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ORIGINAL ARTICLE

Influence of mild cognitive impairment and body mass index on white matter integrity assessed by diffusion tensor imaging

Emma M. Tinney[1,2] | **Psyche Loui**[1,2] | **Lauren B. Raine**[2,3,4] | **Lucy V. Hiscox**[5] | **Peyton L. Delgorio**[5] | **Mary K. Kramer**[5] | **Hillary Schwarb**[6] | **Christopher R. Martens**[7] | **Arthur F. Kramer**[1,6] | **Charles H. Hillman**[1,2,3] | **Curtis L. Johnson**[5]

[1]Department of Psychology, Northeastern University, Boston, Massachusetts, USA

[2]Center for Cognitive and Brain Health, Northeastern University, Boston, Massachusetts, USA

[3]Department of Physical Therapy Movement Rehabilitation Sciences, Northeastern University, Boston, Massachusetts, USA

[4]Department of Medicinal Sciences, Northeastern University, Boston, Massachusetts, USA

[5]Department of Biomedical Engineering, University of Delaware, Newark, Delaware, USA

[6]Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Champaign, Illinois, USA

[7]Department of Kinesiology and Applied Physiology, University of Delaware, Newark, Delaware, USA

Correspondence
Emma M. Tinney, Department of Psychology, Northeastern University, 125 NI, 360 Huntington Ave, Boston, MA 02115, USA.
Email: tinney.e@northeastern.edu

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Abstract

Mild cognitive impairment (MCI), a prodromal stage of Alzheimer's disease, is characterized by decreased memory and cognition, which are linked to degenerative changes in the brain. To assess whether white matter (WM) integrity is compromised in MCI, we collected diffusion-weighted images from 60 healthy older adults (OA) (69.16 ± 0.7) and 20 older adults with amnestic MCI (72.45 ± 1.9). WM integrity differences were examined using Tract-Based Spatial Statistics (TBSS). We hypothesized that those with MCI would have diminished WM integrity relative to OA. In a whole-brain comparison, those with MCI showed higher axial diffusivity in the splenium (SCC) and body of the corpus callosum (BCC), superior corona radiata (SCR), and the retrolenticular part of the internal capsule (RLIC) (p's $< .05$ TFCE-corrected). Additionally, significant between-group connectivity differences were observed using probabilistic tractography between the SCC, chosen from the TBSS results, and forceps major and minor (p-value's $< .05$). To further relate a physical health indicator to WM alterations, linear regression showed significant interactions between cognitive status and body mass index (BMI) on diffusivity outcome measures from probabilistic tractography (p-value's $< .05$). Additionally, we examined the association between relational memory, BMI, and WM integrity. WM integrity was positively associated with relational memory performance. These findings suggest that these regions may be more sensitive to early markers of neurodegenerative disease and health behaviors, suggesting that modifiable lifestyle factors may affect white matter integrity.

KEYWORDS

aging, body mass index, diffusion tensor imaging, mild cognitive impairment, relational memory, white matter integrity

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1 | INTRODUCTION

Mild cognitive impairment (MCI) refers to the earliest symptomatic stage on the cognitive decline spectrum between normal aging and clinical dementia (Dubois et al., 2010). Those with MCI experience cognitive decline, which is reflected in memory loss, language difficulties, and visuospatial perception problems, but these impairments are typically not severe enough to require daily life assistance and meet the criteria for dementia. Approximately 32% of people with MCI ultimately progress toward the development of severe dementia-related diseases (Murman, 2015). The MCI stage is of particular interest in the cognitive decline process because it is a phase in which both pharmaceutical and lifestyle interventions are potentially more likely to be effective in slowing or even preventing the progression to dementia (Li et al., 2018). Intervening earlier in the MCI process may be beneficial by capitalizing on the relatively subtle impairments at this point in the neurodegenerative process.

Interventions that engage specific lifestyle and health behaviors may be fundamental in slowing, arresting, or reversing the cognitive decline observed in those with MCI. Maintaining an active lifestyle that includes regular physical activity (Benedict et al., 2013; Kramer & Colcombe, 2018) and sufficient cardiorespiratory fitness (Hillman et al., 2008) has been associated with increased structural and functional brain health as well as greater cognitive function across the lifespan. Body mass index (BMI) is another measurable and modifiable health factor that estimates body composition based on height and weight. Previous research has shown that overweight or obesity in midlife is associated with maladaptive brain changes (Gustafson, 2008) and cognitive decline later in life (Whitmer et al., 2005), while a healthier BMI has been related to better brain integrity and behavioral outcomes (Yan et al., 2004). Healthy lifestyle behaviors are quite valuable, particularly in the context of aging and dementia, as they have been found to be protective of age-related and pathological brain changes (Stern et al., 2020). As such, modifying health behaviors in individuals at risk for dementia could be crucial toward decreasing the possibility of experiencing more severe deficits.

Previous neuroimaging studies have shown that BMI is negatively associated with brain volume in older adults, particularly in gray matter regions (Colcombe et al., 2006; Erickson et al., 2014; Gunstad et al., 2008; Ward et al., 2005; West et al., 2020). However, research involving the associations between these lifestyle factors and integrity of white matter (WM), which is known to also undergo change during aging and dementia, is limited. WM consists primarily of bundles of myelinated axons, the integrity of which support efficient cognitive processing. WM integrity can be measured noninvasively using diffusion-based magnetic resonance imaging (MRI) measures, most commonly diffusion tensor imaging (DTI). DTI works to quantify cellular structure by measuring the diffusion of water molecules. Specifically, DTI provides four common metrics to identify diffusion, fractional anisotropy (FA), axial diffusivity (AxD), radial diffusivity (RD), and mean diffusivity (MD). MD and FA quantify the random translation motion of water molecules. They are seen to reflect various pathological states (Kanaan et al., 2006). AxD measures the diffusion coefficient along the direction of the maximum diffusivity, reflecting changes in barriers along that direction (Basser et al., 2000; le Bihan, 2003). RD measures the diffusion coefficient perpendicular to the direction of maximum diffusivity, reflecting changes in the axonal membrane and myelin sheath (Song et al., 2005). Previous work has investigated the relationship between BMI and WM integrity in middle-aged adults, reporting decreases in FA in the corpus callosum and fornix associated with increased BMI (Kullmann et al., 2015, 2016; Papageorgiou et al., 2017; Stanek et al., 2011; Xu et al., 2013); however, few studies examine other metrics of white matter integrity such as axial and radial diffusivity. In addition, these studies tend to focus specifically on obesity (Kullmann et al., 2015, 2016; Papageorgiou et al., 2017; Stanek et al., 2011) instead of examining a relatively normal BMI population. Lastly, these studies examine this relationship in middle-aged adults, demonstrating need for studies in older adults.

