

# White matter abnormalities and cognition in patients with conflicting diagnoses and CSF profiles

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## Abstract

### Objective

To determine whether white matter changes influence progression of cognitive decline in individuals with clinically diagnosed Alzheimer disease (AD) and differing biomarker profiles.

### Methods

Two hundred thirty-six individuals from the Alzheimer's Disease Neuroimaging Initiative database with clinical diagnoses of cognitively normal older adult (older controls [OCs]), mild cognitive impairment, and AD were studied. Support vector machine experiments were first performed to determine the utility of various biomarkers for classifying individuals by clinical diagnosis. General linear models were implemented to assess the relationships between CSF measures of  $\beta$ -amyloid 1–42, phosphorylated tau<sub>181p</sub>, and MRI-based white matter signal abnormality (WMSA) volumes and cognitive decline. Analyses were performed across all patients as well as within subgroups of individuals that were defined by clinical cutoff points for both CSF measures.

### Results

CSF biomarkers alone classified individuals with AD vs OCs with 82% accuracy, and the addition of WMSA did not enhance this. Both CSF biomarkers as well as WMSA volume significantly contributed to predicting cognitive decline in executive and memory domains when assessed across all 236 individuals. In individuals with pathologic levels of both CSF biomarkers, WMSA only significantly contributed to models of future executive function decline. In individuals with subpathologic CSF biomarker levels (levels similar to those in OC individuals), WMSA significantly contributed to prediction of memory decline and were the sole significant predictor of executive function decline.

### Conclusions

WMSA hold additional predictive power regarding cognitive progression in older individuals and are most effective as biomarkers in individuals who are cognitively impaired but do not fit the expected CSF biomarker profile of AD.

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## Glossary

$A\beta_{42}$  =  $\beta$ -amyloid 1–42; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **ADNI-EF** = Alzheimer's Disease Neuroimaging Initiative–executive function; **ADNI-MEM** = Alzheimer's Disease Neuroimaging Initiative–memory; **GLM** = general linear model; **MCI** = mild cognitive impairment; **MCI-C** = mild cognitive impairment–conversion; **MCI-NC** = mild cognitive impairment–no conversion; **OC** = older control; **p-tau<sub>181p</sub>** = tau phosphorylated at threonine 181; **Q** = quadrant; **RSS** = residual sum of squares; **SVM** = support vector machine; **WMSA** = white matter signal abnormality.

Dementia refers to a varied collection of cognitive impairment syndromes whose underlying causes are often difficult to elucidate. Of these, the most common is Alzheimer disease (AD), which is pathologically diagnosed based on abnormal amyloid and tau pathology but is also highly comorbid with additional pathologic processes.<sup>1,2</sup> To date, clinical trials that target amyloid and tau have been largely unsuccessful, suggesting that other factors that affect cognition either independently or in concert with amyloid and tau are at play and warrant deeper consideration.<sup>3</sup>

CSF levels of  $\beta$ -amyloid 1–42 ( $A\beta_{42}$ ) and tau phosphorylated at threonine 181 (p-tau<sub>181p</sub>) are two of the most clinically utilized biomarkers of AD<sup>4–6</sup> and are related to the presence of  $A\beta$  plaques and tau neurofibrillary tangles in the cerebral cortex.<sup>7</sup> Autopsy studies, however, have demonstrated the presence of AD pathologies in the cerebral cortices of individuals who had fully intact cognitive functioning, as well as a lack thereof in individuals who passed away with a clinical diagnosis of AD.<sup>8,9</sup>

There is a strong body of evidence suggestive of a cerebrovascular component to AD.<sup>9–11</sup> White matter signal abnormalities (WMSA) as seen on MRI are used as a surrogate marker of cerebrovascular damage in vivo<sup>12,13</sup> and are associated with cognitive decline and dementia.<sup>14,15</sup> Previous work ranges from suggesting a synergistic role of WMSA and CSF biomarkers on cognition to no relationship between the two.<sup>9,16–28</sup> Of note, it is unclear whether WMSA have a prominent role in future cognitive decline and how they are related to CSF biomarkers in this context.

The purpose of this study was to assess the relationships among WMSA,  $A\beta_{42}$ , and p-tau<sub>181p</sub> and their combined effect on cognitive decline. We assessed the ability of these markers to classify clinical diagnoses as well as to predict longitudinal changes in cognition. Finally, we assessed the relationships of  $A\beta_{42}$ , p-tau<sub>181p</sub>, WMSA, and cognitive decline in a specific subgroup of these individuals who demonstrated a “healthy” CSF profile.

