Patients with Mild Cognitive Impairment May be Stratified by Advanced Diffusion Metrics and Neurocognitive Testing

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ABSTRACT

BACKGROUND AND PURPOSE: **Mild cognitive impairment (MCI) is a prevalent disorder, with a subset of patients progressing to dementia each year. Although MCI may be subdivided into amnestic or vascular types as well as into single or multiple cognitive domain involvement, most prior studies using advanced diffusion imaging have not accounted for these categories. The purpose of the current study was to determine if the pattern of diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) metrics in patients with amnestic MCI (aMCI) correlate to specific cognitive domain impairments.**

METHODS: **Nineteen consecutive patients with aMCI referred for brain magnetic resonance imaging (MRI) were included. All subjects underwent neurocognitive testing. A *z*-score was calculated for each domain and a composite of all four domains. Brain MRI included standard structural imaging and diffusion imaging. Volumetric, DTI, and DKI metrics were calculated and statistical analysis was performed with adjustments for multiple measures and comparisons.**

RESULTS: **Statistically significant correlations between diffusion metrics and cognitive *z*-scores were detected: visuospatial-visuoconstructional *z*-scores only correlated with alterations in the corpus callosum splenium, executive functioning *z*-scores with the corpus callosum genu, memory testing *z*-scores with the left hippocampus, and composite *z*-scores with the anterior centrum semiovale.**

CONCLUSION: **Neuroimaging studies of patients with aMCI to date have assumed a population with homogeneous cognitive impairment. Our results demonstrate selective patterns of regional diffusion metric alterations correlate to specific cognitive domain impairments. Future studies should account for this heterogeneity, and this may also be useful for prognostication.**

Keywords: Mild cognitive impairment, MCI, diffusion imaging, DTI, DKI.

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Introduction

Mild cognitive impairment (MCI) is a prevalent disorder, affecting 3-19% of adults over 65 years old,[1] and is defined by cognitive decline greater than expected for age and education level with only a mild impact upon an individual's activities of daily living.[2] MCI may be subdivided based upon etiology, amnestic MCI (aMCI) or vascular MCI,[2,3] and aMCI may be further classified as single or multiple domain if cognitive domains other than memory are also impaired, such as visuospatial-visuoconstructional, executive function, or language.[2] MCI may be conceptualized as a transitional stage between mild cognitive decline related to normal aging and dementia.[4] Patients with MCI progress to dementia, generally Alzheimer's disease (AD), at a rate of up to 18% per year[5] and it has been estimated that up to 80% of patients with aMCI develop dementia after 6 years.[6] Therefore, it is important both to diagnose MCI and, potentially, to stratify patients into disease subtype as well as likelihood and timeline of progressing to dementia. In addition, while clinical diagnosis and research studies of patient conversion from aMCI to dementia primarily focus on memory dysfunction, impairment across multiple domains, particularly executive function, is prognostic and predicts a more rapid decline.[7,8]

Several studies have demonstrated diffusion metric alterations in patients with MCI using advanced MRI diffusion techniques, such as diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI). Two of the most widely reported DTI metrics, fractional anisotropy (FA) and mean diffusivity (MD), have been shown to be altered in patients with MCI in comparison to healthy controls. Decreased FA and/or increased MD has been reported in the multiple white matter tracts, including the corpus callosum and cingulate bundle,[9] as well as within the hippocampus.[10,11] Mean kurtosis (MK) is a metric of DKI that describes the degree to which a structure deviates from a Gaussian distribution and, therefore, may be simplistically defined as a measure of tissue heterogeneity.[12] A few studies have demonstrated decreased MK in the gray and white matter of patients with MCI.[13–15]

Prior reports of altered diffusion metrics have largely combined patients with MCI or were restricted to aMCI and frequently did not consider phenotypic variations in these patient populations. A recent study by Liu et al stratified patients with aMCI into those with restricted memory deficits versus

Table 1. Population Demographics and Comorbidities

Demographic	Number Mean ± SD
Men	8 (42%)
Women	11 (58%)
Age (years)	72.7 + 8.6
Formal education (years)	14.5 ± 3.2
Disease duration (years)	3.9 ± 2.3
Comorbidity	**Number**
Hypertension	15 (79%)
Hyperlipidemia	12 (63%)
Diabetes	4 (21%)
Coronary artery disease	3 (16%)
Tobacco use	4 (21%)
Obstructive sleep apnea	0 (0%)
Atrial fibrillation	1 (5%)
Chronic renal disease	0 (0%)
Migraine	0 (0%)
Prior cerebral infarction*	1 (5%)
Anticardiolipin antibody status	1 (5%)

*Lacunar infarction. No territorial or large vessel infarctions.
SD = standard deviation.

patients with impairments in multiple cognitive domains.[16] They reported that while FA was decreased in the right superior longitudinal fasciculus in both aMCI groups compared to control subjects, there was a distinct pattern of FA in single domain aMCI compared to multiple domain aMCI, with the former group characterized by decreased FA in the left uncinate fasciculus and left inferior longitudinal fasciculus and increased FA in the left anterior thalamic radiation. Furthermore, these alterations were significantly correlated with the Boston Naming and Trail Making Tests.