Increased BMI has been shown to negatively affect cognition across the lifespan with studies showing that being overweight or obese in midlife may be more detrimental to subsequent age-related cognitive decline (Bischof & Park, 2015) as well as adiposity being negatively associated with relational memory in children (Khan et al., 2015). However, there is limited research on this relationship in older adults. Relational memory is the ability to remember arbitrary or indirect associations between objects, places, people or events, directly impacting quality of life. Studies have shown associations between relational memory and WM integrity in older adults; however, there are many mixed results throughout the literature (Charlton et al., 2010; Rizio & Diaz, 2016). By examining the corpus callosum, we can gather information about the white matter tracts that allow information to pass across the brain to enable relational memory (Rubin et al., 2017). The present study can refine our understanding of the neural substrates of relational memory by investigating diffusivity measures in its associated regions.

Accordingly, the primary aim of this study was to assess differences in WM integrity between older adults with and without MCI using DTI, with the goal of providing insight into which WM tracts are particularly affected

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among older adults, as well as the mechanisms underlying the influence of health metric on the integrity of these tracts, and their influence on cognition. Based on previous evidence, the most prominent group differences were expected in the corpus callosum (Douaud et al., 2011), the superior longitudinal fasciculus (Douaud et al., 2011), the forceps minor (Bartzokis, 2011), and the retrolenticular part of the internal capsule (Shim et al., 2017). The secondary aim of this study was to understand the role of specific health markers in this relationship. Specifically, BMI was expected to correlate with diffusion metrics, in support of previous voxel-based morphometry investigations (Makizako et al., 2013), with normal BMI benefiting WM integrity. The last aim of this study was to investigate the relationship between relational memory and white matter using a spatial reconstruction task. Such findings stand to benefit public health by providing novel information regarding the relationship of health factors for cognition and brain health in older adults.

2 | METHOD

2.1 | Participants

Table 1 provides the behavioral and neuroimaging data from the present sample, which were collected as a part of a larger, ongoing study; data from this sample have been reported previously (Delgorio et al., 2022). Participants were recruited through the Delaware Center for Cognitive Aging Research using flyers, advertisements, and direct mailings targeting individuals with memory complaints. Interested participants underwent an interview to determine their eligibility for the study (i.e., age, health, ability to undergo MRI, etc.). To screen for MCI, a modified telephone interview for cognitive status (TICS-m)(Cook et al., 2009) was administered via phone. If the individual scored within a range that was considered a high likelihood for amnestic MCI (TICS-m between 21 and 34, or delayed recall subscore of 10 or less), they were invited to the lab with a study partner for additional screening. Participants completed an objective battery of cognitive tests including the mini-mental state exam (MMSE), the Hopkin's verbal learning test (HVLT-R), and either the brief visuospatial memory test (BVMT) or the logical memory test from the Wechsler memory scale (WMS-R) while their study partner completed an interview to determine the Clinical Dementia Rating (CDR). Participants were included in the MCI group if they produced at least one score on an objective memory test that was ≤1.5 standard deviations below an age-matched normative sample on any of the tests (HVLT-R, BVMT, or logical memory), while also scoring greater than 21 on the MMSE and having a Clinical Dementia Rating less than 1 from an informant interview, indicating that there are cognitive impairments but not dementia. These cutoffs were based on the "Peterson Criteria" and in line with the 2011 NIA_AA workgroup criteria (Albert et al., 2011). All participants provided written, informed consent to participate in this study approved by the University of Delaware Institutional Review Board.

TABLE 1 Demographic information of participants.

Characteristics, mean ± SD	OA ($n = 60$, $f = 33$)	MCI ($n = 20$, $f = 13$)	t-tests
Age (years)	69.9 ± 5.3	72.5 ± 8.6	$p = .04$
BMI (kg/m^2)	27.8 ± 4.8	25.5 ± 5.9	$p = .08$
BMI group[a]	0, 27, 16, 17	3, 7, 6, 4	
SES[b]	16.7 ± 2.2	14.2 ± 2.3	$p < .01$
SRT misplacement[c]	235.2 ± 68	296.9 ± 91	$p < .01$
SRT accuracy[d]	2.51 ± .61	2.02 ± .91	$p = .03$

[a]BMI group = number of participants underweight, normal weight, overweight, obese.

[b]SES = socioeconomic status, determined by years of education.

[c]Score from SRT, higher score is indicative of worse relational memory performance.

[d]Score from SRT, higher score is indicative of better relational memory performance.

2.2 | Procedures

2.2.1 | Body composition assessment

Standing height and weight measurements were completed with participants wearing no shoes and lightweight clothing. Height and weight were measured with a digital scale (Health o meter professional scale, McCook, IL USA). Body mass index (BMI) was calculated by dividing body mass (kg) by height (m) squared (kg/m^2).

2.2.2 | Cognitive assessment

All subjects underwent a battery of neuropsychological assessments, testing a range of cognitive domains. In this current analysis, relational memory was the primary focus and was assessed using a spatial reconstruction task (SRT) (Horecka et al., 2018; Schwarb et al., 2016; Watson et al., 2013). On each trial, participants studied the locations of five novel line drawings for 20 s. After a 4-s blank delay period, the line drawings appeared again aligned at the top of the screen, and participants used the mouse to drag each drawing back to its original location. Performance on this task was analyzed according to the

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metrics outlined by Horecka et al. (2018). Overall accuracy and misplacement were reported as they are the purest measure of relational memory. Accuracy was computed by determining whether a given line drawing was placed back in its studied location. Accuracy was reported as the number of line drawings placed in their correct location, so the maximum was five on each trial. Misplacement was measured as the distance between the location where a line drawing was placed at reconstruction and the location in which it was studied, calculated in pixels.

2.2.3 | Magnetic resonance imaging acquisition

Imaging data were acquired using a Siemens 3T Prisma scanner and a 64-channel head RF-receive coil (Siemens Medical Solutions; Erangen, Germany). Participants underwent a 0.9-mm^3 T_1-weighted magnetization prepared rapid gradient echo (MPRAGE) scan. The diffusion tensor imaging protocol included a multiband-accelerated, single-shot echo-planer imaging sequence at a $1.5\times1.5\times1.5$ mm resolution and 138 encoding directions in shells of $b=1500$ and 3000 s/mm^2. Imaging parameters included: repetition time (TR) = 3520 ms, echo time (TE) = 95.2 ms, flip angle = 78°, field of view = 210×210 mm^2, 92 slices with 1.5 mm slice thickness.

