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Independent value added by diffusion MRI for prediction of cognitive function in older adults☆

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ABSTRACT

The purpose of this study was to determine whether white matter microstructure measured by diffusion magnetic resonance imaging (dMRI) provides independent information about baseline level or change in executive function (EF) or memory (MEM) in older adults with and without cognitive impairment. Longitudinal data was acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study from phases GO and 2 (2009–2015). ADNI participants included were diagnosed as cognitively normal (n = 46), early mild cognitive impairment (MCI) (n = 48), late MCI (n = 29), and dementia (n = 39) at baseline. We modeled the association between dMRI-based global white matter mean diffusivity (MD) and baseline level and change in EF and MEM composite scores, in models controlling for baseline bilateral hippocampal volume, regional cerebral FDG PET metabolism and global cerebral AV45 PET uptake. EF and MEM composite scores were measured at baseline, 6, 12, 24 and 36 months. In the baseline late MCI and dementia groups, greater global MD was associated with lesser baseline EF, but not EF change nor MEM baseline or change. As expected, lesser hippocampal volume and lesser FDG PET metabolism was associated with greater rates of EF and MEM decline. In ADNI-GO/2 participants, white matter integrity provided independent information about current executive function, but was not sensitive to future cognitive change. Since individuals experiencing executive function declines progress to dementia more rapidly than those with only memory impairment, better biomarkers of future executive function decline are needed.

1. Introduction

Prediction of age-related cognitive decline is needed to differentiate normal aging processes from disease courses that call for intervention. While episodic memory is the primary cognitive domain measured in cognitive aging, impairment in multiple domains, especially executive function, predicts more rapid progression to dementia (Gross et al., 2012; Knopman et al., 2015). However, executive function encompasses a broad set of cognitive skills and is determined by a broad set of neural circuitry. Diffusion magnetic resonance imaging (dMRI) has the potential to capture broad inter-regional white matter connectivity properties that give rise to successful executive function, and thus is a promising candidate predictor of future executive function declines (Madden et al., 2012; Bennett and Madden, 2014). dMRI-based covariates are modified by aging, cardiovascular risk factors, depression, and cerebral amyloid in older adults (Chao et al., 2013; van Uden et al., 2015; Kim et al., 2016; Marnane et al., 2016). In turn, dMRI metrics are associated with measures of executive function cross-sectionally in this population (Grieve et al., 2007; Bennett and Madden, 2014).

However, the relative time courses of white matter integrity decline and executive function change in aging are not well understood—in particular, it is not known whether diminished dMRI measures at a particular point in time are associated with executive function declines over the near term (for example, over a 1 to 2 year period). In addition, it is not clear whether dMRI provides unique information about executive function, or whether the associations are merely recapitulations of established associations between other biomarkers of aging (such as MRI-based hippocampus volume, cerebral glucose metabolism from (18)-fluorodeoxyglucose (FDG) PET, or amyloid PET uptake) (He et al.,

☆ Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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2012; Voineskos et al., 2012; Zhang et al., 2014). Prior studies have shown that dMRI measures are associated with concurrent executive functioning (Gibbons et al., 2012; Madden et al., 2012; Hedden et al., 2016), and additional studies have suggested that additional MRI markers of the white matter (predominantly white matter lesion burden from FLAIR) are associated with both concurrent executive functioning and declines over time (Gibbons et al., 2012; Madden et al., 2012; Hedden et al., 2016). More common are studies in the memory domain, with the emerging consensus view that markers from structural MRI (cortical thickness, hippocampal volume) and FDG PET (hypometabolism) predict future declines (Mormino et al., 2009; Crane et al., 2012; Gross et al., 2012; Dore et al., 2013; Wirth et al., 2013a, b). To our knowledge, the unique value of dMRI as a predictor of concurrent executive functioning or executive function changes has not been fully explored in aging populations with memory impairments.

Therefore we assessed whether global or regional dMRI measures predict executive function declines in older adults across the range of functioning from normal cognition to dementia. Importantly, we simultaneously account for the contributions of other well-established predictors of memory or executive function—MRI structural measures, cerebral glucose metabolism, and amyloid pathology to executive function—to clearly identify any additive value of dMRI. In this study, we model the effects of these variables on annual change in both episodic memory and executive function within the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set. Further, we tested the effects of each predictor within diagnostic groups (cognitively normal, early and late mild cognitive impairment, and dementia) to determine whether the combined group effects were driven by a single group. We hypothesized that white matter microstructure parameters, as measured by dMRI, would add predictive value to executive function, after accounting for other age and disease-associated variables.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

Data used here were obtained from 202 ADNI-GO and ADNI-2 cognitively normal (CN), early mild cognitive impairment (MCI), late MCI, and dementia (AD) participants followed longitudinally between 2009 and 2015. Data was extracted from the ADNI databases on March 15, 2016. Cognitive assessments at baseline, 6, 12, 24, and 36 months were selected. Baseline-associated data was selected for other variables. Group clinical and demographic data are reported in Table 1.