## Methods

### Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) and are described here as directed by

ADNI. Two hundred thirty-six individuals were used in the analyses; 61 of these had a diagnosis of AD, 56 were cognitively healthy age-matched older controls (OCs), and 119 had a diagnosis of amnesic mild cognitive impairment (MCI). Diagnoses were based on clinical assessment that included standard neuropsychological test batteries and interviews, and were made *independently* of CSF biomarker values. Within the 36-month duration of the ADNI-1 study, 64 of the patients with MCI converted to a diagnosis of AD, creating a further stratification of individuals with MCI who converted to having AD within 36 months (MCI-C; n = 64) and those who did not convert (MCI-NC; n = 55). All individuals underwent genetic screening for the presence of 0, 1, or 2 APOE  $\epsilon$ 4 alleles. Demographic data, such as age, sex, years of education, history of hypertension, history of endocrine-metabolic disorder, composite memory scores (ADNI-MEM), and composite executive function scores (ADNI-EF), were additionally acquired from the ADNI database (table 1).

### Standard protocol approvals, registrations, and patient consents

Each participating ADNI site (1) received approval from an ethical standards committee on human experimentation before study initiation, and (2) obtained written informed consent for research from all individuals participating in the study.

### Neuropsychological MRI acquisition

All data were acquired on a 1.5-tesla scanner at rigorously validated sites, which all followed a previously described standardized protocol.<sup>29</sup> The protocol included a high-resolution, T1-weighted, sagittal volumetric magnetization-prepared rapid-acquisition gradient echo sequence and axial proton density-weighted/T2-weighted fast spin echo sequence. The ADNI MRI core optimized the acquisition parameters of these sequences for each make and model of scanner included in the study. All scanner sites were required to pass a strict scanner validation test before authorization to scan ADNI participants. In addition, each scan of ADNI participants included a scan of the phantom, which was required to pass strict validation tests.

### MRI preprocessing

Cortical reconstruction and volumetric segmentation was performed using FreeSurfer's standard recon-all stream (surfer.nmr.mgh.harvard.edu, version 5.1). The technical details of these procedures are described in prior

**Table 1** Demographic information of individuals in the 3 diagnostic groups

	AD	MCI	OC
Age, y	75.98	75.18	75.20
Sex, % male	56	66	38
Education, y	14.95	15.70	15.45
Hypertension, %	48	45	45
Hypocholesteremia, %	20	9	11
CSF p-tau <sub>181p</sub> , pg/nL <sup>a</sup>	42.45	36.90	23.55
CSF Aβ <sub>42</sub> , pg/nL <sup>a</sup>	144.28	156.76	208.80
Total WMSA <sup>b</sup>	10.07	9.96	9.86
Baseline ADNI-MEM <sup>c</sup>	-0.89	-0.24	0.94
Baseline ADNI-EF <sup>c</sup>	-0.77	-0.11	0.69
One-year ADNI-MEM change <sup>d</sup>	-0.20	-0.07	0.04
One-year ADNI-EF change <sup>a</sup>	-0.30	-0.17	0.20

Abbreviations: Aβ<sub>42</sub> = β-amyloid 1–42; AD = Alzheimer disease; ADNI-EF = Alzheimer's Disease Neuroimaging Initiative–executive function; ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative–memory; MCI = mild cognitive impairment; OC = older control; p-tau<sub>181p</sub> = tau phosphorylated at threonine 181; WMSA = white matter signal abnormality.

Total WMSA values are the log of the total WMSA volume in cubic millimeters.

<sup>a</sup> AD and MCI significantly different from OC ( $p < 0.05$ ).

<sup>b</sup> AD and OC significantly different ( $p < 0.05$ ).

<sup>c</sup> All 3 groups significantly different from each other ( $p < 0.05$ ).

<sup>d</sup> AD significantly different from MCI and OC ( $p < 0.05$ ).

publications.<sup>30–34</sup> Automatic segmentation and volumetric measurement of WMSA was done using a FreeSurfer-based validated tool described in our previous work that uses T1-weighted, T2-weighted, and proton density-weighted images as inputs.<sup>35</sup>

### CSF biomarker data

In the ADNI study, participants receive a lumbar puncture at their baseline visit to obtain CSF for assays of Aβ<sub>42</sub>, total tau, and p-tau<sub>181p</sub>. Sample collection and analysis procedures are described in detail in reference 36. In the present study, CSF biomarker quadrants were created across all 238 individuals based on the median Aβ<sub>42</sub> and p-tau<sub>181p</sub> values in the participants with MCI (figure 1). For Aβ<sub>42</sub>, this median value was 144 pg/mL, and for p-tau<sub>181p</sub>, this median value was 35 pg/mL. Individuals who were classified in Q1 as demonstrated in figure 1 had pathologic levels of both CSF biomarkers, while individuals in Q3 had normal levels of both CSF biomarkers, and based on these values alone, would be expected to present as healthy older individuals. While there is no definitive consensus for clinical cutoff points for CSF biomarkers in determining AD diagnosis, these 2 values are reflective of what is typically used in the clinical setting.<sup>37–39</sup> In these data, it is important to note that ADNI diagnosis of individuals is done independently of the CSF biomarker profile.