2.3 | Diffusion data analysis

Imaging analyses were performed using FSL 6.0 (FMRIB Software Library). The preprocessing of each participant's data included motion and eddy current correction and removal of non-brain tissue using Brain Extraction Tool (Smith, 2002). Field inhomogeneities were corrected using TOPUP (Andersson et al., 2003) and the tensor model was fitted at each voxel with DTIFIT tools in FSL. ANTS was used to co-register the anatomical T1 scan; the inverse transform was then calculated to ensure values were measured within native space. These steps produced fractional anisotropy (FA) maps from the first, second, and third eigenvalues (λ_1, λ_2, and λ_3). FA ranges from 0 to 1, with higher values representing increased directionality of diffusion. Higher FA represents water traveling more parallel to a tract than perpendicular. Eigenvalues were also used to produce axial diffusivity (AxD), mean diffusivity (MD), and radial diffusivity (RD) images. AxD is the diffusion along the first diffusion eigenvalue (λ_1) of the diffusion tensor. MD is an average of all the eigenvalues, $(\lambda_1+\lambda_2+\lambda_3)/3$. RD is the average of the second and third eigenvalue, $(\lambda_2+\lambda_3)/2$. This is reflective of diffusivity perpendicular to the major axis of the tensor (Baser, 1995; Song et al., 2002).

Once these images were acquired, tract-based diffusion maps were defined using TBSSv1.2 (Tract-Based Spatial Statistics) (Smith et al., 2006). Each participant's FA map was aligned into the $1\,mm\times1\,mm\times1\,mm$ standard Montreal Neurological Institute (MNI152) using the FMRIb58 template with FSL's nonlinear registration tool (Andersson et al., 2007), creating a mean FA image. This image was thinned to make an average skeleton of WM tracts shared by all participants. Values for each individual participant was obtained using the FA mean skeleton aligned with each participants FA data. The data of each participant were projected onto the skeleton to obtain FA values. AxD, MD, and RD values were obtained in a similar fashion. The AxD, MD, and RD maps of each participant were projected onto the mean skeleton.

Regions of interest (ROI) were created for the significant WM tracts obtained from the comparison between the OA and MCI mean AxD skeleton. The tracts were hand drawn using the JHU ICBM-DTI-81 WM labels atlas (Mori et al., 2008) as an outline. The ROIs created were the splenium (SCC) and body of the corpus callosum (BCC), superior corona radiata (SCR), and the retrolenticular part of the internal capsule (RLIC). AxD values were calculated for each participant within each ROI in native space.

We performed probabilistic tractography to allow for a subsequent, in-depth analysis providing sensitivity for tract profiling. It was used to identify connections between the body of the corpus callosum to forceps major and minor. BedpostX was used to estimate probability distributions for fiber orientations in each voxel (Behrens et al., 2007). Next, PROBTRACKX (Behrens et al., 2007), a probabilistic Bayesian framework, was used to delineate tracts between regions. PROBTRACKX was run with 5000 samples per voxel, step size of 0.5, and curvature threshold of 0.2. Values were then extracted for FA, AxD, MD, and RD and use to compare WM integrity between groups and with cognitive and health outcomes (Table 2).

2.4 | Statistical analyses

Age, sex, and socioeconomic status (SES; using highest education level as a metric) were used as potential confounding variables in this analysis. Variables which predicted the outcome measure with a $p\leq.05$ were defined as confounders and added to the final model. Our primary neuroimaging hypothesis was that patients with MCI would have diminished WM integrity in regions determined by the mean skeleton comparison. Simple two sample *t*-tests were performed to determine differences between groups in WM integrity. These were further assessed using a multivariate ANOVA with AxD of the splenium and body of the corpus callosum, superior corona radiata, and retrolenticular part of the

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TABLE 2 Mean and standard error of diffusion measure.

Diffusion measure, mean ± SD	OA	MCI	*t*-tests
AxD BCC	4.8e−4 ± 4.0e−6	4.9e−4 ± 6.3e−6	$p = .04$
AxD SCC	6.2e−4 ± 4.6e−6	6.4e−4 ± 8.3e−6	$p = .02$
AxD SCR	6.5e−4 ± 5.8e−6	6.8e−4 ± 9.1e−6	$p = .01$
AxD RLIC	8.1e−4 ± 6.1e−6	8.3e−4 ± 1.0e−5	$p = .03$
AxD forceps major	8.3e−4 ± 4.8e−6	8.3e−4 ± 9.9e−6	$p = .98$
AxD forceps minor	8.1e−4 ± 5.7e−6	7.9e−4 ± 1.1e−5	$p = .35$
FA forceps major	0.57 ± .01	0.53 ± .02	$p = .01$
FA forceps minor	0.56 ± .01	0.51 ± .02	$p < .01$
MD forceps major	4.8e−4 ± 3.2e−6	4.7e−4 ± 4.8e−6	$p = .01$
MD forceps minor	4.7e−4 ± 4.8e−6	4.9e−4 ± 8.7e−6	$p = .02$
RD forceps major	3.1e−4 ± 3.9e−6	3.3e−4 ± 1.4e−5	$p = .01$
RD forceps minor	3.1e−4 ± 4.7e−6	3.4e−4 ± 1.5e−5	$p = .03$

internal capsule, as dependent variables, group (OA or MCI) as a fixed variable, with age, sex, and SES as covariates.

Furthermore, lower BMI and higher relational memory scores were hypothesized to correlate with greater WM integrity. This was assessed using linear regressions with diffusion metrics as dependent variables then adding BMI or relational memory as independent variables to the model, with age, sex, and SES as covariates only in the healthy older adult group. The relationship between BMI and DTI metrics in regions found to significantly differ between groups was examined using stepwise linear regressions. Demographic variables that were significantly correlated with each brain outcome were included in Step 1 and BMI was added in Step 2. Significant regressions ($p < .05$) are reported below in detail below with all significant and nonsignificant regressions reported in Table 3.

Next, we examined the relationship between BMI and relational memory with WM regions that showed differences between OA and MCI. Each region was analyzed to determine how BMI and relational memory predict WM tissue integrity in each of these regions observed to be affected in MCI. We examined this in the OA group, as that group had a sufficiently large sample size to power this analysis. Age was included as a covariate in all linear regression models preformed, as it was the only covariate that correlated with brain measures.