The purpose of the current study was to determine if the pattern of DTI and DKI metrics in patients with aMCI correlate to impairments in specific cognitive domains. We hypothesize that performance in each cognitive domain will correlate with alterations of diffusion metrics in brain region(s) that are thought to be primarily responsible for that cognitive function. These specific patterns may eventually help predict subclinical deficits and stratify patients with aMCI for future therapeutic interventions.

Methods

Subjects

The study was approved by our Institution Review Board (IRB). Informed consent was not obtained for this retrospective study. A total of 19 consecutive patients diagnosed with aMCI and referred for brain MRI were included in the study (Table 1). Clinical diagnosis of MCI was made using the National Institute on Aging-Alzheimer's Association guidelines.[17] Review of the electronic medical record for each patient was performed to assess for the presence or absence of comorbidities as listed in Table 1.

All of the subjects underwent formal neurocognitive testing at our institution, which included the Montreal Cognitive Assessment (MoCA) test. In addition, the following tests that assess specific cognitive domains were administered to each subject: Benson Figure Copy (visuospatial-visuoconstructional); Boston Naming Test (language); Controlled Oral Word Association, FAS version, and Trail Making Test, part B (executive function); and Word List Recall and Benson Figure Delay (memory testing). A *z*-score was calculated for each of these domains and a composite *z*-score was also calculated, which was the average of the tests of all four domains.

Image Acquisition

All subjects were referred for clinical brain imaging that included standard sequences in addition to advanced diffusion imaging. All MR scans were obtained on the same 3T Magnetom Tim Trio scanner (Siemens, Erlangen, Germany) including the following sequences: T1 MPRAGE (TR/TE = 2,300/2.74 ms, FoV 256 mm, slice thickness 1.2 mm), T2 FLAIR (TR/TE = 8,000/91 ms, FoV 240 mm, slice thickness 5.0 mm), T2 TSE (TR/TE = 6,000/84 ms, FoV 240 mm, slice thickness 5 mm), T2 GRE (TR/TE = 668/20 ms, FoV 230 mm, slice thickness 5.0 mm), and DTI (TR/TE = 6,800/92 ms, FoV 220 mm, slice thickness 2.0 mm, b values 0/1,000/2,000 s/mm^2, 30 directions). All images were reviewed by a board certified Neuroradiologist and a clinical report was generated separate from the analysis described below.

Data Processing and Analysis

The anatomic T1 MPRAGE images for each subject were processed for volumetric analysis using NeuroQuant, an automated segmentation software package that provides volumes for 11 structures: forebrain, cortical gray matter, lateral ventricle, inferior lateral ventricle, hippocampus, amygdala, caudate, putamen, globi palladi, thalamus, and cerebellum. NeuroQuant has been previously demonstrated to reliably segment these structures in comparison to manual segmentation.[18]

Estimates of cerebral small vessel disease burden for each subject were performed using the technique described by Staals et al.[19] In brief, T2, T2 FLAIR, and T2 GRE images were scored by a Neuroradiologist blinded to the cognitive testing results for the following features: lacunes, microbleeds, perivascular spaces, and white matter hyperintensities. A composite score from 0 (no evidence of small vessel disease) to 4 (severe disease) was generated for each subject.

Diffusion postprocessing was performed using the Diffusion Kurtosis Estimator software.[20] FA, MD, axial diffusivity, radial diffusivity, MK, axial kurtosis, and radial kurtosis maps were generated for each subject. These maps were aligned and regions of interest (ROI) were manually drawn on the b0 images for the following structures: anterior centrum semiovale, posterior centrum semiovale, corpus callosum genu, corpus callosum splenium, posterior limb of the internal capsule, thalamus, and hippocampus (Fig 1). These ROI were then propagated across all of the diffusion maps and the metric values were recorded. B0 images were chosen for ROI placement as the anatomic structures of interest were easily identified on this sequence and the use of b0 images mitigated the effects of motion and potential biases introduced during alignment of anatomic sequences to the diffusion maps. The Neuroradiologist placing ROI was blinded to the cognitive testing results of the subjects.