2.2. Cognitive assessments

Executive function (ADNI-EF) (Gibbons et al., 2012) and memory (ADNI-MEM) (Crane et al., 2012) composite z-scores were calculated from the ADNI neuropsychological battery of tests and have been described in detail elsewhere.

2.3. PET imaging and analysis

PET scans were acquired using a standardized protocol, which can be obtained from the ADNI database. We used Florbetapir (AV45) as a marker of cerebral amyloid (Landau et al., 2013) and FDG-PET as a measure of cerebral metabolism (Landau et al., 2011). AV45 cortical standard uptake volume ratio (SUVR) was normalized by whole cerebellum as our summary measure of interest. Mean FDG-PET SUVR from five metaROIs was used for the present analysis.

2.4. MRI imaging and analysis

Structural MRI T1 weighted and FLAIR scans were used for four-tissue segmentation into gray matter, normal appearing white matter, white matter hyperintensities, and cerebrospinal fluid (Carmichael et al., 2012). Bilateral hippocampal volumes were extracted from volumetric segmentations of T1 weighted images by FreeSurfer v5.3 (Mormino et al., 2009).

Processing and analysis of DTI maps has been described elsewhere (Nir et al., 2013). In brief, diffusion weighted images (DWI; 256×256 matrix; voxel size: $2.7 \times 2.7 \times 2.7$ mm^3; TR = 9000 ms; scan time = 9 min) were collected. 46 separate images were acquired for each DTI scan: 5 T2-weighted images with no diffusion sensitization (b_0 images) and 41 diffusion-weighted images (b = 1000 s/mm^2). Prior to estimating diffusion parameters, the raw dMRI were registered to the structural MRI by validated methods (Nir et al., 2013). Then diffusion parameters were calculated for each image—fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AxD). The FA image from The Johns Hopkins University (JHU) DTI atlas (Mori et al., 2008) was applied for ROI labeling to each subject's FA image, resulting in 43 ROIs. Global summary parameters were calculated for average FA, MD, radial diffusivity (RD) and axial diffusivity (AxD) across all ROIs.

2.5. CSF immunoassay

CSF collection procedures can be downloaded from the ADNI database (Shaw et al., 2011) and CSF assay processing and analysis has been previously described (Shaw et al., 2011). We used total CSF $A\beta_{1-42}$, total tau, and p-tau_{181}.

2.6. Statistical analyses

All statistical analyses were conducted with SPSS Statistics v.21. Prior to analysis, continuous summary variables were converted to z-scores based on mean and standard deviation of the baseline CN values.

For each composite score (ADNI-EF and ADNI-MEM), regularized ridge regression models of baseline data were run to guide selection of co-linear variables for linear mixed models (e.g. MD or FA, total GM or hippocampal volume, AV45 or $A\beta_{1-42}$, t-tau or diagnostic group). Variables included in the ridge regression analyses included DTI FA and MD, mean regional FDG-PET, global AV45-PET, CSF measures of $A\beta_{1-42}$ and t-tau, hippocampal, gray matter, normal appearing white matter, white matter hyperintensities, and cerebrospinal fluid volumes (see eTable 1 in Supplement for a complete list of variables). Demographic information, diagnosis, *APOE* ε4 genotype, and intracranial vault (ICV) were also included in the ridge regression to model their effects in evaluating the contributions of the imaging measures to cognition. However, these measures were also included in all later analyses regardless of whether they were significant in the ridge regression. Imaging variables from the ridge regression that survived either the ADNI-EF or ADNI-MEM models were retained for further analyses.

Next, for each composite score, step-wise linear mixed models nested by diagnostic group were built to determine whether any of the imaging variables were associated with baseline scores or modified the rate of change in scores. Every model adjusted for age, sex, education, *APOE* ε4 genotype, and ICV and accounted for random effect of subject. Modifiers of change over time (years) were the selected imaging variables from the ridge regression. All independent variables were fixed baseline-associated values. Models were built step-wise to determine the cumulative variance explained by each for composite scores in the following order: MD (Model A), MD + Hippocampus (Model

Table 1
Study demographics, cognitive scores and imaging metrics at baseline.