3 | RESULTS

3.1 | Participant demographics

Demographic, body composition, and cognitive data are provided in Table 1. Group differences occurred in age and SES, which were accounted for in subsequent models, when appropriate.

3.2 | White matter integrity

Whole brain comparison between OA and MCI groups using TBSS indicated significant voxels at the $p < .05$ TFCE-corrected level. Several clusters were found to have significantly higher AxD in MCI than OA. No voxels passed the TFCE-corrected $p < .05$ level for other diffusion measures. Group differences in AxD values for the SCC, BCC, SCR, and RLIC were compared (Figure 1). To confirm that the results remained unchanged while accounting for covariate factors, a mixed ANCOVA model was performed to determine differences in AxD between the groups while controlling for age and SES. Significant differences were still observed in the SCC [$F(3,77) = 3.35$, $p = .04$, $\eta^2 = 0.07$], BCC [$F(3,77) = 3.21$, $p = .03$, $\eta^2 = 0.02$], SCR [$F(3,77) = 3.53$, $p = .02$, $\eta^2 = 0.05$], and RLIC [$F(3,77) = 4.12$, $p = .01$, $\eta^2 = 0.02$] with OA exhibiting lower AxD than individuals with MCI (Figure 2).

Since there were significant between-group differences in regions of the corpus callosum, and previous research indicates that the forceps exhibits WM degeneration in dementia, probabilistic tractography was performed from the BCC to the forceps major and minor for each participant. Mean AxD, FA, MD, and RD values in the resulting tracts were compared between groups. An ANOVA was performed to determine between-groups differences while accounting for significant covariates (age and SES). Results remained consistent with significant differences found in forceps major in MD [$F(3,71) = 6.75$, $p = .01$, $\eta^2 = 0.10$], RD [$F(3,71) = 7.37$, $p = .01$, $\eta^2 = 0.10$], and FA [$F(3,71) = 7.367$, $p = .01$, $\eta^2 = 0.09$] and forceps minor in MD [$F(3,71) = 4.58$, $p = .04$, $\eta^2 = 0.07$], RD [$F(3,71) = 6.559$, $p = .01$, $\eta^2 = 0.08$], and FA [$F(3,71) = 13.55$, $p < .001$, $\eta^2 = 0.14$] (Figure 3).

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TABLE 3 Diffusivity hierarchical regression analysis for the relationship between cognition and BMI after controlling for the variance associated with descriptive variables.

OA AxD BCC				OA AxD SCC			
	Beta	***t***	***p*-value**		***B***	***t***	***p*-value**
Step 1				Step 1			
Age	1.4e−6	0.36	.72	Age	1.0e−6	1.23	.22
Step 2				Step 2			
Sex	1.4e−6	0.36	.19	Sex	1.0e−6	1.23	.22
Step 3				Step 3			
BMI	−1.8e−6	−1.92**	.05**	BMI	−8.6e−7	−0.86	.39
Step 3				Step 3			
AP	−1.6e−5	−2.37**	.03**	AP	−1.2e−5	−1.47	.15
Step				Step 3			
OM	1.2e−7	2.05*	.04**	OM	1.1e−7	1.49	.14
OA AxD SCR				**OA AxD RLIC**			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 1			
Age	−5.5e−7	−0.45	.73	Age	−2.0e−6	−1.66	.10
Step 1				Step 1			
Sex	−5.5e−7	−1.45	.23	Sex	−2.0e−6	−0.41	.68
Step 2				Step 2			
BMI	−2.8e−6	−0.32	.73	BMI	−1.4e−6	−1.06	.29
Step 2				Step 2			
AP	−1.9e−5	−1.85*	.07*	AP	6.4e−6	−0.59	.55
Step 2				Step 2			
OM	1.9e−7	1.84	.07*	OM	2.7e−8	0.27	.79
OA AxD forceps major				**OA AxD forceps minor**			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 1			
Age	−1.9e−6	2.38**	.02**	Age	2.7e−6	2.81**	.02**
Step 1				Step 1			
Sex	−1.9e−6	2.38**	.99	Sex	2.7e−6	2.81**	.97
Step 2				Step 2			
BMI	−4.8e−7	−0.46	.64	BMI	−1.7e−7	−0.15	.88
Step 2				Step 2			
AP	−1.2e−5	−1.44	.16	AP	1.6e−5	−1.69	.09*
Step 2				Step 2			
OM	9.5e−8	1.27	.21	OM	1.6e−4	1.94*	.05*
OA FA forceps major				**OA FA forceps minor**			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 1			
Age	−8.8 to 5	0.09	.92	Age	0.002	1.72*	.09*
Step 1				Step 1			
Sex	−1.5e−2	−1.67	.10	Sex	0.002	1.72*	.09*

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TABLE 3 (Continued)

OA FA forceps major				OA FA forceps minor			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 2			
BMI	−.003	−2.49**	.01**	BMI	0.002	0.48	.64
Step 1				Step 2			
AP	−0.02	−2.39**	.02**	AP	−0.007	−0.78	.44
Step 1				Step 2			
OM	1.6e−04	1.94*	.06*	OM	2.7e−05	0.32	.75
OA MD forceps major				**OA MD forceps minor**			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 1			
Age	−3.5e−7	0.53	.59	Age	−7.1e−7	0.86	.39
Step 1				Step 1			
Sex	−7.3e−7	1.04	.30	Sex	−1.5e−6	−0.14	.88
Step 2				Step 2			
BMI	1.2e−6	1.90*	.06*	BMI	−4.2e−7	−0.39	.69
Step 2				Step 2			
AP	−1.5e−6	0.26	.79	AP	−1.3e−6	−0.114	.89
Step 2				Step 1			
OM	−1.9e−8	−0.35	.73	OM	1.7e−8	0.22	.83
OA RD forceps major				**OA RD forceps minor**			
	Beta	***t***	***p*-value**		**Beta**	***t***	***p*-value**
Step 1				Step 1			
Age	−2e−08	−0.02	.98	Age	−7.2e−7	−0.73	.46
Step 1				Step 1			
Sex	7.9e−07	1.0	.32	Sex	9.7e−7	0.90	.38
Step 2				Step 2			
BMI	2.1e−6	2.59**	.01**	BMI	7.9e−7	0.66	.51
Step 2				Step 2			
AP	7.9e−6	1.1	.27	AP	−4.1e−6	−0.45	.652
Step 2				Step 2			
OM	−7.4e−8	−1.13	.26	OM	3.7e−8	0.44	.66

**$p < .05$; *$p < .10$.

3.3 | Associations between brain measures and BMI

3.3.1 | BCC AxD and BMI

The full model was significant [$F(3,57) = 3.22$, adjusted $R^2 = .10$, $p = .03$, $\eta^2 = 0.11$] (Figure 4). Age as a covariate was entered in Step 1, which was not significant in predicting BCC AxD [$t(3,57) = 1.23$, $\beta = 8.8e{-}07$, $SE = 7.2e{-}07$, $p = .22$, $\eta^2 = 0.03$]. Sex as a covariate was entered in Step 1, which was not significant in predicting BCC AxD [$t(3,57) = 1.07$, $\beta = 8.92e{-}06$, $SE = 8.26e{-}06$, $p = .28$, $\eta^2 = 0.02$]. BMI was entered as Step 2 and significantly improved prediction of BCC AxD [$t(3,57) = -1.92$, $\beta = -1.64e{-}06$, $SE = 8.52e{-}07$, $p = .05$, $\eta^2 = 0.11$], indicating that lower BMI is associated with increased axial diffusivity in the BCC.