### Classification

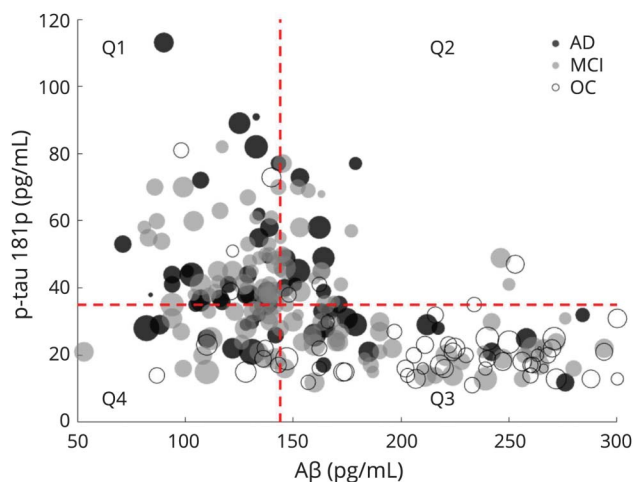
Support vector machine (SVM) classification experiments were conducted to determine whether CSF biomarkers and

WMSA volumes contained information sufficient to predict diagnoses. In these experiments, we implemented a k-fold cross-validation scheme in which we used 90% of patients to train an SVM to classify between 2 diagnostic groups, and then tested this SVM on the remaining 10% of patients. For each SVM paradigm, this process was repeated 1,000 times with a random training subset of 90% of patients and tested on the remaining 10%. The average accuracy of all 1,000 iterations is the classification accuracy for a given paradigm.

### Cognitive measures

To assess cognition in participants in the current study, we utilized the ADNI-MEM and ADNI-EF composite scores of memory and executive functioning that are available in the ADNI dataset (table 1). These scores were created and rigorously validated in previous works.<sup>40,41</sup> Briefly, the ADNI-MEM score is a composite score of results from the Rey Auditory Verbal Learning Test, Alzheimer's Disease Assessment Scale–Cognitive, Mini-Mental State Examination, and Logical Memory neuropsychological examinations. This composite memory score has been shown to detect changes in memory functioning over time in individuals with MCI and AD, and is also a strong predictor of conversion from MCI to AD.<sup>40</sup> The ADNI-EF score is a composite score of results from Trails A and B, Category Fluency, Clock Drawing, Wechsler Adult Intelligence Scale–Revised Digit Symbol Substitution, and backward Digit Span examinations. Similarly to the ADNI-MEM composite score, ADNI-EF has been shown to be a strong predictor of AD conversion in an MCI

**Figure 1** CSF biomarker data for all 236 study individuals



The radius of each point reflects the total white matter signal abnormality burden for that individual. Horizontal and vertical dashed lines are MCI-derived median cutoff points for each of the 2 CSF biomarkers, which reflect clinical standard values, dividing the entire study population into 4 quadrants, with the upper left-hand quadrant deemed quadrant 1 (Q1) and the lower right-hand quadrant deemed quadrant 3 (Q3). Individuals in Q1 demonstrate the most pathologic burdens of both CSF biomarkers, and individuals in Q3 fall into the normal range of both CSF biomarkers and would be expected to be cognitively healthy based on these values.  $A\beta$  =  $\beta$ -amyloid; AD = Alzheimer disease; MCI = mild cognitive impairment; OC = older control; p-tau<sub>181p</sub> = tau phosphorylated at threonine 181.

cohort, is associated with MRI-derived measures of structures involved in frontal systems, and is associated with baseline CSF measures of  $A\beta_{42}$ , total tau, and p-tau<sub>181p</sub>.<sup>41</sup>

## Statistical analyses

To assess the relationships among CSF biomarkers, WMSA, and continuous measures of cognition, we used a general linear model (GLM) with cognitive scores as the dependent variables in each separate model. Significance values are reported for each independent variable in each different model to reflect that variable's contribution to the model. For each model, residual sum of squares (RSS) is reported as a measure of model performance.

## Data availability

All data used in this article are available in the ADNI public data repository. Anonymized patient identification numbers from the ADNI cohort used in this article are available by request from any qualified investigator.

## Results

### Biomarker relationships

The Pearson product moment correlation coefficient was computed between each pair of measures and demonstrated that p-tau<sub>181p</sub> and  $A\beta_{42}$  are highly correlated across all individuals ( $r = -0.4757$ ,  $p < 0.0001$ ), and this relationship remained significant at  $p < 0.01$  when assessing each diagnostic subgroup individually. There was no observed

significant correlation between  $A\beta_{42}$  and total WMSA across all 236 individuals ( $r = -0.0559$ ,  $p = 0.39$ ) and none existed in any of the diagnostic subgroups. There was a significant correlation between p-tau<sub>181p</sub> and total WMSA ( $r = -0.1206$ ,  $p = 0.06$ ) across all 236 individuals at baseline. This relationship was not statistically significant in the AD or OC subgroups alone but was in the MCI cohort ( $r = -0.3307$ ,  $p < 0.001$ ). Figure 1 demonstrates the relationships among  $A\beta_{42}$ , p-tau<sub>181p</sub>, and WMSA across all 236 individuals in all 3 diagnostic groups at baseline.

