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White Matter Degradation is Associated with Reduced Financial Capacity in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract

Financial capacity (FC) is a cognitively complex activity of daily living that declines in mild cognitive impairment (MCI) and Alzheimer's disease (AD), limiting an individual's ability to manage one's finances and function independently. The neural underpinnings of this decline in function are poorly understood but likely involve age-related and disease-related degradation across structural networks. The purpose of the current study was to determine if altered white matter integrity is associated with declining FC in persons with MCI and AD compared to older controls. Individuals with MCI due to AD (n = 31), mild dementia (n = 39), and cognitively healthy older adults (n = 60) were administered a neuropsychological battery including the FC Instrument, a performance-based measure of FC. All 130 participants also underwent diffusion tensor imaging (DTI) upon which tract-based spatial statistics were performed. Both FC and white matter integrity decreased in accordance with disease severity with little to no effect in healthy elderly, significant effects in MCI, and greater effects in AD. Regional white matter degradation (increased diffusivities and decreased fractional anisotropy) was associated with reduced FC in both MCI and AD groups even after controlling for age, education, and gender. Specifically, in MCI, decreased fractional anisotropy, but not increased diffusivities, was associated with poorer FC in widespread cingulo-parietal-frontal and temporo-occipital areas. In AD, rather than anisotropy, increased mean and axial diffusivities in anterior cingulate, callosum, and frontal areas associated with poorer FC. These findings suggest a severity gradient of white matter degradation across DTI metrics and AD stages that predict declining financial skill and knowledge.

Keywords

Aging; financial management; Alzheimer's disease; brain; diffusion tensor imaging; magnetic resonance imaging; mild cognitive impairment; white matter connectivity

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INTRODUCTION

Financial capacity (FC) is a cognitively complex instrumental activity of daily living (IADL) which is critical to autonomy and independence [1, 2]. FC is composed of a broad range of everyday skills ranging from counting coins/currency, managing a checkbook and paying bills, to financial investing [1]. Due to its complexity, FC is highly vulnerable to neurodegenerative disorders such as Alzheimer's disease (AD) [3], is often one of the first IADLs affected in mild cognitive impairment (MCI) [4, 5], and can be used to track clinical progression in MCI due to AD [6]. Although well-understood in its clinical relevance (see Triebel et al. for a review [7]), the neural underpinnings of declining FC have just begun to be studied and thus are poorly understood.

Structural morphometry, conducted by our group, has shown associations between FC and gray matter volume of the angular gyrus in individuals with MCI [8] and associations between FC and medial frontal cortex gray matter volume in AD [9]. These findings suggest that degradation to frontal-parietal network connectivity might be one factor that underlies loss of FC across disease stages. However, to better understand the neural underpinnings of FC, investigations into the association between white matter connectivity and FC are required.

White matter connectivity, as measured via MRI-based diffusion tensor imaging (DTI), quantifies the flow of water molecules in the brain and thus provides information unique from traditional structural MRI [10, 11]. The most commonly reported DTI metrics are those of fractional anisotropy (FA) and directional diffusivities (e.g., radial (RD) and axial diffusivity) which are computed from the tensor eigenvalues (i.e., $\lambda 1$, $\lambda 2$, $\lambda 3$ values). FA is a scalar value that ranges from 0–1 where lower values reflect isotropy (i.e., random diffusivity as in cerebrospinal fluid) and higher values reflect increased anisotropy (i.e., highly directionally constrained non-random diffusivity as in white matter fiber bundles). In healthy white matter tracts, higher anisotropy is the result of intact neuronal bundles causing increased directionality to the flow of water within a measured voxel [10–12]. Degradation of cell membranes, density of axons, or fiber organization results in more isotropic values or a reduction in FA. For the directional diffusivity metrics, increased speed of water diffusion is generally associated with poorer white matter integrity in normal aging [13] and various patient population studies [14–18], as it can reflect less hindrance to diffusion at cellular boundaries due to loss of neuronal structure (e.g., myelin thinning, reduced density of axons in bundles, shrinking axon diameter) within a measured voxel. More specifically, RD (or the sum of $\lambda 2 + \lambda 3$) reflects the speed of diffusion perpendicular to the fiber bundles, and has been suggested as a proxy metric for dys- or de-myelination based on animal studies. Axial diffusivity ($\lambda 1$) reflects the speed of diffusion parallel to the fiber bundle, the principal eigenvector, and in animal studies has been suggested as a proxy for damage to the axons themselves, however, the biological mechanisms comprising axial and RD are not well understood [19, 20]. Mean diffusivity (MD or the average of $\lambda 1$, $\lambda 2$, $\lambda 3$) is a directionally non-specific metric of general speed of water diffusion across a voxel. Thus, these DTI metrics can serve as an indirect proxy for the microstructural integrity of white matter, the type of degradation, and relative severity, lending insights to research in cognitive aging and neurological disorders [21, 22]. Reduced FA is routinely observed in healthy aging across

