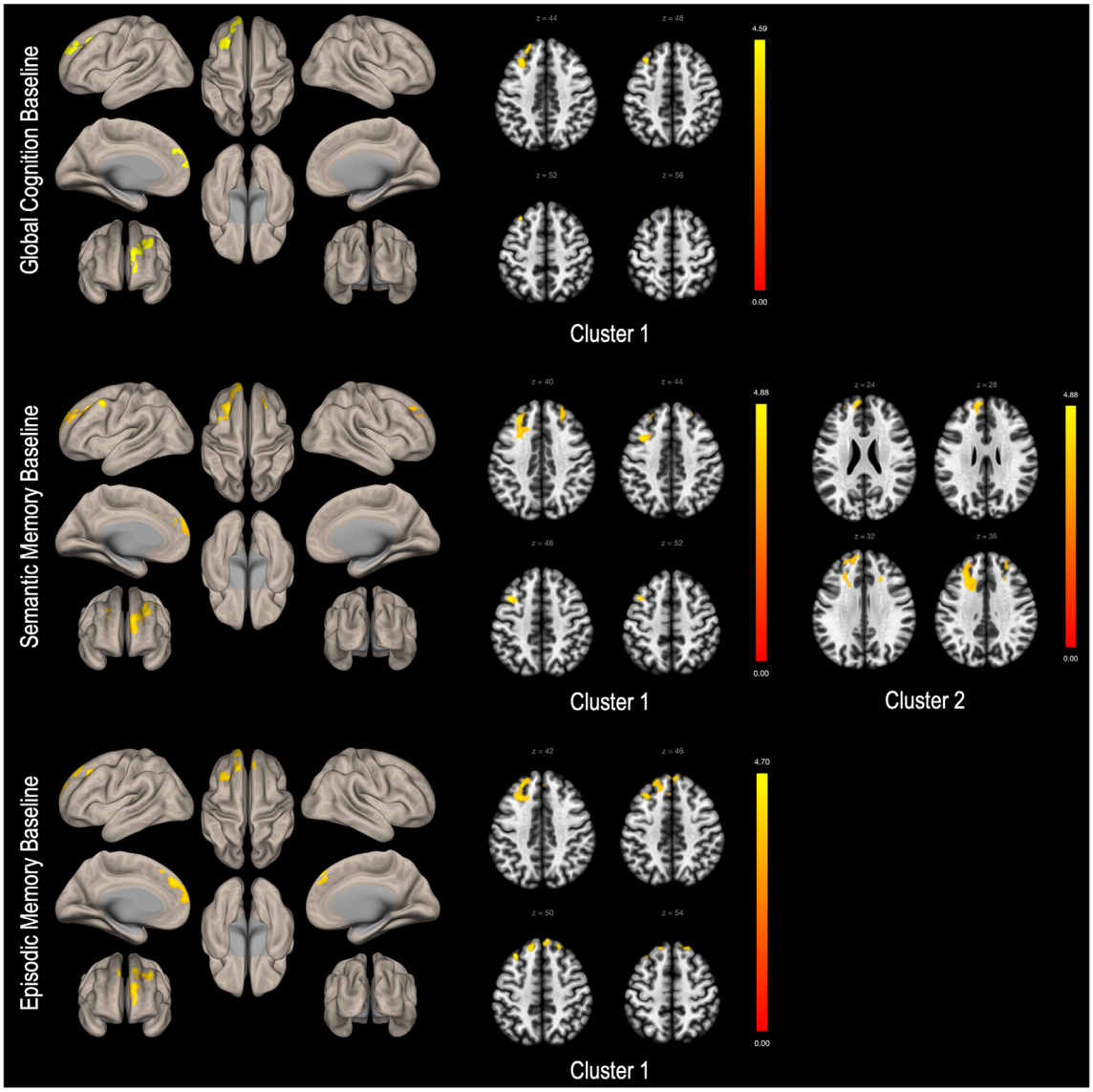

FIGURE 1 Whole-brain voxel-wise functional connectivity to the averaged hippocampus defined by the Harvard-Oxford Brain Atlas for cognition variables at analytic baseline (at time of scan). All significant clusters are visually presented on a standard smoothed brain, neurologic orientation. Then, each cluster is visually presented in four axial slices.

memory slopes were positively associated with the averaged hippocampus. To be more specific, greater functional connectivity was associated with less cognitive decline. The clusters for the perceptual speed slope were negatively associated with the averaged hippocampus. That is, greater functional connectivity was associated with more cognitive decline. No significant clusters were observed for working memory, visuospatial ability, or episodic memory slopes.