	Cognitively normal	Early MCI	Late MCI	Dementia
Participants at baseline	46	48	29	39
6 months	77%	79%	78%	66%
1 year	76%	76%	81%	61%
2 years	64%	64%	57%	16%
Sex (male)	50.0%	56.3%	72.4%	64.1%
APOE ε3/4 or 4/4	28.3%[a,b,c]	50%[d]	79.3%	61.5%
White—not Hispanic/Latino	84.8%	91.7%	100.0%	87.2%
Age (years)	72.9(5.9)	72.9(7.8)	72.4(6.4)	74.4(8.5)
Education (years)	16(3)	16(3)	16(3)	15(3)
Memory composite (*Z*-score)	0.88(0.52)[a,b,c]	0.37(0.47)[d,e]	−0.07(0.47)[f]	−0.67(0.51)
Executive function (Z-score)	0.81(0.72)[a,b,c]	0.19(0.62)[d,e]	0.19(0.79)[f]	−0.78(0.81)
Hippocampus (cm^3)	7.5(0.9)[b,c]	7.1(1.0)[d,e]	6.6(0.9)[f]	6.0(0.8)
Total white matter hyperintensities (WMH) (cm^3)	7.2(15.7)[b,c]	7.4(6.4)[d]	10.0(9.6)	11.7(11.8)
Intracranial vault (ICV) (cm^3)	1420(135)[b]	1462(144)	1508(159)	1443(166)
Total CSF (%ICV)	22%(2%)[b,c]	21%(3%)[d,e]	23%(3%)[f]	24%(2%)
Total gray matter (%ICV)	39%(2%)[b,c]	39%(3%)[d,e]	38%(3%)	38%(2%)
Total normal appearing white matter (NAWM) (%ICV)	31%(2%)[c]	32%(3%)[d,e]	31%(3%)	30%(2%)
Mean FA	$34.8 \times 10^{-2}(2.2 \times 10^{-2})$[c]			
$34.0 \times 10^{-2}(2.6 \times 10^{-2})$[e]	$34.5 \times 10^{-2}(2.3 \times 10^{-2})$[f]			
$33.1 \times 10^{-2}(2.1 \times 10^{-2})$				
Mean MD				
$9.9 \times 10^{-4}(8.0 \times 10^{-4})$[a,b,c]	$10.3 \times 10^{-4}(1.0 \times 10^{-4})$[e]			
$10.4 \times 10^{-4}(1.0 \times 10^{-4})$[f]	$11.0 \times 10^{-4}(1.0 \times 10^{-4})$			
Mean RD				
$8.1 \times 10^{-4}(8.0 \times 10^{-5})$[a,b,c]	$8.1 \times 10^{-4}(1.0 \times 10^{-4})$[e]	$8.5 \times 10^{-4}(1.0 \times 10^{-4})$[f]	$9.2 \times 10^{-4}(1.0 \times 10^{-4})$	
Mean AxD				
$13.6 \times 10^{-4}(8.0 \times 10^{5})$[a,b,c]	$14.0 \times 10^{4}(9.0 \times 10^{-5})$[e]			
$14.1 \times 10^{-4}(1.0 \times 10^{-4})$[f]	$14.7 \times 10^{4}(1.0 \times 10^{-4})$			
FDG (SUVR)	1.40(0.21)[a,b,c]	1.34(0.22)[d,e]	1.16(0.21)[f]	1.08(0.12)
AV45 (SUVR)	5.32(0.83)[a,b,c]	6.23(0.56)[d,e]	6.53(0.61)[f]	6.52(0.68)
CSF $A\beta_{1-42}$ (pg/ml)	210.9(51.8)[a,b,c]	168.2(49.1)[d,e]	155.5(51.8)[f]	135.6(33.9)
CSF t-tau (pg/ml)	62.9(25.1)[a,b,c]	79.2(61.3)[e]	114.3(57.3)[f]	139.3(71.7)
CSF p-tau_{181} (pg/ml)	33.3(12.4)[a,b,c]	36.9(26.5)[e]	49.9(26.0)[f]	65.7(41.8)

[a] CN v. early MCI ($p < 0.05$).
[b] CN v. late MCI ($p < 0.05$).
[c] CN v. AD ($p < 0.05$).
[d] Early MCI v late MCI ($p < 0.05$).
[e] Early MCI v. AD ($p < 0.05$).
[f] Late MCI v. AD ($p < 0.05$).

B), MD + Hippocampus + FDG (Model C), and MD + Hippocampus + FDG + AV45 (Model D). Secondary analyses substituted by RD or AxD for MD in Model A to test whether either of these components of MD was significantly associated with the composite scores.

Lastly, the specificity of the association between overall white matter MD and composite scores was tested in two steps. First, the association between composite score and each ROI MD were tested in independent linear mixed models (eTable 4–5 in Supplement). Second, a principal components analysis (PCA) was run on baseline ROI MD to determine subsets of correlated tracts independent of composite scores. Four components were estimated and optimized with varimax rotation. ROIs were associated with the component with greatest factor loading >0.5; ROIs with a loading <0.5 were not grouped with a component. The regression coefficients for each component were extracted and used as predictors nested by diagnosis in linear mixed models for composite scores analogous to Model A.

3. Results

3.1. Sample characteristics

Diagnostic groups differed in cognitive, imaging and biomarker characteristics as expected (Table 1). ADNI-MEM and ADNI-EF were significantly lower in each diagnostic group (CN > *E*-MCI > L-MCI > AD, $p < 0.05$). Similarly, elevating mean MD and lessening hippocampal volume showed stepwise differences between diagnostic groups ($p < 0.05$). Likewise, lessening FDG-PET SUVR and elevating AV45 uptake differed by diagnostic group in a stepwise fashion ($p < 0.05$).