the lifespan (e.g., [20]) and has been shown to progress in severity with AD progression [19]. Increased RD is also observed in normal aging, but not increased axial diffusivity [23]. Increases in axial diffusivity are however seen in conditions of frank pathology, such as in multiple sclerosis, amyotrophic lateral sclerosis, and AD [14–16] and, in AD, seem to precede increases in RD [19]. Therefore, we can loosely use these DTI metrics as a proxy for white matter degradation severity staging [19].

Given the disruption of structural connectivity, which leads to impaired network function, it seems likely that degraded white matter underlies, in part, the complex cognitive functions necessary to maintain financial independence. However, no studies have yet investigated the white matter connectivity correlates of FC loss seen in MCI and AD patients. To address this gap in knowledge, we administered a standardized, performance-based measure of FC (i.e., the Financial Capacity Instrument [FCI] [1]) and collected DTI scans from both MCI and AD patient groups, as well as a group of cognitively-healthy older adults. We hypothesized that white matter integrity would be degraded in a manner relative to disease severity (i.e., healthy controls < MCI < AD) and that poorer white matter integrity in the MCI and AD groups would be associated with poorer performance on the FCI, highlighting the importance of structural connectivity to maintaining financial competency.

MATERIALS AND METHODS

Participants

Participants included 130 individuals (31 with MCI, 39 with mild AD dementia, and 60 healthy controls) recruited as part of a study of functional change in MCI (Cognitive Observations in Seniors 2: COINS2). All study participants were evaluated clinically at the University of Alabama at Birmingham (UAB) by consensus conference team members including a neurologist and neuropsychologist. All individuals with MCI or mild AD dementia were recruited through the Memory Disorders Clinic and Alzheimer's Disease Center at UAB and were well-characterized based upon medical, neurologic, psychiatric, and neuropsychological screening. Diagnoses of MCI were made in consensus conference using original Mayo criteria [24]. Participants with MCI were further classified according to probable etiology. For the purpose of this study, only participants clinically determined to have MCI likely due to AD were included. Diagnoses of MCI likely due to AD were further made in the diagnostic consensus conference using recommendations from the National Institute on Aging-Alzheimer's Association (NIA/AA) workgroups on diagnostic guidelines for AD [25]. In total, 20 participants were excluded due to the etiology of MCI being determined unclear or other than AD: 12 unclear, 6 vascular, and 2 behavioral variant frontotemporal dementia. Diagnoses of probable AD dementia were made in the diagnostic consensus conference using NINCDS-ADRDA criteria [26]. Participants with mild AD had significant short-term memory and other cognitive deficits, and significant impairments in IADL and other higher order everyday functions, that distinguished them from our participants with MCI and also from more functionally impaired participants with moderate AD. Healthy controls were classified according to consensus conference and received a Clinical Dementia Rating [27] staging score of 0. Informed consent was obtained from all participants. This study was approved by the UAB Institutional Review Board.