4 | DISCUSSION

We investigated functional connectivity associations of the bilateral hippocampus to the whole brain with measures of cognition at scan and cognitive decline in a large cohort of older Black adults without dementia. Our findings suggest that functional connectivity of the hippocampus to multiple dorsolateral prefrontal regions correlates with global cognitive decline in persons without dementia. When considering declines in cognitive domains, semantic memory decline was positively associated with functional connectivity of the hippocampus to the left and right precentral gyrus, and perceptual speed decline was associated inversely with functional connectivity of the hippocampus to the bilateral intracalcarine cortex and the right fusiform gyrus. To our knowledge, this is the first functional brain connectivity study of cognitive decline in older Black adults.

Our results suggest functional connectivity between the hippocampus and dorsolateral prefrontal cortex is an important mechanism underlying cognitive decline in the context of aging, similar to what has been demonstrated in studies comprised of mostly older White adults. To be more specific, stronger functional connectivity between the hippocampus and dorsolateral prefrontal cortex is associated with slower decline, and weaker functional connectivity is associated with faster decline. As stated, the importance of hippocampal–dorsolateral

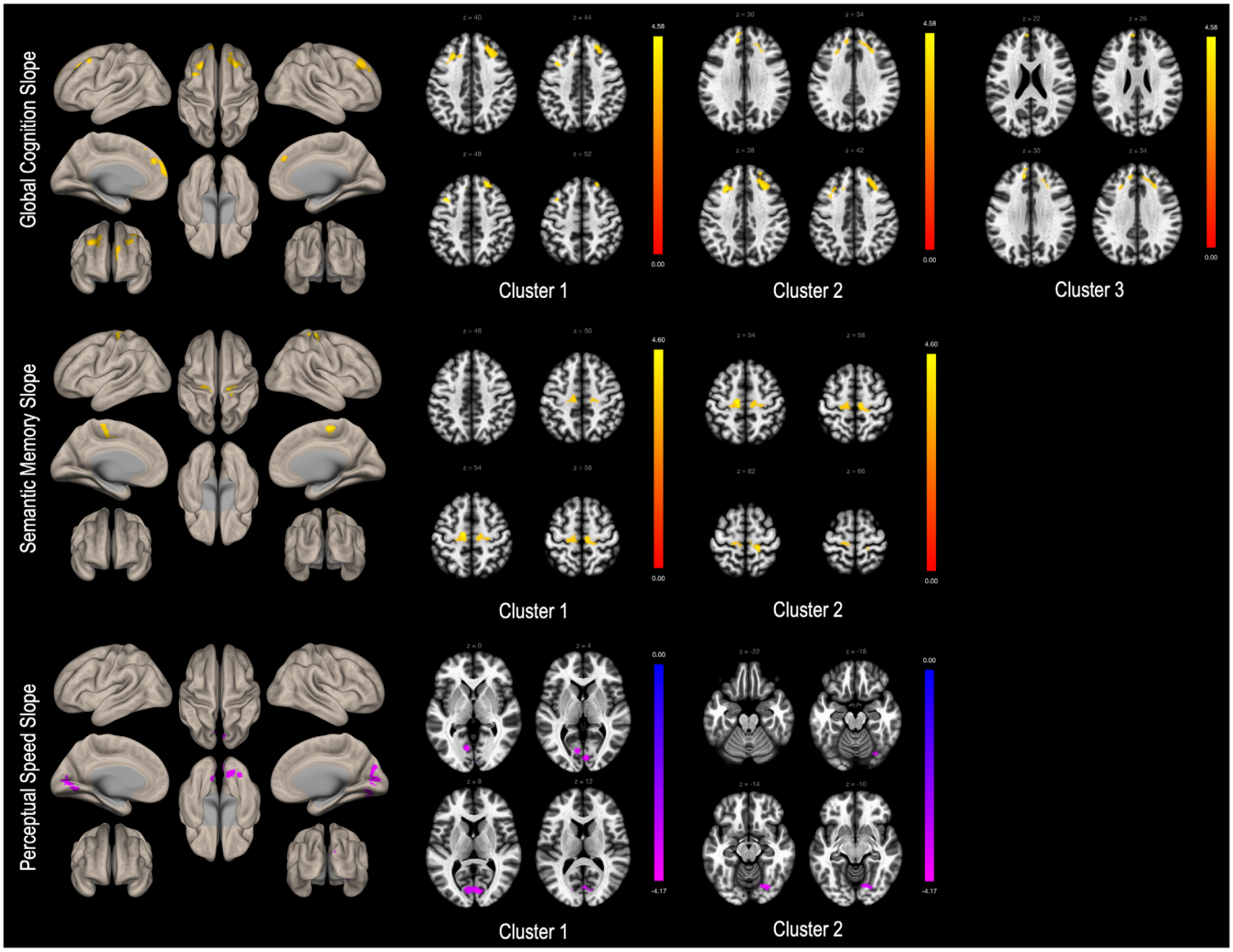

FIGURE 2 Whole-brain voxel-wise functional connectivity to the averaged hippocampus defined by the Harvard-Oxford Brain Atlas for slope rate of change in cognition variables. All significant clusters are visually presented on a standard smoothed brain, neurologic orientation. Then, each cluster is visually presented in four axial slices.

prefrontal connectivity for cognition has been recognized in other work utilizing different methods with White adults (Allen et al., 2007; Beason-Held et al., 2021; Nyberg et al., 2019; Sigurdsson & Duvarci, 2016; Wang et al., 2006). For example, Nyberg et al. (2019) observed aberrant functional connectivity between the hippocampus and prefrontal