Statistical analysis was performed between the volumetric measurements and the subject cognitive testing *z*-scores as well as between the diffusion metrics for each ROI and the subject cognitive testing *z*-scores. Kendall tau coefficients were calculated for each of these. Adjustment for multiple

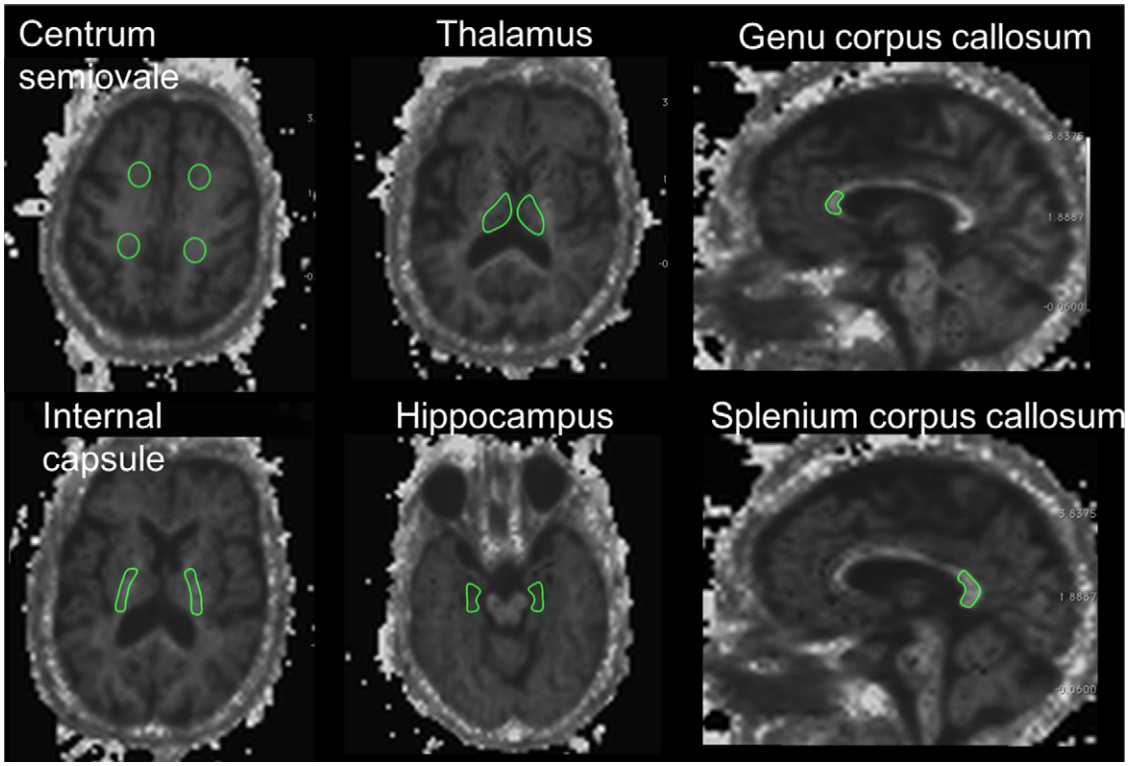

Fig 1. Placement of region of interest (ROI) for diffusion metrics. Fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, mean kurtosis, axial kurtosis, and radial kurtosis maps were generated for each subject. These maps were aligned and ROI were manually drawn for the following structures: anterior centrum semiovale, posterior centrum semiovale, thalamus, corpus callosum genu, corpus callosum splenium, posterior limb of the internal capsule, and hippocampus (outlined in green). These ROI were then propagated across all of the diffusion maps and the metric values were recorded.

Table 2. Cognitive Testing Population Mean Scores

Cognitive Domain/Test*	Mean ± SD
Visuospatial-visuoconstructional	−2.19 ± 4.61
Language	−2.02 ± 2.52
Executive functioning	−1.17 ± 1.50
Composite	−5.04 ± 4.07
MoCA	19.84 ± 5.80

*MoCA is raw score mean ± SD; cognitive domains are *z*-scores ± SD.
MoCA = Montreal Cognitive Assessment; SD = standard deviation.

measures and comparisons was performed using false discovery rate correction as described by Benjamini and Hochberg.[21] P values $\leq .05$ were considered significant.

Results

Cognitive Testing

The study population *z*-score mean and standard deviation for each cognitive testing domain and MoCA are listed in the Table 2.