Financial capacity measure

The FCI [1] is a performance-based measure that consists of over 100 items to directly assess financial skills across 20 tasks, covering eight domains, and computed into three potential global scores. Tasks consist of items that measure simple (i.e., counting currency) or complex (i.e., preparing bills for mailing) knowledge or skills. Specific task scores are summed to establish Domain scores, which represent higher-order financial skills that represent independent clinical significance (see Table 2 for Domains). Domain scores were summed to establish FCI Total score. The FCI has demonstrated high levels of reliability and content and construct validity in previous studies of healthy controls and persons with MCI and AD [1, 28]. Higher scores indicate better financial skills. For the current study, Domains 1–7 were summed to obtain FCI Total (with a maximum score of 285) as Domain 8 (related to knowledge of assets and estate arrangements) is considered experimental.

Cognitive measures

The Dementia Rating Scale – Second Edition (DRS-2) [29] is a measure of general cognitive functioning that is widely used in geriatric, clinical, and research assessments. For DRS-2 Total, higher values indicate better cognitive functioning. The Mini-Mental State Examination (MMSE) [30] is a brief screening measure of general cognitive functioning. Total scores range from 0 to 30, with higher values indicating better cognitive function. Trained technicians administered and scored the cognitive measures, including the FCI using well-operationalized criteria [1].

Neuroimaging protocol

Diffusion weighted images were obtained using a Siemens Allegra 3 Tesla MRI system with a quadrature head coil (Erlangen, Germany). Sixty-four contiguous axial slices were acquired along 34 diffusion-weighted directions (b-value = 1000 s/mm^2) and 1 non-diffusion weighted b_0. Isotropic voxels of 2.2 mm were collected within a 112 × 112 matrix at a TR/TE of 7300 ms/82 ms, respectively.

DTI pre-processing

Diffusion images were assessed to ensure that acquired data was of sufficient quality for analysis. Manual quality assessment was performed by examining each slice of each gradient in all participants to identify scanner artifacts and abnormal brain features. Brain extraction was performed separately on the b_0 and for each diffusion gradient using FSL's brain extraction tool [31] which is part of FSL v5.0.8 [32]. Semi-automated quality assessment was then applied via the software package DTIPrep v1.2.4 [33] which identifies slice-wise, interlace-wise, and gradient-wise intensity artifacts. Corrections were applied by removing gradients that failed to meet the default thresholds. Additionally, correction for eddy-current distortion and motion was applied within DTIPrep by registering each diffusion gradient to the b_0 image. Finally, diffusion directions were adjusted to account for reorientation of individual gradients [34].

Custom scripts were used to apply the TBSS (tract-based spatial statistics) pipeline [35] to these data to assess differences in diffusion parameters among groups at each white matter voxel. FSL's DTIFIT was applied to calculate diffusion tensors and generate axial diffusivity

(λ1), FA and MD maps. λ2 and λ3 were averaged to create RD maps for each participant. These metric maps were then registered to the MNI152 1 mm template (Montreal Neurological Institute, McGill University, Canada) to create a multi-volume image in which each volume is a separate participant in MNI space. A skeleton map was then created to isolate the voxels at the center of the white matter by averaging FA volumes and applying the TBSS skeleton function. The skeleton was then trimmed using the default threshold value of FA > 0.2 to more accurately represent voxels containing white matter. This skeleton mask was applied to all diffusion-metrics of interest resulting in skeletonized white matter tracts for each λ1, FA, MD, and RD.

TBSS output was submitted to FSL's randomize v2.9 nonparametric permutation inference package [36] to model group differences. Both between-group unpaired *t*-tests and within-group effects were modeled using a null distribution built over 5,000 permutations with threshold-free cluster enhancement (TFCE) optimized specifically for TBSS [37] and family-wise error correction at $p < 0.05$. Additional covariates of age, education, and gender were included in all models.