cortex among older adults who dropped out of a longitudinal memory and neuroimaging study versus older and younger adults who stayed in the study (dropping out was considered a proxy of pathological aging by the study authors). To our knowledge, our study is the first brain functional connectivity study to show the importance of hippocampal–prefrontal connections for cognitive decline in older Black adults. This is significant because older Black adults are at greater risk for AD, and the replication of findings among this population not only demonstrates generalizability of the findings from White populations, but strengthens the importance of this pathway for documenting disease progression and assessing the efficacy of potential cognitive interventions.

Decline in semantic memory was associated with functional connectivity of the hippocampus with bilateral precentral gyrus regions. Given the known functions of the precentral gyrus in voluntary motor movement, the significance of this finding is unclear. However, the semantic memory domain consists of verbal fluency and naming measures, and previous neuroimaging work has noted an association between precentral gyrus activation and these tasks (Halari et al., 2006; Kiyosawa et al., 1996). Decline in perceptual speed was associated inversely with functional connectivity of the hippocampus with two regions, the bilateral intracalcarine cortex and the right fusiform gyrus. Since both regions are involved in visual perception (Grill-Spector & Malach, 2004), greater connectivity between the hippocampus and these regions may signal a compensatory response to decline in perceptual speed ability. Age-related compensatory mechanisms have been noted in neuroimaging research whereby greater activity of functionally connected brain regions may occur in order to compensate for declining functions (Han et al., 2009). Finally, it is notable that we did not observe any associations with episodic memory decline, but did observe associations with episodic memory at baseline. The reasons for this are unclear, though it should be noted that in recent work applying deformation-based brain morphometry