3.2. Variable selection

Detailed report of baseline ridge regression can be found in Supplemental Materials (eTable 1). Based on these results, we selected mean MD, hippocampal volume, and PET FDG and AV45 to test as imaging correlates of ADNI-EF and ADNI-MEM in a stepwise fashion nested by diagnostic group.

3.3. Executive function

Predictors of baseline ADNI-EF score and change in score were modeled progressively in linear mixed models nested by diagnostic group at baseline ($N = 202$, data points = 498). ADNI-EF score significantly declined with time ($F = 5.996$, $p < 0.001$) in the combined group and within late MCI and AD, in models containing only an intercept and slope term.

In the initial model in which MD was the only modifier of change over time (Model A_{EF}), greater baseline ADNI-EF was significantly associated with lower average MD ($F = 3.348$, $p = 0.001$). This effect was significant within late MCI (Beta = −0.647, $p = 0.003$), and AD (Beta = −0.377, $p = 0.001$). MD did not significantly modify the rate of ADNI-EF decline in late MCI or AD, which did have a significant change in score (late MCI: Beta = −0.187, $p < 0.001$; AD: Beta = −0.269, $p = 0.006$). These results did not change significantly with the substitution of RD or AxD for MD. With the addition of hippocampal volume to the model (Model B_{EF}), greater baseline ADNI-EF remained significantly associated with lower MD in the combined group ($F = 5.699$, $p < 0.001$) and within late MCI and AD (Table 2).

Table 2
Longitudinal Model B for executive function.

	Overall		Cognitively normal		Early MCI		Late MCI		Dementia	
	F	p	Beta	p	Beta	p	Beta	p	Beta	p
Time (years)	2.028	0.090	0.059	0.146	0.050	0.095	−0.033	0.698	−0.297	0.082
Average MD	**5.699**	**0.000**	−0.156	0.253	0.065	0.586	**−0.681**	**0.005**	**−0.441**	**0.000**
Average MD*time	1.030	0.391	−0.052	0.271	−0.027	0.285	0.062	0.456	0.083	0.274
Hippocampal volume	0.759	0.554	−0.066	0.669	0.086	0.352	−0.015	0.931	−0.232	0.162
Hippocampal volume*time	**2.815**	**0.025**	0.013	0.776	**0.065**	**0.017**	**0.141**	**0.021**	−0.017	0.846
Age	**2.649**	**0.036**	−0.293	0.107	−0.045	0.727	**0.555**	**0.037**	0.214	0.067
Years of education	**4.006**	**0.004**	0.146	0.200	**0.321**	**0.001**	0.177	0.109	0.080	0.410
Male	1.753	0.143	−0.085	0.749	**−0.707**	**0.024**	−0.409	0.256	**−1.427**	**0.001**
APOE ε3/4 *or* 4/4	**2.916**	**0.024**	−0.091	0.739	−0.079	0.689	**1.247**	**0.002**	0.311	0.177
Intracranial vault	2.201	0.072	0.273	0.060	−0.158	0.188	−0.158	0.499	0.301	0.087

Bold values indicate significance at $p < 0.05$.

Lesser hippocampus volume was associated with greater ADNI-EF decline over time in the combined group ($F = 2.815$, $p = 0.025$). This effect was also significant within early and late MCI (Table 2). Model B_{EF} is reported in Table 2 to show the parameter estimates in the MRI-only markers. Prototypical trajectories by diagnostic group and by high or low global MD predicted by Model B_{EF} are illustrated in Fig. 1.

Next, PET FDG was modeled (Model C_{EF}, eTable 2 in Supplement) to test the additional value of PET markers. Lower MD was associated with greater baseline ADNI-EF in the combined group ($F = 3.191$, $p = 0.015$) and within late MCI ($p = 0.004$). In addition, greater baseline ADNI-EF was significantly associated with higher FDG SUVR ($F = 4.407$, $p = 0.002$) in the combined group and within early MCI ($p = 0.029$). Greater decline in ADNI-EF was also associated with lower FDG SUVR in the combined group ($F = 3.052$, $p = 0.017$) and within early ($p = 0.043$) and late MCI ($p = 0.008$). Adding PET AV45 to this model (Model D_{EF}) did not significantly modify the effect of baseline MD on either baseline or change in ADNI-EF.

In summary, MD and FDG were associated with contemporaneous ADNI-EF and hippocampal volume or FDG predicted the rate of change in ADNI-EF.