Statistical analyses used to evaluate demographics and FCI performance

Demographic variables of the patient and control groups were analyzed using one-way analysis of variance (ANOVA) (age, education) and Pearson's chi-square tests (gender, race). Group comparisons on the FCI were also conducted using a one-way ANOVA. For age, education, and FCI variables, follow-up contrasts were computed using Tukey's Honestly Significant Difference (Tukey's HSD) to protect against Type I error. A conservative alpha of 0.01 was used for all non-imaging analyses.

RESULTS

Sample characteristics and general cognitive function

Sample characteristics and general cognitive function by participant group are presented in Table 1. The three participant groups were well-matched on demographics and only differed on years of education ($p < 0.01$). *Post-hoc* analyses (i.e., Tukey's HSD) revealed that the healthy control group have more years of education than the mild AD group ($p < 0.001$). As expected, both MMSE and DRS-2 Total scores decreased across study group severity.

FC performance

FCI performance by participant group can be found in Table 2. Significant main effects of group were observed for all FCI variables, with performance significantly declining in accordance with disease severity (all p's < 0.001). See Table 2 for all pairwise comparisons.

Differences in white matter integrity across participant groups

We first examined differences in white matter integrity across the three groups to provide a measure of disease staging severity (from normal aging to MCI to AD and across DTI metrics) as it relates to different white matter regions and to place this sample in the context of the extant literature.

Healthy controls versus mild AD

Significant differences in white matter properties were observed between the healthy control group and the mild AD group beyond the effects of age, education, and gender (Fig. 1A, B). Healthy older adults showed widespread regions of greater FA in the parietal, occipital, and frontal lobes compared to those with AD (red voxels in Fig. 1A). Specific white matter tracts included the corpus callosum genu, body, and splenium), left cingulum (all limbs), uncinate fasciculus (UF), inferior projections of the superior longitudinal fasciculus (SLF), posterior portions of the inferior fronto-occipital fasciculus (IFOF), and anterior thalamic radiations. These regions were adjacent to medial frontal and orbitofrontal cortex, precuneus and lateral parietal cortex, and medial and lateral occipital cortex. Notably, these early changes to FA were not located in limbic or temporal regions. Higher $\lambda 1$ was found in the mild AD group compared to the healthy control group more focally in the corona radiata and corticospinal tract, the splenium of the corpus callosum and the posterior cingulate, as well as in the anterior thalamus (blue and violet voxels in Fig. 1B). RD was greater in AD than in controls across the entire corpus callosum, SLF, posterior portions of the IFOF, left hippocampal projection from posterior cingulum, and external capsule (yellow and violet voxels in Fig. 1B). Notably, most regions of RD increase were overlapping with regions of FA decrease (including medial and orbitofrontal regions, cingulate, callosum, occipital, and precuneus and lateral parietal areas); interestingly, regions that did not overlap with FA include medial and lateral temporal regions [including hippocampal cingulate and inferior longitudinal fasciculus (ILF)] and diencephalic projections. Taken together, these results support those in the literature that alterations to FA and RD are largely overlapping, whereas those that show altered $\lambda 1$ are early specific signs of disease markers (diencephalic, posterior cingulate, and splenium). RD also was altered in a manner independent from FA in medial and lateral temporal regions.

MCI versus mild AD

In the transition from MCI to AD, a later stage as compared to the healthy control versus AD above, further white matter degradation was observed. As was the case with healthy older adults compared to AD, we found widespread regions of white matter with greater FA in the MCI group compared to the mild AD group, with the most robust differences occurring in projections in the parietal and occipital lobes as well as the external capsule and ILF (red voxels in Fig. 1C). Those regions that showed increases in FA from MCI to AD, beyond those observed from HC to AD, included lateral temporal (ILF), external capsule, and uncinate fasciculus. Interestingly, and consistent with recent literature, there were no regions where $\lambda 1$ progressed in the later transition from MCI to AD (i.e., those axial changes may occur earlier in disease course). However, RD worsened from MCI to AD in lateral and medial occipital areas, splenium and posterior cingulate including the right hippocampal projection from the posterior cingulum, and the precuneus. No worsening of RD was seen in the diencephalic or temporal areas (yellow voxels in Fig. 1D). These alterations in RD showed regional overlap with FA in contrasts between MCI and AD patient groups.