TABLE 2 Significant clusters identified in functional connectivity analyses

Cognition variable	Cluster #	Location (x, y, z)	Total # voxels in cluster	Brain regions implicated by cluster	# voxels in specific region	*t*-Value	Size *p*-value FDR	Size *p*-value FWE
Baseline (at scan)								
Global cognition	1	−34, 30, 52	963	Frontal pole left	425	4.88	.000036	.000016
				Middle frontal gyrus left	313			
				Superior frontal gyrus left	44			
				Paracingulate gyrus left	3			
				Not labeled	178			
Semantic Memory	1	−40, 12, 48	1339	Frontal pole left	483	5.09	.000001	.000001
				Middle frontal gyrus left	389			
				Superior frontal gyrus left	57			
				Paracingulate gyrus left	7			
				Not labeled	403			
	2	22, 24, 32	246	Frontal pole right	149	4.52	.047715	.047434
				Middle frontal gyrus right	15			
				Superior frontal gyrus right	13			
				Not labeled	69			
Episodic memory	1	−34, 28, 50	1578	Frontal pole left	423	5.01	<.000001	<.000001
				Middle frontal gyrus left	251			
				Superior frontal gyrus left	242			
				Frontal pole right	108			
				Superior frontal gyrus right	107			
				Paracingulate gyrus left	75			
				Paracingulate gyrus right	28			
				Not labeled	344			
Slope rate of change								
Global cognition	1	22, 38, 48	652	Frontal pole right	217	4.54	.000873	.000358
				Middle frontal gyrus right	189			
				Superior frontal gyrus right	80			
				Paracingulate gyrus right	11			
				Not labeled	155			
	2	−28, 24, 38	384	Middle frontal gyrus left	261	4.73	.009344	.007627
				Superior frontal gyrus left	33			
				Not labeled	90			
	3	−10, 42, 30	276	Frontal pole left	110	4.19	.026039	.031497
				Superior frontal gyrus left	50			
				Paracingulate gyrus left	12			
				Not labeled	104			
Semantic memory	1	−12, −16, 54	430	Precentral gyrus left	154	4.45	.005047	.004321
				Postcentral gyrus left	2			
				Supplementary motor cortex left	2			
				Not labeled	272			
	2	16, −30, 62	389	Precentral gyrus right	175	4.35	.005047	.007146
				Postcentral gyrus right	56			
				Not labeled	158			

TABLE 2 (Continued)

Cognition variable	Cluster #	Location (x, y, z)	Total # voxels in cluster	Brain regions implicated by cluster	# voxels in specific region	*t*-Value	Size *p*-value FDR	Size *p*-value FWE
Perceptual speed	1	6, −82, 8	593	Intracalcarine cortex right	154	−4.28	.000804	.00066
				Intracalcarine cortex left	140			
				Lingual gyrus left	108			
				Cuneal cortex right	71			
				Supracalcarine cortex right	37			
				Occipital pole right	12			
				Lingual gyrus right	1			
				Not labeled	70			
	2	22, −72, −14	271	Occipital fusiform gyrus right	166	−4.29	.020694	.033444
				Lingual gyrus right	94			
				Cerebellum 6 right	11			

Abbreviation: FDR, false discovery rate.

to cognitive level and decline in older Black adults without dementia from our group, the same pattern emerged (Fleischman et al., 2022). Our study therefore extends the notion that neuroimaging characteristics of the hippocampus may not be as useful for predicting rate of episodic memory decline in older Black adults.

The study has limitations. The participants in this study may not represent the diversity of older Black adults within the general community. Studies of older Black adults with a wider distribution of age, education, and sex beyond an urban region in the Midwest are needed to replicate these findings. We have not considered a broad range of social determinants of health or other contextual factors beyond demographics. Finally, the exclusion of older adults with dementia may be considered a limitation. We chose to focus on older Black adults without dementia until enough persons across the spectrum of cognition, including those with AD dementia, have been imaged to study fMRI correlates of this transition.

The present study has many notable strengths. While previous rsfMRI literature has illuminated network and brain region functional connectivity deterioration patterns in the context of AD (Dennis & Thompson, 2014), our study makes a unique contribution to the literature by leveraging annual comprehensive cognitive assessments to determine individual rates of cognitive decline in a large cohort of older Black adults without dementia. Our results suggest specific functional pathways between the hippocampus and multiple brain regions that might be targets for clinical and therapeutic interventions aimed at reduction of cognitive decline and delay or prevention of AD dementia in older Black adults.

ACKNOWLEDGMENTS

This work was supported by the National Institute on Aging at the National Institutes of Health grants RF1AG022018 and R01AG056405 to LLB, P30AG010161 and R01AG017917 to DAB, UF1NS100599 to KA, and R01AG055430 to SDH. The authors gratefully thank the Minority Aging Research Study and Rush Memory and Aging Project staff and participants.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data in this study are publicly available through a data repository and can be requested at https://www.radc.rush.edu.

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How to cite this article: Han, S. D., Fleischman, D. A., Yu, L., Poole, V., Lamar, M., Kim, N., Leurgans, S. E., Bennett, D. A., Arfanakis, K., & Barnes, L. L. (2022). Cognitive decline and hippocampal functional connectivity within older Black adults. *Human Brain Mapping*, *43*(16), 5044–5052. https://doi.org/10.1002/hbm.26070