3.3.2 | FA forceps major and BMI

The full model was significant [$F(3,57) = 3.62$, adjusted $R^2 = .13$, $p = .02$, $\eta^2 = 0.13$] (Figure 4). Age as a covariate was entered in Step 1, which was not significant

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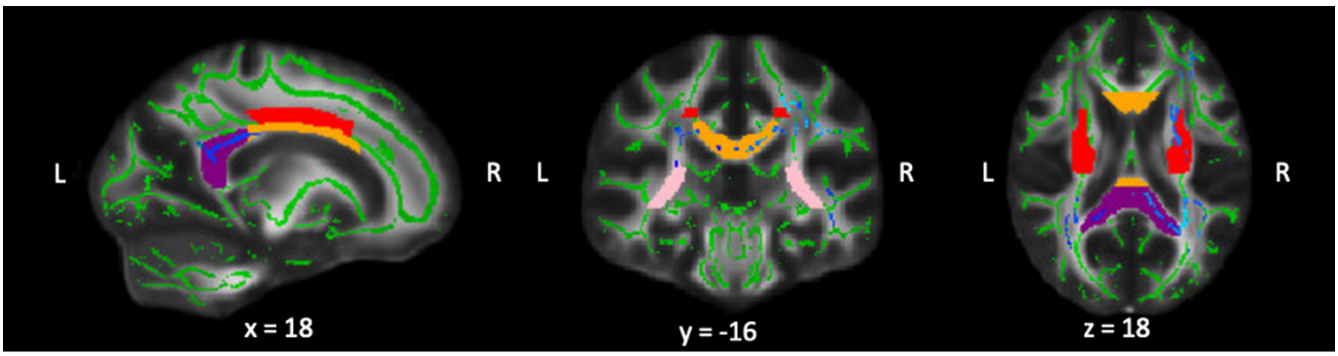

FIGURE 1 ROIs from JHU atlas laid over AxD skeleton with significant voxels in blue. Red reflects superior corona radiata, pink shows the retrolenticular part of the internal capsule, purple shows the splenium, and orange shows the body of the corpus callosum.

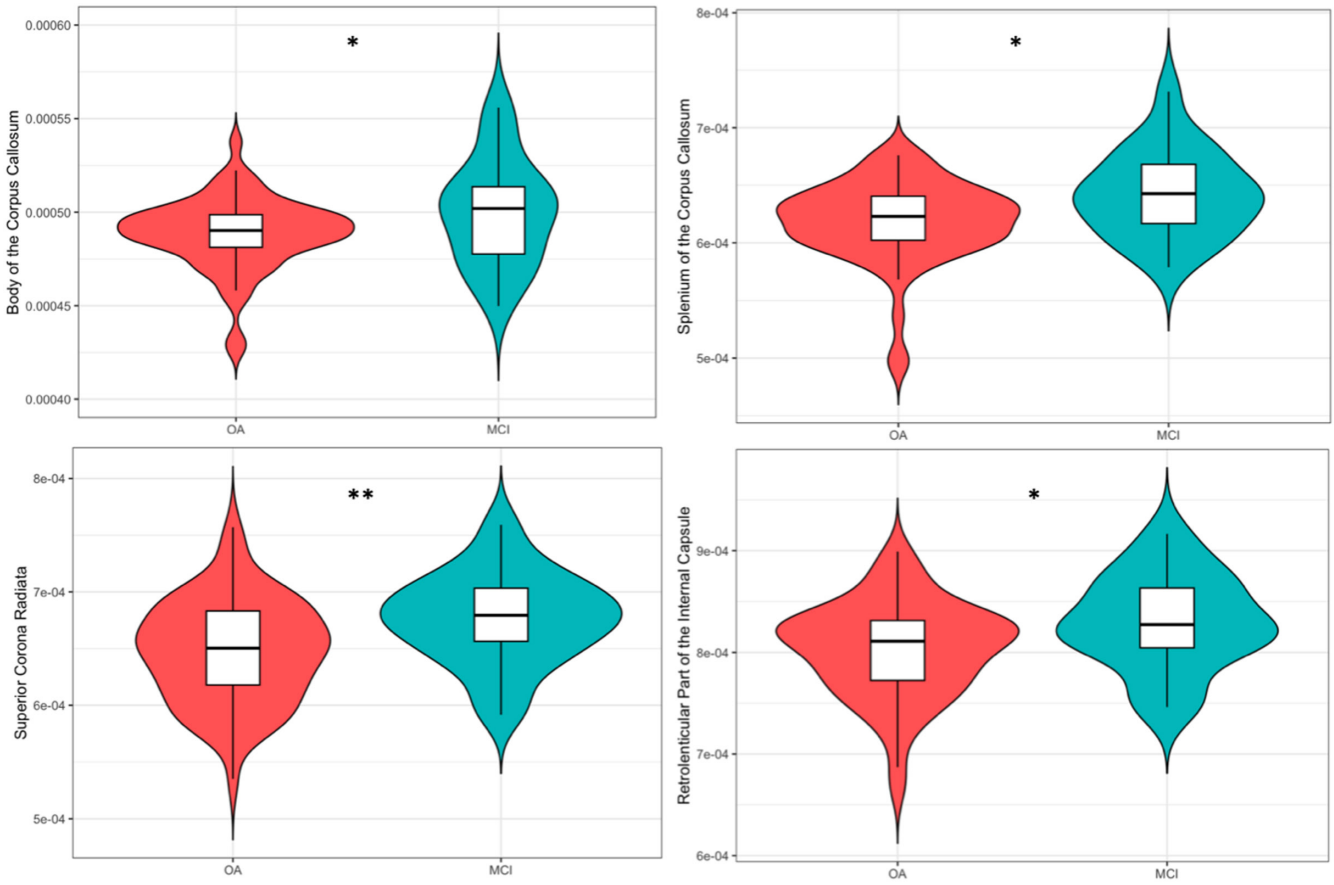

FIGURE 2 Between-group differences in ROIs, *$p < .05$, **$p < .01$. OA, shown in red, shows lower AxD values throughout the BCC, SCC, SCR, and RLIC, compared to MCI, shown in gray.