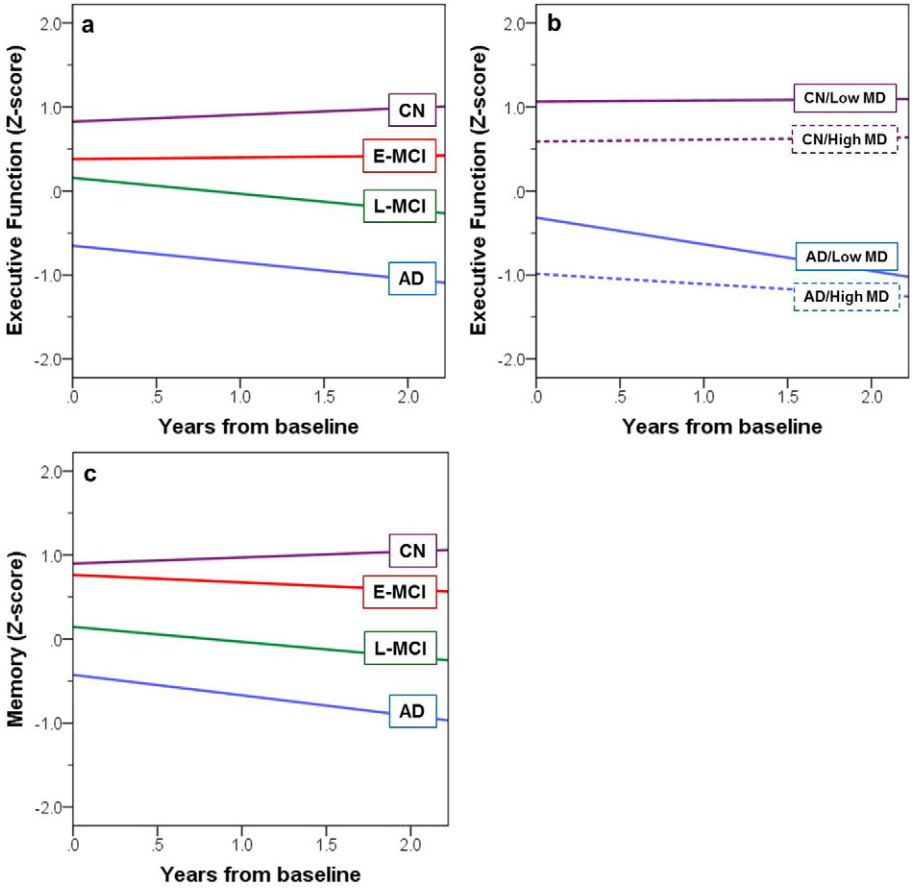

Fig. 1. Prototypical executive function and memory trajectories. Using parameter estimates from Tables 2 and 3 (Model B), estimated trends from baseline of (a) executive function and (c) memory scores are shown for prototype individuals in each diagnostic group: cognitively normal (CN, purple), early mild cognitive impairment (E-MCI, red), late mild cognitive impairment (L-MCI, green), and dementia (AD, blue). For each, the intercept represents a 74 year-old, *APOE ε4* negative male with a high school education and average intracranial volume as well as group-based average MD and hippocampus volume. In (b), the effect of low (−1 standard deviation, solid) and high (+1 standard deviation, dashed) MD is illustrated for CN and AD groups.

Table 3
Longitudinal Model B for memory.

	Overall		Cognitively normal		Early MCI		Late MCI		Dementia	
	F	p	Beta	p	Beta	p	Beta	p	Beta	p
Time (years)	**3.059**	**0.017**	**0.077**	**0.031**	**−0.064**	**0.013**	−0.081	0.272	−0.036	0.806
Average MD	0.344	0.848	0.000	0.996	−0.038	0.646	−0.089	0.591	−0.080	0.352
Average MD*time	0.134	0.970	0.020	0.628	0.011	0.610	0.004	0.961	0.013	0.847
Hippocampal volume	2.025	0.094	−0.081	0.446	**0.158**	**0.015**	0.130	0.289	−0.065	0.574
Hippocampal volume*time	**2.988**	**0.019**	0.044	0.272	**0.056**	**0.018**	0.087	0.106	0.120	0.114
Age	**4.435**	**0.002**	**−0.408**	**0.001**	−0.052	0.554	**0.376**	**0.037**	0.107	0.185
Years of education	1.516	0.202	−0.075	0.333	**0.142**	**0.032**	0.028	0.709	−0.033	0.616
Male	**3.213**	**0.015**	−0.316	0.081	**−0.471**	**0.028**	**−0.649**	**0.010**	**−1.544**	**0.000**
APOE ε3/4 or 4/4	**3.100**	**0.018**	**−0.454**	**0.016**	−0.223	0.100	0.473	0.087	0.133	0.401
Intracranial vault	2.071	0.088	0.164	0.096	0.017	0.831	−0.105	0.508	**0.271**	**0.027**

Bold values indicate significance at $p < 0.05$.