Healthy controls versus MCI

We observed no significant differences in DTI metrics between the healthy older adults and the MCI individuals in either direction (healthy control > MCI or MCI > healthy control). These results are interesting in that they may reflect that very early MCI changes to the white matter are subtle and may spatially overlap with normal aging changes.

Association of financial capacity and white matter integrity

We next tested our primary study hypothesis by examining the relationship between DTI white matter metrics and FCI Total score within the three participant groups to identify the white matter substrates of FC loss. In the healthy older adult group, we found no associations among white matter metrics and FC, likely reflecting the fact that FC is relatively intact in this group and reductions in white matter metrics are reflections of normal aging. In the MCI group, however, we found significant associations between FA and FCI score, where poorer FC was associated with lower FA in widespread areas of white matter. The regions include the anterior, body, and posterior portions of the corpus callosum, the UF, left SLF, left posterior cingulum, left IFOF, the anterior thalamic radiations, and external capsule (red voxels in Fig. 1E). These areas are adjacent to precuneus, lateral and medial occipital, lateral temporal and lateral prefrontal cortices. These findings suggest that the mild impairment in FC seen in MCI patients is related to degradation of white matter tracts in these regions. No other DTI metrics showed significant associations with FCI in MCI individuals.

In the mild AD group, rather than altered FA, FCI Total score was associated with increased $\lambda 1$ and mean diffusivities (Fig. 1F), constrained to the anterior portions of the brain. Specifically, lower FC was associated with higher $\lambda 1$ in the genu and anterior body of the corpus callosum, right UF, left anterior portions of the IFOF, and anterior cingulum (dark blue voxels in Fig. 1F). Higher MD was also associated with lower FC in a few overlapping brain areas as $\lambda 1$ (light blue voxels in Fig. 1F), with the addition of the internal capsule, left UF, external capsule, anterior thalamic radiations, and right anterior portions of the IFOF (green voxels in Fig. 1F). Of these regions associated with FC, many overlap between the MCI and AD groups, with the notable exception of anterior portions of the IFOF/SLF in AD as compared to MCI. This would be in accord with the later spread of AD pathology to frontal regions with disease severity and symptomatology.

DISCUSSION

In this study, we investigated the association between FC and brain white matter integrity in individuals with MCI likely due to AD, individuals with mild AD dementia, and a group of cognitively healthy older adults. The current study represents the first investigation into white matter integrity in MCI and AD using a standardized, performance-based measure of FC. Results of the current study indicate that white matter integrity in MCI and AD is degraded in relation to healthy older adults in a manner consistent with disease stage severity. In addition, white matter degradation was shown to be associated with poorer overall FC in both the MCI group and the AD group even after controlling for age, gender,

and years of education. Thus, diminished financial skill and knowledge appear to be affected by white matter degradation that begins early in the AD process.