Volumetric Analysis

With the exception of a positive association between left hippocampal volume and a higher performance on memory testing, there were no statistically significant correlations between any structural volumes calculated by NeuroQuant and the cognitive testing *z*-scores (Table 3). Furthermore, the combined hippocampal volume for each subject was greater than the age-matched 5th percentile volume as provided by NeuroQuant.

Cerebral Small Vessel Disease Burden Analysis

The average small vessel disease score for the included subjects was .79 with a standard deviation of 1.08 using the method described by Staals et al (range 0-4).[19] As shown in Table 1, only a single subject had a prior lacunar infarct. The overall small vessel disease burden for subjects ranged from none to mild.

DTI/DKI Analysis

Statistically significant correlations were detected between diffusion metrics and cognitive testing *z*-scores (Table 4). A higher *z*-score for each cognitive test indicates higher performance. Therefore, negative correlations indicate that this metric is increased in subjects with poor performance and positive correlations indicate that this metric is decreased in subjects with poor performance.

Visuospatial-visuoconstructional testing *z*-scores were solely correlated with alterations in corpus callosum splenium diffusion metrics. Corpus callosum splenium MD values were negatively correlated and FA and MK values were positively correlated. Performance on executive functioning was negatively correlated only with corpus callosum genu MD values and positively correlated with FA and MK values. Left hippocampal MD values were negatively correlated only with memory testing *z*-scores. Composite cognitive testing *z*-score was positively correlated solely with MK values in both the right and left anterior centrum semiovale. No significant correlations were

Table 3. Correlation between NeuroQuant Segmentation Volumes and Cognitive Domain *Z*-Scores

NeuroQuant Segmentation		Cognitive Domain *Z*-Score: Correlation Estimate (*P*-Value)				
		Visuospatial-Visuoconstructional	Language	Executive	Memory	Composite
Cortical gray	R	.40 (.26)	.18 (1.00)	.09 (.82)	.16 (.94)	.23 (.68)
	L	.32 (.72)	.04 (.97)	.08 (.76)	.20 (.97)	.11 (.91)
Forebrain	R	.39 (.29)	.08 (1.00)	.21 (.82)	.14 (.94)	.14 (.68)
	L	.33 (.72)	−.01 (.97)	.24 (.76)	.11 (.97)	.13 (.91)
Hippocampus	R	−.01 (1.00)	−.17 (1.00)	.25 (.82)	.38 (.31)	.19 (.68)
	L	−.06 (.85)	−.08 (.97)	.28 (.76)	.56 (.01)*	.22 (.91)
Amygdala	R	−.10 (1.00)	−.04 (1.00)	−.04 (.82)	.36 (.40)	.09 (.68)
	L	−.03 (.85)	.01 (.97)	.21 (.76)	.46 (.08)	.19 (.91)
Caudate	R	.05 (1.00)	−.31 (.90)	−.07 (.82)	−.16 (.94)	−.14 (.68)
	L	.11 (.85)	−.29 (.97)	−.09 (.76)	−.01 (.97)	−.12 (.91)
Putamen	R	.26 (1.00)	.04 (1.00)	.16 (.82)	−.18 (.94)	.10 (.68)
	L	.08 (.85)	.13 (.97)	.26 (.76)	.02 (.97)	.14 (.91)
Pallidum	R	.16 (1.00)	.00 (1.00)	.21 (.82)	.03 (.94)	.07 (.68)
	L	.08 (.85)	.13 (.97)	.18 (.76)	.07 (.97)	.11 (.91)
Thalamus	R	.26 (1.00)	.11 (1.00)	.08 (.82)	−.11 (.94)	.20 (.68)
	L	−.09 (.85)	−.26 (.97)	−.05 (.76)	.12 (.97)	.02 (.91)

R = right; L = left.
*$P \leq .05$

Table 4. Correlation between Cognitive Testing *Z*-Scores and Diffusion Metrics

Cognitive Test ROI	Diffusion Metric	Correlation Estimate	*P*-Value
Visuospatial-Visuoconstructional			
Corpus callosum splenium	MD	−.379	.05*
	FA	.398	.04*
	MK	.507	<.01*
Executive Functioning			
Corpus callosum genu	MD	−.283	.10
	FA	.603	<.01*
	MK	.407	.02*
Memory			
Right hippocampus	MD	−.322	.06
	FA	.172	.32
	MK	−.244	.21
Left hippocampus	MD	−.380	.02*
	FA	.272	.12
	MK	−.107	.88
Composite Score			
Right anterior centrum semiovale	MD	−.126	.52
	FA	−.010	.96
	MK	.485	<.01*
Left anterior centrum semiovale	MD	−.282	.15
	FA	−.087	.65
	MK	.354	.04*

ROI = region of interest; FA = fractional anisotropy; MD = mean diffusivity; MK = mean kurtosis.
*$P \leq .05$

identified for brain ROI, diffusion metrics, or cognitive testing *z*-scores not listed in Table 4.