3.4. Memory

ADNI-MEM significantly declined annually in the combined group ($F = 3.059$, $p = 0.017$) and within early MCI ($p = 0.013$). ADNI-MEM increased with time in the CN group ($p = 0.031$). Those who were younger ($F = 4.435$, $p = 0.002$) and female ($F = 3.213$, $p = 0.015$) had greater ADNI-MEM at baseline in the combined group, and those CN individuals who were APOE ε4 negative had greater baseline ADNI-MEM ($p = 0.016$).

In Model A_{MEM} and all subsequent models, ADNI-MEM at baseline or change in ADNI-MEM was not significantly associated with mean MD (nor by RD or AxD substitutions). Lesser hippocampus volume was associated with faster decline in ADNI-MEM in the combined group ($F = 2.998$, $p = 0.019$, Model B_{MEM}; $F = 2.602$, $p = 0.036$, Model C_{MEM}), and within early MCI ($p = 0.018$). Lesser baseline FDG SUVR was associated with faster decline in ADNI-MEM in the combined group ($F = 8.068$, $p < 0.001$, Model C_{MEM}; $F = 5.487$, $p < 0.001$, Model $D_{MEM;}$ eTable 3 in Supplement). AV45 was not significantly associated with baseline or change in ADNI-MEM. Fig. 1c shows prototypical ADNI-MEM trajectories by diagnostic group.

In summary, none of the selected imaging parameters were significantly associated with contemporaneous ADNI-MEM score, yet both hippocampal volume and FDG were associated with change in ADNI-MEM.

3.5. Regional specificity of MD associations with ADNI-EF

Based on PCA of forty-six white matter ROIs, tracts grouped together into four distinct components (Fig. 2). *Component 1* (31.6% variance explained) included all corpus callosum regions (GCC, BCC, SCC), sagittal stratum (SS), all corona radiata (ACR, SCR, PCR), posterior thalamic radiation (PTR), fornix (Fx) and fornix/stria terminalis (FxST). *Component 2* (17.7% variance explained) included all parts of the internal capsule (ALIC, PLIC, RLIC), external capsule (EC), superior longitudinal fasciculus (SLF), and body of the cingulum (CGC). *Component 3* (12.0% variance explained) included the cerebellar peduncles (SCP, ICP), corticospinal pathways (CST, ML). *Component 4* (10.5% variance explained) included the hippocampal part of the cingulum (CGH), unicate fasciculus (UNC), and inferior fronto-occipital fasciculus (IFO).

Greater ADNI-EF score was significantly associated with lower MD for *Component 1* ($F = 5.799$, $p < 0.001$) and *Component 2* ($F = 3.959$, $p = 0.005$) in the combined group and within late MCI (*Component 1* $p = 0.001$, *Component 2* $p < 0.001$) (Table 4). As with global MD, MD in none of the components predicted ADNI-EF change.

4. Discussion

In this ADNI sample, global white matter integrity, measured by MD, provided additional predictive value to contemporaneous executive function across all diagnoses, especially with more severe cognitive impairment. Though we tested many metrics of dMRI for white matter integrity, we did not find unique strength in any of these to modify the rate of cognitive decline. Therefore, we lack evidence that global diffusion parameters extracted from single-shell HARDI dMRI technology are promising predictors of two to three year executive function change (Kim et al., 2016). The temporal disconnect may be due to the time course of age-related white matter integrity decrement, which is estimated at 3% per decade over the life-span (Grieve et al., 2007). White matter microstructural integrity at baseline may not be sufficiently sensitive to the subtle changes in executive function over this short timeframe.

Predictors of executive function are important because impairment in this domain increases the likelihood of conversion to dementia

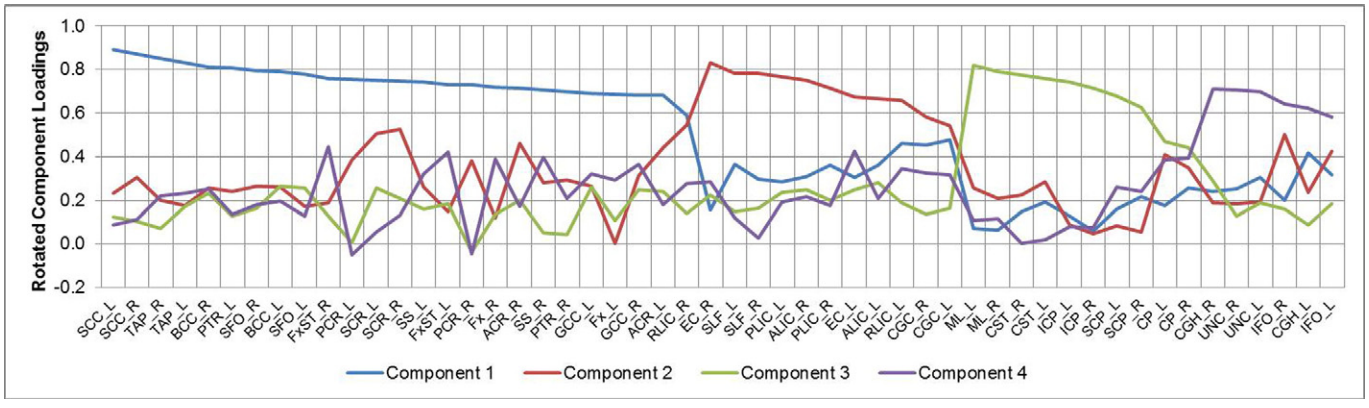

Fig. 2. Rotated component loadings for each ROI MD. (1 = blue, 2 = red, 3 = green, 4 = purple). ROI definitions are listed in the results. Key to ROI abbreviations listed in eTable 5.