White matter degrades from healthy elderly to MCI to mild AD dementia

Our findings are interesting in that loss of white matter integrity followed a disease-severity gradient, implicating reduced white matter connectivity as a concomitant pathological process in AD [38] beyond those that occur with normal aging [39, 40]. We report increasingly degraded white matter properties with AD progression, in a stepwise severity gradient from normal to MCI to AD, with no regions of white matter significantly degraded beyond those due to normal aging in MCI individuals, while large differences in white matter integrity were observed between MCI and AD individuals. The lack of noticeable white matter degradation between healthy elderly and MCI individuals could indicate that MCI pathology is perhaps not sufficient to manifest an impact on the white matter tracts (beyond the expected deleterious effects of aging alone). This would be well within expectations if a Wallerian degeneration hypothesis was considered, as cell death is likely not profound at the early stage of MCI. In support of recent research [19], we found that whereas decreased FA was widespread across the brain in AD patients relative to healthy older adults, increased axial diffusivity was focal and selective to splenium, posterior cingulate, and diencephalic projections. Further, increased RD mostly appeared in regions with decreased FA in AD patients versus healthy elderly, with the notable exception of temporal lobe white matter. These increases in axial diffusivity did not progress from MCI to AD, however, increased areas of RD did become more severe. These findings are consistent with other MCI and AD studies of white matter integrity. Increased $\lambda 1$ in the splenium of the corpus callosum and cingulate/limbic structures are most indicative of AD [16, 19, 39], which would be expected given the mnemonic impairment seen in the disease. Additionally, broad decreases in FA, driven by increases in RD, have not only been shown to be typical of disease progression [18], but have been proposed as a “staging biomarker” to classify AD [19].

Financial capacity declines from healthy elderly to MCI to mild AD dementia

Similar to the above findings of white matter degradation occurring as individuals transition from healthy to MCI to AD, the current findings also showed that FC performance varied according to disease severity. Relative to controls, the MCI group scored lower on FCI Total, and on five of seven FCI Domains, while the AD group scored poorer on all FCI variables. Thus, these findings are consistent with previous investigations by our group [7] and demonstrate the need for further study into the neuroanatomical factors mediating decline in FC as people progress through the dementia process.

White matter integrity effects on financial capacity

In the current study, we found that better overall FC was associated with better white matter integrity in both the MCI group and the mild AD group. In the MCI group, better performance on the FCI significantly corresponded with higher FA. In other words, those individuals with MCI who showed greater anisotropy in a number of white matter regions also tended to score higher on the FCI, indicating the importance of these structural connections in maintaining overall FC. In the mild AD group, poorer FCI performance was

associated with both increased $\lambda 1$ and increased MD. Thus, the pattern of white matter degradation associated with poorer FC varied according to diffusion metrics (Fig. 1E, F). For those with MCI due to AD, a widespread set of mostly association white matter tracts was associated with poorer FCI due to decreased FA. Decreases in FA are widely associated with normal aging throughout association white matter tracts [39, 41] as are increases to RD with aging [42]. Normal aging, however, is not generally associated with increases in axial diffusivity [42]. AD research, however, suggests that the earliest specific changes in the disease are increased axial diffusivity, that is detectable early, and then does not progress, whereas FA and RD are in largely overlapping regions and do progress along with the disease [19]. This suggests that increases to axial diffusivity can be viewed as more "pathological" relative to FA and RD. These diffusivity indices also, but arguably so, may lend insight toward changes in axonal versus myelin microstructure [43] and have been shown to be more predictive of cognitive decline across patient groups [18]. This would suggest that FA/RD alteration is a milder and earlier change, consistent with our findings for MCI, which has also been suggested by other groups [18]. Furthermore, for those already diagnosed with clinically symptomatic AD, white matter tracts with increases in diffusivity are associated with worsening FC performance predominantly in frontal regions of the anterior cingulum, UF, and corpus callosum. It may be that FC is associated with frontal-parietal function and relies on intact structural connections between these cortices. Healthy adults show no evidence of this due to their high FCI performance and healthy neuronal connections. However, with the emergence of white matter degradation in MCI, evidenced by declines in FA throughout frontal and parietal connections, and a progression toward more severe increases in diffusivity throughout the frontal cortices in mild AD, this relationship would emerge. Interestingly, this white matter severity staging pattern from MCI to AD (to more parietal and then frontal regions) mirrors the gray matter staging pattern of neuropathology in AD progression, with Braak and Thal indices progressing from temporal regions to eventual neocortical areas in frontal and parietal lobes [44].