### Diagnostic classification

SVM experiments were conducted to classify individuals with AD and OCs and then again to classify individuals with MCI-C and MCI-NC using different combinations of CSF biomarkers and WMSA. Adding total WMSA volume to classification paradigms consisting of CSF biomarkers only incrementally increased accuracies when classifying between individuals with AD and OCs, and showed no improvement when classifying between individuals with MCI-C and MCI-NC. CSF biomarkers alone achieved a maximum classification accuracy of 82% when classifying between individuals with AD and OCs, which increased to 83% when additionally using WMSA. CSF biomarkers alone were only able to classify individuals with MCI-C vs MCI-NC at an accuracy of 59%, which reduced to 57% when additionally adding WMSA. When using WMSA alone as a classifying feature, 60% accuracy was achieved for AD vs OCs and 56% accuracy was achieved for MCI-C vs MCI-NC.

### Baseline cognitive performance

To assess the relationships among CSF biomarkers, WMSA, and cognitive functioning, 5 separate GLM experiments were conducted across all patients in all 3 diagnostic groups, using baseline ADNI-MEM as a dependent variable. These 5 experiments were then repeated using baseline ADNI-EF as a dependent variable. As expected based on the studies in which ADNI-MEM and ADNI-EF were created and validated, both CSF biomarkers demonstrated significant contributions to the models. Of note, however, the addition of WMSA into both models with baseline ADNI-MEM and ADNI-EF as outcome measures yielded a significant WMSA model coefficient ( $p < 0.001$ ) for both cognitive domains.

### Continuous measures of cognitive functioning: Longitudinal analyses

We next assessed the relationships among CSF biomarkers, WMSA, and cognitive changes over a 1-year duration using GLM experiments. The results of these experiments are reported in table 2. Only p-tau<sub>181p</sub> demonstrated a significant contribution to predicting a 1-year change in ADNI-MEM. The additions of  $A\beta_{42}$  and WMSA did not significantly decrease the RSS, and neither variable rendered a significant model coefficient. When assessing 1-year changes in ADNI-EF, however, all 3 independent variables ( $A\beta_{42}$ , p-tau<sub>181p</sub>, and WMSA) significantly contributed to the model.

**Table 2** Results of general linear model experiments conducted using 1-year changes in memory scores and 1-year changes in executive function scores as dependent variables across all study patients, regardless of diagnosis

	p-tau <sub>181p</sub>		Aβ <sub>42</sub>		Total WMSA		RSS	No.
	β	p	β	p	β	p		
<b>One-year change in ADNI–MEM as a dependent variable</b>								
Model 1	0.0047 <sup>a</sup>	0.0002 <sup>a</sup>	—	—	—	—	23.7442	236
Model 2	—	—	0.0002	0.0701	—	—	24.9310	236
Model 3	-0.0047 <sup>a</sup>	0.0001 <sup>a</sup>	0.0002	0.9778	—	—	23.7441	236
Model 4	—	—	—	—	-0.0378	0.4660	25.2409	236
Model 5	-0.0049 <sup>a</sup>	0.0006 <sup>a</sup>	0.0004	0.9070	-0.0599	0.2403	23.5961	236
<b>One-year change in ADNI–EF as a dependent variable</b>								
Model 1	-0.0057 <sup>a</sup>	0.0011 <sup>a</sup>	—	—	—	—	46.8124	236
Model 2	—	—	0.001 <sup>a</sup>	6.2579e-04 <sup>a</sup>	—	—	46.5989	236
Model 3	-0.0037	0.0597	0.001 <sup>a</sup>	0.0328 <sup>a</sup>	—	—	45.8592	236
Model 4	—	—	—	—	-0.1770 <sup>a</sup>	0.0136 <sup>a</sup>	47.7883	236
Model 5	-0.0045 <sup>a</sup>	0.0217 <sup>a</sup>	0.001	0.0686	-0.1889 <sup>a</sup>	0.0073 <sup>a</sup>	4	236

Abbreviations: Aβ<sub>42</sub> = β-amyloid 1–42; ADNI-EF = Alzheimer’s Disease Neuroimaging Initiative–executive function; ADNI-MEM = Alzheimer’s Disease Neuroimaging Initiative–memory; p-tau<sub>181p</sub> = tau phosphorylated at threonine 181; RSS = residual sum of squares; WMSA = white matter signal abnormality.  
<sup>a</sup> Variable coefficients and p values that attained statistical significance.