in predicting FA in the forceps major [$t(3,57) = 0.09$, $\beta = 0.001$, $SE = 0.001$, $p = .92$, $\eta^2 = 2.05e{-}04$]. Sex as a covariate was entered in Step 1, which was not significant in predicting FA in the forceps major [$t(3,57) = -1.88$, $\beta = 0.001$, $SE = -1.875$, $p = .07$, $\eta^2 = 0.07$]. Step 2 was significant [$t(3,57) = -2.85$, $\beta = -3.049e{-}03$, $SE = 1.069e{-}03$, $p < .01$, $\eta^2 = 0.13$], with BMI accounting for an incremental amount of variance in FA beyond associated demographic variables indicating that decreased BMI is associated with increased fractional anisotropy.

3.3.3 | RD forceps major and BMI

The full model was significant [$F(3,57) = 3.23$, adjusted $R^2 = .11$, $p = .03$, $\eta^2 = 0.12$] (Figure 4). Age as a covariate was entered in Step 1, which was not significant in predicting FA in the forceps major [$t(3,57) = 0.47$, $\beta = 3.461e{-}07$, $SE = 7.362e{-}07$, $p = .64$, $\eta^2 = 3.99e{-}03$]. Sex as a covariate was entered in Step 1, which was not significant in predicting FA in the forceps major [$t(3,57) = 1.77$, $\beta = 1.469e{-}05$, $SE = 8.315e{-}06$, $p = .08$, $\eta^2 = 0.06$]. Step 2 was significant

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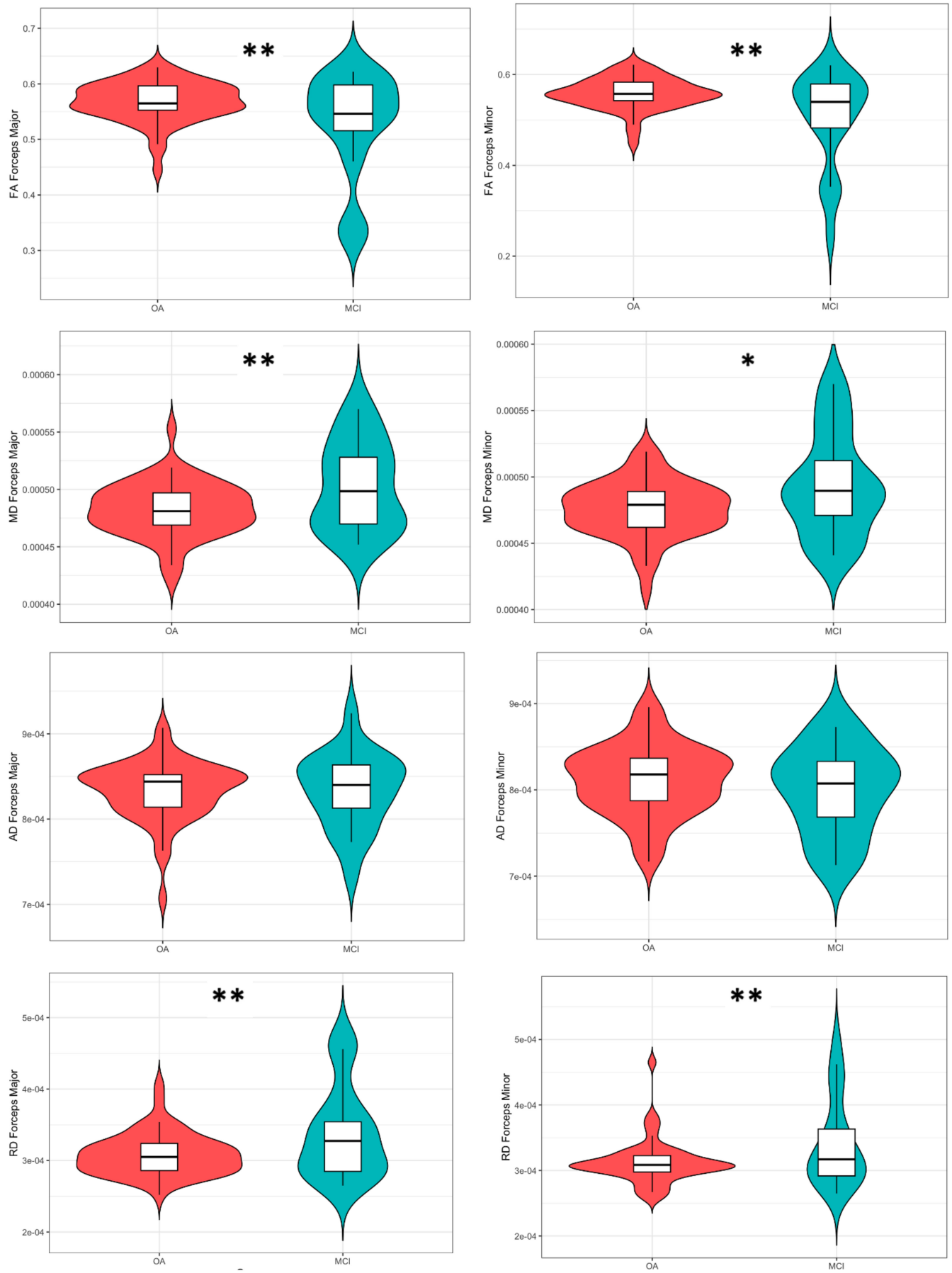

FIGURE 3 Between-group differences in forceps major and minor, $^{**}p < .01$, $^{*}p < .05$ OA, shown in red, shows lower MD and RD values throughout the tracts to the forceps major and minor, compared to MCI, shown in gray. Higher FA was seen in OA compared to MCI.