Notably, the white matter tracts implicated in the current study are those that connect gray matter regions that we have previously shown to be associated with FC (e.g., angular gyrus) [8] to the anterior portions of the brain (e.g., medial prefrontal gray matter) [45]. This lends even greater support to the idea that frontal-parietal control systems largely mediate FC activities. This cross-sectional study suggests that parietal regions such as angular gyrus are altered in earlier disease stages, such as MCI, and are detrimental to FC, with a later expansion to frontal cortices in AD and showing more detrimental effects on FC. The only other study to investigate white matter integrity's role in the financial domain investigated financial literacy, or how well individuals are able to consume information about monetary issues, in healthy older adults [46]. Our study expands upon this concept by comparing MCI and AD to healthy older adults using varied DTI metrics, beyond FA, to gauge disease severity staging involvement while using a sophisticated measure of FC that incorporates many domains of a person's financial capabilities. Relatedly, lower functional connectivity in frontal-parietal networks such as the salience network has been associated with financial exploitation in healthy older adults [47]. We show that the regions involved in FC are largely overlapping with those used in cognitive control, and it seems likely that better preservation of these frontal-parietal cognitive control mechanisms is related to better or longer retention

of IADLs, such as the independence afforded by the continued ability to handle one's own financial affairs.

The current study should be interpreted in the context of its limitations and strengths. First, similar to other university-based studies, our sample may not be fully representative of the general MCI and AD populations as participants in the current study were able to complete several hours of testing, provide informed consent, and did not have other central nervous system disorders. This likely resulted in a more select group of people and, therefore, might not generalize to all individuals with MCI and AD. More diverse samples should be examined in future studies. Second, the sample utilized in the current study was somewhat limited in size, and studies of FC and white matter integrity in larger samples of people with MCI and AD are needed. Third, white matter differences were evaluated using TBSS in the current study, which has potentially limited statistical power [48] and potentially less precise tract anatomy [49, 50] compared to other DTI methods, such as a tractography-driven approach [51]. However, TBSS is an ideal tool for hypothesis generation and tract selection when *a priori* hypotheses are not warranted, as in this first study of white matter and FC. For example, it is likely that different brain regions mediate different aspects of FC (e.g., prefrontal decision-making regions may mediate investment decisions while parietal arithmetic regions may mediate basic monetary skills) and this study, having now established this basic relationship between white matter and FC, *a priori*, allows for further domain-level associations with white matter integrity to be evaluated in future studies.

Conclusion

The decline and loss of FC in MCI and dementia has been associated with a number of troubling difficulties such as making sound investments, difficulties paying bills, and eventually difficulties carrying out basic financial transactions [52]. Thus, declining FC represents a significant risk factor for the loss of independence in individuals with a dementing disorder. The current findings are the first to demonstrate that decreased FC is associated with poorer white matter integrity in MCI and AD in a manner suggesting a severity gradient.

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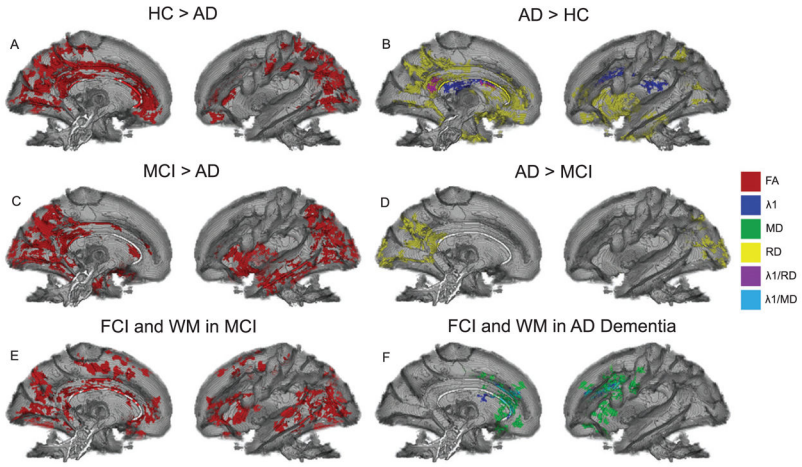

Fig. 1.