### Quadrant structural differences

When assessing structural differences between individuals with impairment (MCI + AD) in Q1 (those with pathologic levels of CSF biomarkers) vs those in Q3 (normal levels of CSF biomarkers), hippocampal volume showed no significant difference ( $p = 0.50$ , figure 2, A and B). Individuals with impairment in these 2 quadrants did, however, differ in total WMSA volume ( $p < 0.01$ , figure 2C), with those in Q3 having higher overall WMSA burdens. WMSA burden between individuals with impairment and OCs in Q3 was also assessed, and figure 2 shows significantly higher WMSA in the Q3 individuals with impairment than in Q3 OC individuals ( $p < 0.01$ ).

### Quadrant genetic differences

The 2 quadrants of interest showed strikingly different genetic profiles. Of the individuals with impairment in Q1, 29% were homozygous APOE ε4 carriers (APOE ε4 +/+), but only 2% of individuals with impairment in Q3 were homozygous carriers. This imbalance was also seen in heterozygous APOE ε4 carriers whereby 49% of Q1 individuals with impairment fit this profile and only 29% of individuals with impairment in Q3 did.

### Biomarkers and cognitive outcomes

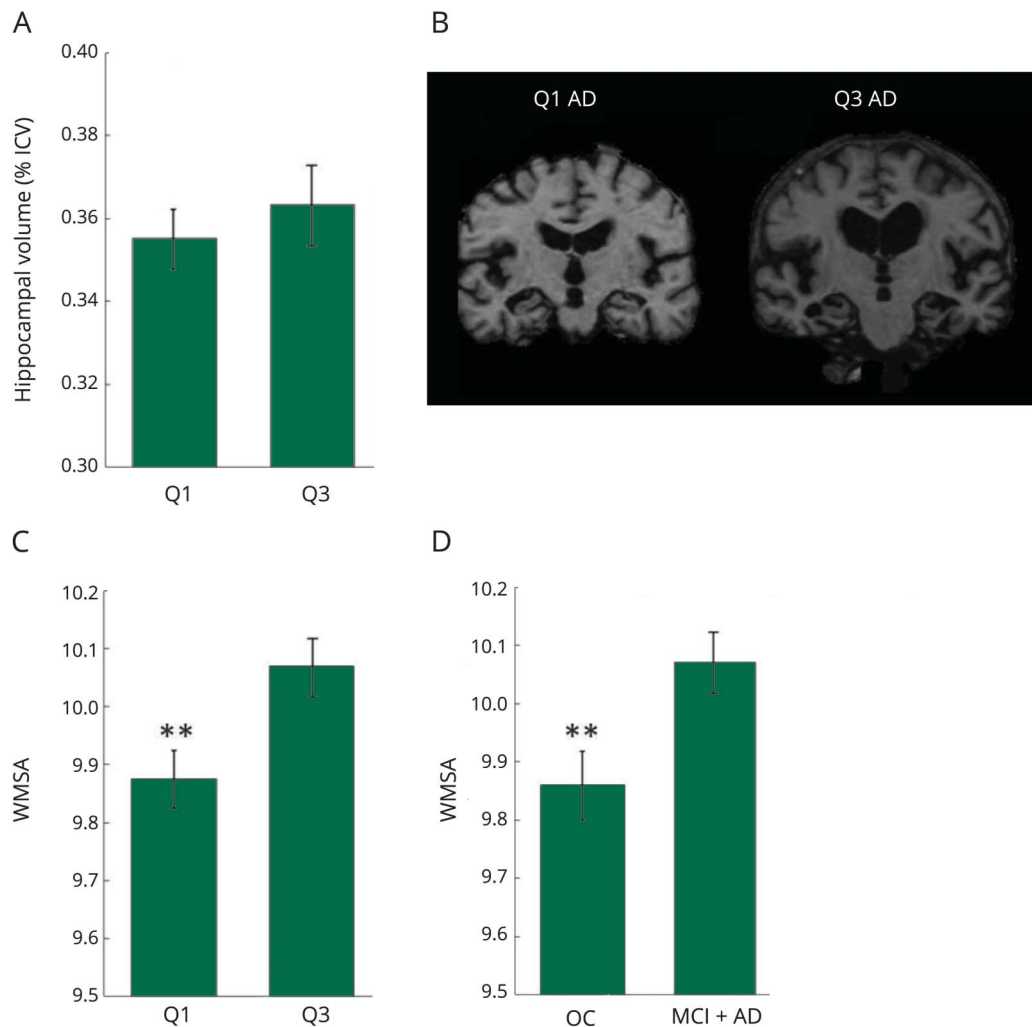
When assessing 1-year changes in ADNI-MEM in Q1, there were surprisingly no significant relationships with either CSF biomarker or with WMSA. However, when assessing 1-year change in ADNI-EF in Q1, only WMSA demonstrated a significant coefficient, and adding both CSF

biomarkers into the model did not significantly decrease the RSS (table 3). In Q3, when each of the CSF biomarkers and WMSA were tested individually in modeling 1-year changes in ADNI-MEM, WMSA alone showed the lowest RSS and most significant model coefficient. Aβ<sub>42</sub> did not show a significant relationship with 1-year change in ADNI-MEM in any model configuration. For 1-year changes in ADNI-EF in Q3, only WMSA demonstrated a significant relationship with cognitive outcome (table 3).