Discussion

While prior studies have demonstrated alterations in advanced diffusion metrics in patients with MCI, the majority of these have either included all subjects clinically diagnosed with MCI, irrespective of their particular cognitive deficit or etiology, or have divided subjects into two broad classifications–vascular and amnestic MCI. Here, we demonstrate that in patients with aMCI, specific cognitive deficits correlate with alterations in diffusion metrics solely in specific brain regions. Our data suggest that it is important to consider the heterogeneity of patients with aMCI when designing and interpreting neuroimaging studies and the grouping of patients with aMCI with a variety of deficits may account for the wide range of sometimes conflicting alterations in DTI metrics that have been described in the literature. Furthermore, if these findings are validated in larger longitudinal studies, the specific patterns of diffusion metric alterations may potentially be beneficial in stratifying patients by their risk of developing AD or other neurodegenerative disorders.

The correlations described in the current study between DTI/DKI metric alterations and particular cognitive domain testing followed an expected pattern. Decreased FA and MK and increased MD within the corpus callosum splenium correlated with visuospatial-visuoconstructional *z*-scores. Given that lesion analysis studies map several deficits in figure copying to the parietal and occipital lobes,[22] it is not unexpected that the major interhemispheric white matter tracts linking these regions should be the only fiber tracts that correlate with impairment in this domain. Similarly, this pattern of diffusion metric changes was correlated with executive functioning *z*-scores, but only within the corpus callosum genu, reflecting the frontal lobe localization of the executive functioning testing used in the current study.[23] Although only left hippocampal MD changes were selectively significantly correlated with memory *z*-scores, with a trend for right hippocampal MD metrics, this is consistent with working memory localization to the hippocampus.[24] It is likely that the right hippocampal metrics did not reach significance due to the relative small sample size included in the study. While this is a simplistic reduction of the complexity of brain activation that likely occurs with each of the cognitive tests used, the patterns of deficits follow the conventional brain localization for each of the domains tested.

Cognitive testing composite *z*-score was only correlated with MK in the bilateral anterior centrum semiovale, which may be a result of the composite score, by its definition, reflecting multiple cognitive domains. Our results are similar to those recently described by Liu et al, who also failed to identify a specific pattern in DTI metric alterations in patients with multiple domain aMCI. We hypothesize that the selective correlation found in the current study between MK and the composite *z*-score, which is expected to be higher in patients with multiple domain aMCI, may be driven by those subjects with the most widespread alterations as the heterogeneity of specific brain regions and diffusion metric correlations may be statistically "canceled" on a group level.

It is interesting that the standard DTI metrics were not significantly correlated with the composite *z*-score, whereas MK was the only metric to correlate with the composite *z*-score, in addition to MK correlated with additional selective brain regions and several cognitive tests (Table 4). In a recent study by Gong et al in patients with aMCI, of the diffusion metrics, MK also was found to have the largest number of regions with significant abnormalities in comparison to control subjects.[15] Furthermore, MK has also been found to be significantly altered in patients with mild traumatic brain injury at a delayed time point, a time at which conventional DTI metrics were unchanged.[25] Coupled with our results, this suggests that MK may be a more sensitive marker of tissue injury, irrespective of etiology.

There are several limitations to the current study. The relatively small sample size limits the number of subjects that demonstrated deficits in particular cognitive domains; however, frank deficits in a domain were not required as we investigated correlations between the score and imaging metrics. We also only used a limited number of cognitive tests for each domain. The tests used do represent some of the most commonly used clinical tests and are reflective of the cognitive battery currently used in our Memory Clinic. Finally, the presence of small vessel disease that is present on average in patients of the age included in the study may impact the distribution of diffusion metric alterations. However, the average small vessel disease burden of the study population was low (.78 on a scale of 0-4), mitigating the impact of small vessel disease. Despite these limitations, several imaging metrics were correlated with cognitive testing performance in select brain regions proposed to be primarily involved in that cognitive domain.

Although neuroimaging studies of patients with aMCI to date have implicitly assumed a homogeneous patient population in reference to cognitive impairment, the current study demonstrates that there is a selective pattern of regional diffusion metric alterations that correlate to specific cognitive domain testing. This heterogeneity should be considered in future studies and, with further study, may prove useful in prognostication.

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