White matter degradation across the three groups: healthy elderly controls, mild cognitive impairment, and Alzheimer's disease patients, and associations with poorer FC in MCI and AD patients. Diffusion metrics are shown on 3-dimensional renderings of medial and lateral left hemisphere white matter. Significant voxel clusters are colored for each diffusion metric and are regressed on age, gender, and education at $p < 0.05$ FWE corrected. Panel A shows widespread decreased FA in AD patients compared to healthy controls (red voxels). Panel B shows significantly increased radial (yellow voxels) and axial (blue voxels) diffusivity in AD patients relative to controls. Panel C shows further decreases in FA in AD patients than MCI patients. Panel D shows further increases in radial diffusivity in AD compared to MCI patients. Panel E shows white matter regions where lower FA correlates with poorer FC index in MCI patients. Panel F shows white matter regions where increased axial and mean diffusivity is correlated with poorer FC in AD patients. FC, financial capacity; HC, healthy control; MCI, mild cognitive impairment; AD, Alzheimer's disease; FA, fractional anisotropy; $\lambda 1$, axial diffusivity; MD, mean diffusivity; RD, radial diffusivity.

Table 1

Sample demographics and general cognition

	Healthy Controls (*n* = 60)	MCI (*n* = 31)	Mild AD (*n* = 39)	F/χ^2	*p*
Age	70.6 (7.0)	71.9 (7.1)	71.3 (8.0)	0.4	0.665
Education	16.0 (2.3)	15.2 (2.5)	14.1 (2.6)	8.0	0.001
Gender				5.3	0.071
Female	44 (72.1)	23 (69.7)	22 (51.2)		
Male	17 (27.9)	10 (30.3)	21 (48.8)		
Race				1.9	0.392
Caucasian	56 (91.8)	32 (97.0)	38 (88.4)		
Other	5 (8.2)	1 (3.0)	5 (11.6)		
General Cognition					
DRS-2	138.9 (2.8)	130.7 (4.9)	113.9 (12.5)	137.4	<0.001
MMSE	29.1 (1.2)	26.9 (2.1)	21.7 (5.1)	85.8	<0.001

For age and education, cells are mean (standard deviation). For gender and race, cells are frequency (percent). F/χ^2, *F* or Pearson's Chi-square statistic; MCI, mild cognitive impairment; AD, Alzheimer's disease; DRS-2, Dementia Rating Scale, Second Edition; MMSE, Mini-Mental State Evaluation.

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Table 2

FCI performance by diagnostic group

FCI Variable	FCI Performance (Mean (SD))			ANOVA Results		Tukey's HSD		
	Healthy Controls (*n* = 60)	MCI (*n* = 31)	Mild AD (*n* = 39)	*F*	*p*	HC>MCI	HC>AD	MCI>AD
D1. Basic Money Skills	32.5 (2.8)	29.9 (4.0)	22.9 (6.8)	53.3	<0.001		X	X
D2. Financial Concepts	31.3 (2.5)	27.9 (3.6)	23.3 (5.9)	47.8	<0.001	X	X	X
D3. Cash Transactions	21.4 (2.2)	18.5 (4.1)	14.2 (4.6)	50.0	<0.001	X	X	X
D4. Checkbook Use	83.1 (7.0)	72.3 (13.6)	48.5 (20.0)	81.5	<0.001	X	X	X
D5. Bank Statement Use	35.2 (3.5)	29.1 (4.0)	19.3 (8.2)	105.5	<0.001	X	X	X
D6. Identifying Fraud	14.5 (1.7)	13.0 (2.5)	11.6 (3.4)	16.2	<0.001		X	
D7. Bill Payment Skills	43.5 (4.3)	37.7 (7.4)	26.5 (10.3)	67.3	<0.001	X	X	X
FCI Total	261.5 (13.9)	228.3 (24.9)	166.3 (49.0)	116.5	<0.001	X	X	X

F, *F* statistic; FCI, Financial Capacity Instrument; HC, healthy controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; SD, standard deviation; D, domain.