## Discussion

The results presented in this work provide new insights into the role that WMSA have in the clinical presentation of AD. Along with these new insights, our results confirm much of what is already known regarding the clinical-pathologic mismatch seen in AD diagnosis. The results of our classification experiments reflect real-world clinical misdiagnosis rates of AD that have been reported to be as high as 25% in the literature.<sup>8,42</sup> Based on previous studies of WMSA and cognitive decline, we hypothesized that WMSA would hold predictive power for changes in continuous cognition measurements.<sup>25,43</sup> Across all patients, regardless of diagnosis, WMSA showed a strong relationship with a 1-year change in EF but they were not a robust predictor of memory decline. Particularly in the individuals whose cognitive profiles do not match their CSF pathologic profiles (e.g., individuals with impairment in Q3), however, we demonstrate that WMSA provide added information

**Figure 2** Hippocampal volumes, example coronal slices, and WMSA volumes



(A) Hippocampal volumes between Q1 and Q3 in individuals with impairment (MCI + AD). (B) Example coronal slices with hippocampal view for individuals with AD in both Q1 and Q3. (C) WMSA volumes between Q1 and Q3 in individuals with impairment (MCI + AD). (D) WMSA volumes between OCs and individuals with impairment in Q3. \*\*Significantly different at  $p < 0.01$ . AD = Alzheimer disease; ICV = intracranial volume; MCI = mild cognitive impairment; OC = older control; Q = quadrant; WMSA = white matter signal abnormality.

that is predictive of future cognitive decline in both memory and executive functioning domains. Our findings combined with others' suggest that other factors must be at play for the manifestation of AD-like symptoms, and that as the burden of classic AD pathologies increases, the impact of WMSA on cognitive function decreases. This also suggests, however, that WMSA are most important when classic AD pathologies are low and that WMSA may be critically linked to AD conversion, a concept supported by the previous works of others.<sup>9,28,44</sup> To this end, our findings suggest that therapeutic studies focused on the peri-conversion period of the disease process may be most vulnerable to WMSA influence.

Reflective of the accuracy levels that were revealed by our classification experiments, 25% of individuals with an AD diagnosis fell into the biomarker quadrant whose p-tau<sub>181p</sub> and A $\beta$ <sub>42</sub> levels were in a normal clinical range (Q3).

Similarly, 34% of individuals with MCI fell into this quadrant. These individuals presented an opportunity for deeper study and possible discovery of novel biomarkers to explain their cognitive symptoms. In these individuals, WMSA were the strongest predictor of a 1-year change in memory when assessed against the CSF biomarkers, and were the only predictor of a 1-year change in executive function. Because all of the individuals with MCI-C in this study converted to AD within 3 years of the time that CSF measurements were taken, our findings suggest that this 3-year time window is not a sensitive period for A $\beta$ <sub>42</sub> and p-tau<sub>181p</sub> in the CSF, and this is supported by the work of others.<sup>5</sup> These findings are particularly important in the context of choosing participants for clinical trials in which therapeutics are aimed at classic AD pathologies, as it is more likely that WMSA or a related process is the primary cause of the cognitive clinical presentation in individuals similar to those in Q3 of our study.

**Table 3** Results of general linear model experiments conducted within the Q1 and Q3 CSF biomarker quadrants using 1-year changes in ADNI-MEM and ADNI-EF as outcome measures