Table 4
Longitudinal model for executive function with MD component coefficient predictors.

	Overall		Cognitively normal		Early MCI		Late MCI		Dementia	
	F	p	Beta	p	Beta	p	Beta	p	Beta	p
Time (years)	**4.152**	**0.003**	0.124	0.051	0.002	0.947	**−0.137**	**0.038**	**−0.292**	**0.004**
Component 1	**5.798**	**0.000**	0.098	0.693	−0.025	0.846	**−0.971**	**0.001**	**−0.420**	**0.001**
Component 1*time	0.765	0.549	0.038	0.617	−0.053	0.120	−0.010	0.926	0.052	0.540
Component 2	**3.959**	**0.005**	−0.162	0.098	0.041	0.710	**−0.560**	**0.000**	−0.063	0.676
Component 2*time	0.801	0.525	−0.004	0.918	−0.005	0.865	0.040	0.492	0.159	0.102
Component 3	0.543	0.704	−0.093	0.384	0.083	0.366	0.089	0.615	−0.049	0.564
Component 3*time	1.337	0.256	**−0.075**	**0.026**	−0.011	0.743	0.017	0.802	0.023	0.655
Component 4	1.541	0.194	0.071	0.767	−0.175	0.213	−0.076	0.801	**−0.246**	**0.037**
Component 4*time	1.324	0.260	0.005	0.944	−0.084	0.092	−0.194	0.126	0.021	0.767
Diagnosis at baseline	**2.524**	**0.045**	−0.303	0.087	−0.081	0.528	**0.607**	**0.023**	0.144	0.238
Age	**3.354**	**0.012**	0.059	0.641	**0.316**	**0.001**	0.145	0.181	0.048	0.616
Years of education	0.984	0.419	0.041	0.885	**−0.767**	**0.020**	**−0.708**	**0.048**	**−1.050**	**0.003**
Male	**2.677**	**0.035**	−0.127	0.616	−0.132	0.498	1.172	0.004	0.257	0.256
APOE ε3/4 or 4/4	0.657	0.623	0.162	0.313	−0.096	0.424	−0.003	0.990	0.177	0.330
Intracranial vault	**4.152**	**0.003**	0.124	0.051	0.002	0.947	**−0.137**	**0.038**	**−0.292**	**0.004**

Bold values indicate significance at $p < 0.05$.

(Ewers et al., 2014; Cloutier et al., 2015). We and others have observed a more apparent relationship between white matter integrity and executive function compared to that with memory (Hedden et al., 2012; Nir et al., 2013; Chang et al., 2015). The first use of the ADNI-EF composite score with the ADNI-1 cohort demonstrated an association with WMH (Gibbons et al., 2012), but this was not reported in the analysis for the ADNI-MEM composite score (Crane et al., 2012). The ADNI-EF composite is composed of tasks that test working memory, response generation and inhibition, planning and organizing. These tasks are largely dependent on fluid intelligence, which is thought to be more vulnerable to damage to cortical connectivity, in contrast to crystallized intelligence like episodic memory (Madden et al., 2012; Ritchie et al., 2015). Age-related decrement in white matter integrity may be a key factor in executive function performance in older adults, especially in those with comorbid memory impairment. The association between white matter microstructure and executive function observed in the combined groups was driven by those with the most severe memory impairments (late MCI and AD). Thus, the effect of white matter microstructure decrement on executive function may only be apparent in older adults that have other pathological processes impairing cognitive function in this sample which is biased towards those with AD pathology.

Of the various mechanistic possibilities raised, impaired connectivity is the most plausible explanation for the association between executive function and white matter integrity. Some DTI network analyses find that decreased nodal or global efficiency correlates with executive function or working memory (Fischer et al., 2015; Kim et al., 2016). Further, we found no distinction between AxD and RD associations with cognition, which suggests that neither axonal degeneration nor demyelination can be ruled out as contributors to lower MD in mild cognitive impairment and dementia (Nir et al., 2013). Typical age-associated white matter integrity loss is linked to changes in myelination without microglia activation or axonal injury—correlated with change in RD alone (Peters, 2002). In the presence of Alzheimer's-type pathology, axonal injury also compromises white matter integrity as measured by AxD (Peters, 2002; Molinuevo et al., 2014) concurrent with responsive myelin repair processes (Bartzokis, 2011). This is likely why we observed strong correlations with both RD and AxD in those with evident Alzheimer's disease progression—late MCI and AD. However, this interpretation is limited by our use of mean AxD and RD over multiple ROIs. Wheeler-Kingshott and Cercignani demonstrated that changes in a single component of MD can alter the other in regions with complex underlying structure (Wheeler-Kingshott and Cercignani, 2009). Thus we cannot assume that global associations with demyelination or axonal injury extend to individual white matter ROIs.