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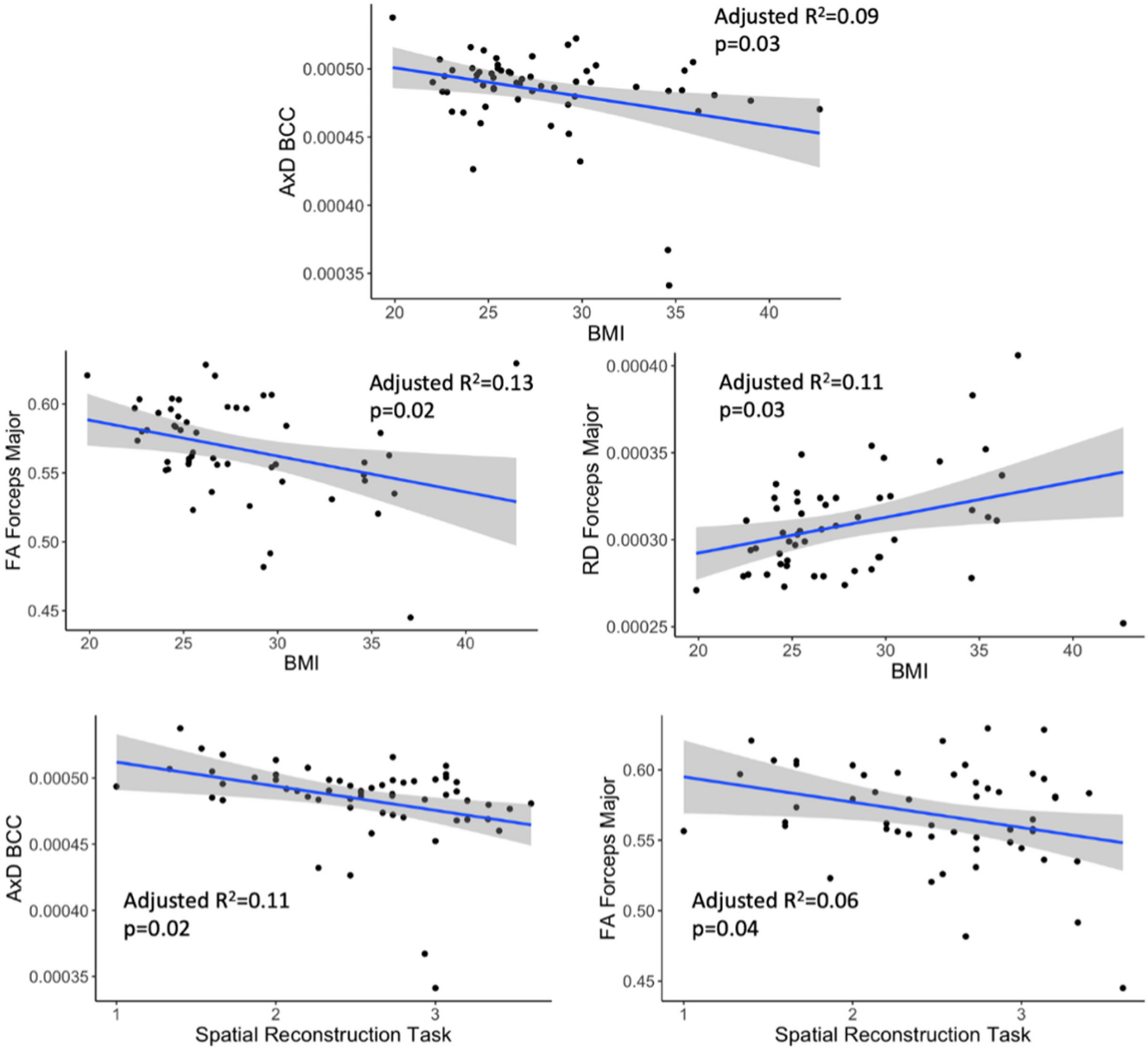

FIGURE 4 Regression graphs demonstrating the relationships with the BCC and forceps major and their associations with relational memory scores and BMI.

[$t(3,57)=2.83$, $\beta=2.426e{-}06$, $SE=8.591e{-}0$, $p<.01$, $\eta^2=0.12$], with BMI accounting for an incremental amount of variance in RD beyond associated demographic variables indicating that decreased BMI is associated with decreased radial diffusivity.

3.4 | Associations between brain measures and relational memory

3.4.1 | AxD BCC and relational memory

The full model was significant [$F(3, 57)=3.69$, adjusted $R^2=.12$, $p=.02$, $\eta^2=0.20$] (Figure 4). Age as a covariate was entered in Step 1, which was not significant [$t(3,57)=0.81$, $\beta=6.040e{-}07$, $SE=7.526e{-}07$, $p=.43$, $\eta^2=0.13$]. Sex as a covariate was entered in Step 1, which was not significant [$t(3,57)=1.49$, $\beta=1.217e{-}05$, $SE=8.124e{-}06$, $p=.14$, $\eta^2=3.51e{-}05$]. Step 2 was significant [$t(3,57)=-2.24$, $\beta=-1.525e{-}05$, $SE=6.821e{-}06$, $p=.029$, $\eta^2=0.20$], with the addition of score in accurate placement accounting for an incremental amount of variance in AxD BCC beyond associated demographic variables, indicating that increased relational memory scores were related to decreased AxD in the BCC.

3.4.2 | FA forceps major and relational memory

The full model was significant [$F(3, 57)=2.72$, adjusted $R^2=.08$ $p=.05$] (Figure 4). Age as a covariate was entered in Step 1, which was not significant [$t(3, 57)=-0.16$,

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$\beta = -0.0002$, $SE = 0.001$, $p = .86$, $\eta^2 = 1.66e{-}03$]. Sex as a covariate was entered in Step 1, which was not significant [$t(3, 57) = -1.16, \beta = -0.01, SE = 0.01, p = .25, \eta^2 = .02$]. Step 2 was significant [$t(3, 57) = -2.37$, $\beta = -0.02$, $SE = 0.01$, $p = .046$, $\eta^2 = 0.11$], with the addition of score in accurate placement accounting for an incremental amount of variance in FA beyond associated demographic variables, indicating that increased relational memory scores were related to decreased FA in the tracts to the forceps major.

4 | DISCUSSION

The results of this investigation are clinically relevant to older adults with MCI, who are at higher risk of developing dementia. The current findings show that older adults with MCI have diminished white matter integrity compared to healthy older adults in the splenium and body of the corpus callosum, superior corona radiata, and the retro-lenticular part of the internal capsule. Several of these impaired white matter tracts, such as the corpus callosum, connect structures known to be involved in the early stages of Alzheimer's disease (Lee et al., 2015). Our results are generally consistent with previous studies demonstrating decreased integrity of white matter during prodromal stages of MCI (Lee et al., 2015). Additionally, our findings suggest that axonal injury may play a role in MCI and the observed decreases in WM integrity may be due to an increase in AxD in specific regions, such as the corpus callosum and superior corona radiata (Li et al., 2016).