	p-tau <sub>181p</sub>		Aβ <sub>42</sub>		Total WMSA		RSS	No.
	β	p	β	p	β	p		
<b>Q1</b>								
<b>One-year change in ADNI-MEM as a dependent variable</b>								
Model 1	-0.0025	0.359	—	—	—	—	7.4587	65
Model 2	—	—	-0.0003	0.89	—	—	7.5576	65
Model 3	-0.003	0.346	-0.001	0.778	—	—	7.4491	65
Model 4	—	—	—	—	0.094	0.378	7.4664	65
Model 5	-0.003	0.318	-0.0001	0.834	0.100	0.354	7.344	65
<b>One-year change in ADNI-EF as a dependent variable</b>								
Model 1	-0.0004	0.913	—	—	—	—	13.3760	65
Model 2	—	—	-0.0003	0.923	—	—	13.3765	65
Model 3	-0.001	0.90	-0.0003	0.91	—	—	13.3731	65
Model 4	—	—	—	—	-0.3054 <sup>a</sup>	0.03 <sup>a</sup>	12.3867	65
Model 5	0.000	0.99	-0.0001	0.77	-0.309 <sup>a</sup>	0.03 <sup>a</sup>	12.3692	65
<b>Q3</b>								
<b>One-year change in ADNI-MEM as a dependent variable</b>								
Model 1	-0.0114 <sup>a</sup>	0.0367 <sup>a</sup>	—	—	—	—	9.81	93
Model 2	—	—	0.0004	0.6515	—	—	10.27	93
Model 3	-0.0116 <sup>a</sup>	0.0422 <sup>a</sup>	-0.0001	0.9161	—	—	9.80	93
Model 4	—	—	—	—	-0.2072 <sup>a</sup>	0.0155 <sup>a</sup>	9.64	93
Model 5	-0.0117 <sup>a</sup>	0.0361 <sup>a</sup>	-0.0003	0.7182	-0.2061 <sup>a</sup>	0.0153 <sup>a</sup>	9.17	93
<b>One-year change in ADNI-EF as a dependent variable</b>								
Model 1	-0.0144	0.0571	—	—	—	—	18.80	93
Model 2	—	—	0.0020	0.0704	—	—	18.87	93
Model 3	-0.0116	0.1375	0.0015	0.1721	—	—	18.4124	93
Model 4	—	—	—	—	-0.2922 <sup>a</sup>	0.0133 <sup>a</sup>	18.2852	93
Model 5	-0.0116	0.1256	-0.0013	0.2494	-0.2732 <sup>a</sup>	0.0191 <sup>a</sup>	17.3041	93

Abbreviations: Aβ<sub>42</sub> = β-amyloid 1–42; ADNI-EF = Alzheimer's Disease Neuroimaging Initiative–executive function; ADNI-MEM = Alzheimer's Disease Neuroimaging Initiative–memory; p-tau<sub>181p</sub> = tau phosphorylated at threonine 181; Q = quadrant; RSS = residual sum of squares; WMSA = white matter signal abnormality.

<sup>a</sup> Coefficients significant at  $p < 0.05$ .

Two interesting findings that add to the complexity of the current picture are the lack of difference in hippocampal volumes of individuals with impairment in Q1 and Q3, and the increase in APOE ε4 prevalence in Q1 individuals with impairment over Q3. While hippocampal atrophy is typically considered to be a hallmark biomarker of AD, it is also associated with other unrelated neurodegenerative conditions such as hippocampal sclerosis, and it is possible that the individuals with impairment in Q3 reflect this process. It is also possible, however, that this AD-like hippocampal atrophy

is due to the same upstream process in all individuals with impairment, but that the cognitive symptom manifestation necessary for a clinical AD diagnosis requires a second hit.<sup>45</sup> Under this hypothesis, the second hit could be the development of tau and amyloid pathologies or it could be a cerebrovascular process such as those that lead to WMSA. The low prevalence of APOE ε4 in the Q3 individuals with impairment further suggests that these individuals are protected from the development of classic AD pathologies. Such complexities between and misalignments of pathologic and

cognitive presentations may be explained by the notion of cognitive reserve<sup>18,46,47</sup> and warrants future study into whether there are common risk factors among individuals in each given quadrant that may explain their susceptibility to a unique manifestation of pathologic findings. For example, there may be particular aspects of cognitive reserve (e.g., level of education) that protect an individual from the development of classic AD pathologies, and if there are other aspects of cognitive reserve that protect an individual from the development of WMSA, then the combination of these protective mechanisms may lower an individual's risk of cognitive decline and development of AD altogether.

Taken together, we interpret our results to suggest the following. Individuals with impairment in Q1 embody the classic AD pathologic profile with high levels of CSF p-tau<sub>181p</sub>, low CSF A $\beta$ <sub>42</sub>, and prevalent APOE  $\epsilon$ 4. These pathologies are the main drivers of memory loss leading to a clinical AD diagnosis in Q1. In these individuals, tau and amyloid have a saturating effect on memory loss and WMSA do not further contribute to impairment. In the Q3 individuals with impairment who lack classic CSF biomarkers, however, WMSA are the dominating pathology that drives memory loss, and their effect can be appreciated in the absence of p-tau<sub>181p</sub> and A $\beta$ <sub>42</sub> saturation. This is further supported by the finding that Q3 individuals with impairment have a greater WMSA burden than those in Q1, which would presumably have a greater effect on memory. Across all individuals and within quadrants, WMSA demonstrate a longitudinal relationship with executive function. This has been reported in other studies as well,<sup>48,49</sup> and perhaps reflects a robust and general association between WMSA and cognitive function that exists even in the presence of other strong neurodegenerative pathologies.

The results presented in this work hold clinical utility in understanding patients who present with AD-like cognitive symptoms but do not have remarkable CSF biomarker profiles. The more immediate value of this work, however, may relate to the researchers who study AD and conduct clinical trials for therapeutic interventions in that it demonstrates an important role of white matter disease in AD. The results of this work suggest that the combined relationship between WMSA and CSF biomarkers of AD should be assessed when designing novel therapeutic interventions. In addition, this work may aid in the task of screening individuals for enrollment in specific clinical trials, which is a current challenge as the relationships between complex biomarker profiles and future cognitive decline are not well understood. Future work should address the more immediate clinical utility of such results by aiming to create disease-related thresholds of white matter disease in the context of other pathologies and risk factors for clinical assessment.