While overall MD and most tracts were significantly associated with executive function in this sample and in a previous analysis of ADNI (Nir et al., 2013), other studies have singled out particular white matter tracts. Previous works analyzing diffusion parameters have linked poorer cognitive control, executive function or processing speed to tracts associated with the cingular cortex and frontal lobe (He et al., 2012; Metzler-Baddeley et al., 2012; Jacobs et al., 2013; Lin et al., 2014; Chang et al., 2015; Santiago et al., 2015). Many of these studies selected white matter ROIs *a priori*, which obviated correlations with other white matter regions. The few studies that surveyed a range of cortical tracts reported associations between higher MD in associative and commissural fibers throughout the cortex and poorer executive function, but did not formally test whether global dMRI associations with executive function were present (Jacobs et al., 2013; Ciulli et al., 2016). We have shown that global MD does have a strong association with executive function as well as which tracts have the strongest associations. In agreement with previous studies of older adults with cerebral small vessel disease (Jacobs et al., 2013; Ciulli et al., 2016), the results of our comprehensive ROI analyses, by individual tracts and by PCA, suggest that poorer white matter microstructure throughout the cortex, not exclusively frontal associated tracts, may serve as an effective indicator of executive function performance. We found that the majority of projection and associative fibers of the cerebral cortex (*Components 1* and *2*) were associated with contemporaneous ADNI-EF, indicating minimal regional specificity in the relationship between MD and ADNI-EF. *Component 1* included primarily large commissural and associative fiber pathways that cover the majority of cortical white matter. While *Component 2* pathways were all associated with frontal and cingular cortex either as associative or projection fibers, which would be the expected regions associated with executive function.

Many of our results are consistent with the previous studies of cognitive correlates in that metabolic changes in the brain and hippocampal atrophy are highly correlated with performance, while amyloid burden is weakly associated temporally. Our findings reinforce the relevance of FDG-PET as an important imaging marker of multi-domain cognitive status (Wirth et al., 2013a, b; Ewers et al., 2014). These effects were most pronounced in the MCI groups, which were undergoing the greatest change in cognitive performance. Amyloid burden was only weakly associated with cognition after accounting for MRI and PET measures (Wirth et al., 2013a, b; Teipel et al., 2015). These results support the validity of our data set and analytic approach.

Future work in other samples should assess the degree to which associations between WM microstructure and executive function are influenced by cerebrovascular injury. Vascular contributions to WM injury, typically identified on MR imaging through white matter hyperintensities or silent infarction, and acceleration of cognitive decline are well established (Gorelick et al., 2011; Lo et al., 2012; van

Norden et al., 2012; Bilello et al., 2015; Snyder et al., 2015). Impaired clearance of amyloid (Rincon and Wright, 2014), damaged blood brain barrier (Farrall and Wardlaw, 2009; Bell et al., 2012), and chronic inflammation (Greer, 2002; Jin et al., 2010) are all associated with vascular risk factors such as hypertension (Baumgart et al., 2015) and cerebral small vessel disease (Snyder et al., 2015). In addition, the microstructural markers we assess here are associated with both vascular risk factors and WMHs (Maillard et al., 2013; Maillard et al., 2014). The ADNI cohort carries a relatively low burden of vascular risk factors and overt vascular diseases, thus limiting our ability to determine whether associations between diffusion MRI metrics and executive function represent contributions from cerebrovascular injury processes. However, the role that diffusion MRI can play in the study of vascular cognitive impairment is clearly important and worthy of future study.

dMRI technologies are evolving quickly. Newer, enhanced dMRI data, such as network analyses or compartmental modeling, could give different results that are sensitive to longitudinal change (Fischer et al., 2015; Kim et al., 2016).

4.1. Conclusion

Cerebral white matter integrity, as measured by global MD, contemporaneously predicts level of executive function, but not memory, in older adults with cognitive impairment. Since multi-domain impairment has been associated with faster functional decline (Gross et al., 2012; Ewers et al., 2014; Chang et al., 2015; Kirova et al., 2015; Knopman et al., 2015), global dMRI white matter diffusivity may disambiguate neural correlates of multi-domain impairment in dementia when MRI alone is available (Voineskos et al., 2012; Hedden et al., 2016).

Disclosures

Authors do not have any conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2017.01.026.

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