Probabilistic tractography has given new insight into the tracts connecting the corpus callosum to forceps major and minor. Specifically, we showed significant differences in the WM tracts from the corpus callosum to forceps major and forceps minor, indicating that those with MCI have lower MD and RD as well as higher FA in these regions. These results are consistent with previous findings, with lower FA and higher RD observed in forceps major in those with MCI (Wen et al., 2019). As increased RD has been associated with myelin damage (harsan et al., 2006; Song et al., 2019), such findings provide preliminary evidence suggesting that demyelination may be an underlying cause of the observed decline in WM integrity in MCI. Additionally, our findings are among the first to illustrate differences between individuals with MCI and their healthy counterparts in the tracts from the BCC to forceps major and minor, providing novel information regarding altered WM integrity in those with MCI.

Previous work shows the importance of maintaining a healthy BMI in order to preserve brain health (Erickson et al., 2014; Gunstad et al., 2008; Ward et al., 2005; West et al., 2020). BMI was observed to be associated with the forceps major tract, as measured by RD and MD, and with the BCC, as measured by AxD. These associations were significant even after accounting for any associated demographic variables. More specifically, the results suggested that higher BMI is associated with decreased AxD in the BCC, as well as increased RD and decreased FA in the forceps major. These results corroborate previous studies investigating obesity and WM integrity (Daoust et al., 2021; Kullmann et al., 2015; Stanek et al., 2013), suggesting that higher BMI is related to the integrity of WM structures and tracts. The relationships found in this study between BMI and diffusivity offered pertinent and innovative evidence concerning the associations between specific diffusivity metrics in WM tracts and body composition as assessed by BMI.

The findings in AxD are notable, as we had lower AxD in OA but also lower AxD with higher BMI. The higher AxD in MCI may be considered a pathological consequence of reduced structural coherence of axonal fibers (Loui et al., 2019; Song et al., 2002). Lower BMI and higher cognitive performance in the healthy older adult sample were shown to be associated with an increase in AxD, while the same group had lower AxD compared to those with MCI. WM integrity may be considerably more damaged in MCI compared to the OA group, providing new insights on MCI pathology.

Cognition, specifically relational memory, was observed to be associated with forceps major tract, as measured by FA, and body of the corpus callosum, as measured by AxD. All associations were significant beyond any related demographic variables. More specifically, better relational memory scores were associated with a decrease in AxD in the body of the corpus callosum and an increase in FA in tracts to the forceps major. These results are consistent with prior research (Oberlin et al., 2016), confirming that the corpus callosum tracts are supporting relational memory performance. The forceps major and minor are known to play a role in cognitive processes, with previous literature examining executive functioning (Mamiya et al., 2018). The relationship between the forceps major and relational memory provides new insights on regions that may support relational memory processes. This association between white matter integrity and relational memory indicates/suggests/highlights that preserving healthy WM integrity, such as through maintaining health factors, may in turn improve relational memory.

We see that health metrics, specifically BMI, are associated with higher levels of WM integrity, which may in turn preserve relational memory in older adults. While we did not observe the MCI relationships, understanding how BMI affects WM tracts in OA, particularly the tracts found to be affected in MCI, suggests that this is a modifiable

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health factor that could contribute to preserving integrity in the MCI population.

The primary limitation of the current study is the cross-sectional nature of the study design, which does not afford causal interpretations. However, such novel findings are often important to identify using noncausal designs to best guide expensive randomized controlled trials, which can afford causal interpretations of the observed relationships. There are several secondary limitations of this study, including the small sample size and that BMI provides only an approximate estimation of body composition that is largely dependent on body height and cannot dissociate between excess visceral versus subcutaneous adiposity or higher fat-free mass. However, BMI is shown to be a reliable estimate of obesity and body composition (Batsis et al., 2016; Cole et al., 1995; Romero-Corral et al., 2008). Additionally, it has been shown to be related to cognitive decline in MCI (Cronk et al., 2010), insulin resistance (Kahn & Flier, 2000), and cardiovascular dysfunction (Cote et al., 2013). More accurate measures of body composition such as hip-to-waist ratio, waist circumference, and the gold standard measure of dual-energy X-ray absorptiometry could be investigated in future studies building on these results. Despite these limitations, our findings are robust and innovative and provide preliminary evidence for further pursuit of this line of inquiry.

Regarding the generalizability of our study results, we used correlational analyses to remove potential covariates from the subsequent regressions. It is unclear how the inclusion of other covariates or a different sample may impact the replication of these regression results. We also did not correct for the multiple comparisons in regression models used for the multiple indices of health behaviors. However, bearing in mind the limited publications in the extant literature, we chose to report all findings without applying conservative multiple comparison correction.

5 | CONCLUSION

In summary, the present study offers important information on how WM integrity may be affected by MCI using DTI. Specifically, our data showed that those with MCI have higher axial diffusivity in the splenium and body of the corpus callosum, superior corona radiata, and the retro-lenticular part of the internal capsule. Furthermore, we demonstrate that health factors such as BMI relate to WM integrity in the corpus callosum and forceps major and minor in healthy older adults. Furthermore, we see that WM integrity relates to cognition, specifically relational memory. Collectively, these findings provide novel information regarding the relationship between MCI and brain structure and suggest that health and lifestyle factors may benefit brain health and cognition during older adulthood.

AUTHOR CONTRIBUTIONS

Emma M. Tinney: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Psyche Loui:** Methodology; supervision; writing – review and editing. **Lauren B. Raine:** Supervision; validation; visualization; writing – review and editing. **Lucy V. Hiscox:** Data curation; project administration; supervision; writing – review and editing. **Peyton L. Delgorio:** Data curation; project administration; writing – review and editing. **Mary K. Kramer:** Data curation; project administration; writing – review and editing. **Hillary Schwarb:** Methodology; validation; visualization; writing – review and editing. **Christopher R. Martens:** Funding acquisition; writing – review and editing. **Arthur F. Kramer:** Supervision; writing – review and editing. **Charles H. Hillman:** Supervision; writing – review and editing. **Curtis L. Johnson:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – review and editing.

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DATA AVAILABILITY STATEMENT

Data and code are available upon request from corresponding author.

ORCID

Emma M. Tinney https://orcid.org/0000-0001-7960-9844
Mary K. Kramer https://orcid.org/0000-0003-1305-9821

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