### Author contributions

Emily Lindemer: study concept and design, analysis and interpretation. Douglas Greve: analysis and interpretation. Bruce Fischl: critical revision of the manuscript for important

intellectual content. David Salat: study supervision. Teresa Gomez-Isla: critical revision of the manuscript for important intellectual content.

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### Disclosure

E. Lindemer and D. Greve report no disclosures relevant to the manuscript. B. Fischl has a financial interest in Cortico-Metrics, a company whose medical pursuits focus on brain imaging and measurement technologies. Dr. Fischl's interests were reviewed and are managed by Massachusetts General Hospital and Partners HealthCare in accordance with their conflict of interest policies. D. Salat and T. Gomez-Isla report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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# White matter abnormalities and cognition in patients with conflicting diagnoses and CSF profiles

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## Study question

How does the relationship between volumes of white matter signal abnormalities (WMSA) and classic CSF biomarkers of Alzheimer disease (AD) affect future cognitive decline?

## Summary answer

WMSA volumes hold particularly strong predictive power for future cognitive decline in individuals with “normal” levels of CSF biomarkers, despite conflicting cognitive profiles.

## What is known and what this paper adds

There is strong evidence for a cerebrovascular component to AD, and MRI-detected WMSA are a surrogate marker for cerebrovascular damage. This study provides evidence that WMSA volumes can help predict cognitive decline in older adults, particularly in individuals who have conflicting cognitive diagnoses and CSF profiles.

## Participants and setting

This study examined data for 236 individuals who were enrolled in the AD Neuroimaging Initiative (ADNI) database. This population included 61 individuals diagnosed with AD (56% male; mean age, 75.98 years), 56 age-matched cognitively normal older controls (38% male; mean age, 75.20 years), and 119 individuals diagnosed with amnesic mild cognitive impairment (66% male; mean age, 75.18 years). All diagnoses were made with neuropsychological test batteries independently of CSF biomarker values. Individuals were further stratified into 4 quadrants based on their CSF biomarker values, agnostic of cognitive clinical diagnoses.

## Design, size, and duration

WMSA volumes were measured with 1.5-T MRI scanners. The protocol included a high-resolution, T1-weighted sagittal volumetric magnetization-prepared rapid gradient-echo sequence and an axial proton-density/T2-weighted fast-spin-echo sequence. CSF levels of  $\beta$ -amyloid<sub>1-42</sub> ( $A\beta_{1-42}$ ) and phosphorylated tau<sub>181p</sub> (p-tau<sub>181p</sub>) were measured from samples collected via lumbar puncture. Composite memory scores and composite executive function scores were derived from the neuropsychological test batteries and assessed at baseline and 1 year thereafter.

## Primary outcomes

The primary outcome was the predictive utility of WMSA volumes for 1-year declines in composite memory scores and composite executive function scores in general linear models (GLMs) within “normal” and “pathological” subgroups as defined by CSF biomarker levels.

	Independent variable	p Value for 1-y change in composite memory scores	p Value for 1-y change in composite executive function scores
Subgroup with “normal” CSF biomarker levels	CSF p-tau <sub>181p</sub>	<b>0.0361</b>	0.1256
	CSF $A\beta_{1-42}$	0.7182	0.2494
	WMSA volumes	<b>0.0153</b>	<b>0.0191</b>
Subgroup with “pathological” CSF biomarker levels	CSF p-tau <sub>181p</sub>	0.318	0.99
	CSF $A\beta_{1-42}$	0.834	0.77
	WMSA volumes	0.354	<b>0.03</b>

## Main results and the role of chance

WMSA volumes and CSF levels of p-tau<sub>181p</sub> and  $A\beta_{1-42}$  all contributed to the predictive power of GLMs for a1-year decline in composite executive function scores, and p-tau<sub>181p</sub> alone contributed to memory decline across all 236 individuals. In individuals with “normal” CSF biomarker levels, WMSA volumes contributed predictive power for one-year declines in both memory and executive function, whereas p-tau<sub>181p</sub> only contributed to memory decline and  $A\beta_{1-42}$  contributed to neither. In individuals with “pathological” CSF biomarker levels, WMSA alone contributed predictive power to a one-year change in executive function.

## Bias, confounding, and other reasons for caution

Understanding the clinical importance of these results will require clarification of the poorly understood relationship between complex biomarker profiles and future cognitive decline. The pathologic basis for imaging changes and CSF values was not available.

## Generalizability to other populations

The study involved a large sample, which favors the generalizability of the results, but assessment of the final models in a confirmation population is needed.

## Study funding/potential competing interests

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