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Increased regional white matter hyperintensity volume in objectively-defined subtle cognitive decline and mild cognitive impairment

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Abstract

White matter hyperintensities (WMH), a marker of small vessel cerebrovascular disease, increase risk of developing mild cognitive impairment (MCI) and Alzheimer's disease (AD). Less is known about the extent and pattern of WMH in pre-MCI stages, such as among those with objectively-defined subtle cognitive decline (Obj-SCD). Five hundred and fifty-nine Alzheimer's Disease Neuroimaging Initiative participants (170 cognitively unimpaired [CU]; 83 Obj-SCD; 306 MCI) free of clinical dementia or stroke completed neuropsychological testing and MRI exams. ANCOVA models compared cognitive groups on regional WMH adjusting for age, sex, and apolipoprotein E (APOE) ε4 frequency. Compared with the CU group, those with Obj-SCD had greater temporal, occipital, and frontal WMH whereas those with MCI had higher WMH volume across all regions (p's<.01). No differences in WMH volume were observed between the Obj-SCD and MCI groups (p's>.05). Findings add to growing evidence of associations between Obj-SCD and imaging biomarkers, providing support for utility of these criteria to capture subtle cognitive changes that are biologically based.

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Keywords

white matter hyperintensities; preclinical Alzheimer's disease; subtle cognitive decline; magnetic resonance imaging; cerebrovascular disease

1. Introduction

Detection of preclinical Alzheimer's disease (AD) has implications for early intervention. Previous studies have shown that subtle cognitive changes can be captured within preclinical stages of AD by utilizing sensitive neuropsychological measures (Bondi et al., 1999; Bondi et al., 1994; Crocco et al., 2021; Jedynak et al., 2012; Thomas et al., 2018b). Many studies rely on subjective reports of cognitive difficulties to determine changes in cognition. However, we have previously operationalized objectively-defined subtle cognitive decline (Obj-SCD) using neuropsychological assessment and incorporating both total scores and sensitive process scores (Thomas, et al., 2018a; Thomas et al., 2020b; Thomas et al., 2020c).

Neuropsychological process scores quantify the number and types of errors that a person may make on a neuropsychological test, or the approach and strategies that are used to complete a task. These scores differ from the traditionally used total scores and provide additional prognostic value to predict progression to mild cognitive impairment (MCI) and dementia beyond previously established AD biomarkers (Thomas et al., 2018b). Indeed, we previously showed that Obj-SCD operationalized using both neuropsychological total scores and sensitive process scores is associated with faster change in positron emission tomography (PET) and plasma AD biomarkers levels over time compared to cognitively unimpaired (CU) individuals (Thomas et al., 2021; Thomas et al., 2020b). In addition, individuals classified as Obj-SCD have cerebrospinal fluid (CSF) biomarker concentrations that are in between the levels of CU and mild cognitive impairment (MCI) participants (Thomas et al., 2021; Thomas et al., 2018a), which highlight the potential of the Obj-SCD classification to identify cognitive changes coincident with accumulating tau and amyloid pathologies.

White matter hyperintensities (WMH) are a marker of small-vessel cerebrovascular disease characterized by increased signals on T2-weighted magnetic resonance imaging (MRI). WMH are thought to be pathologically heterogeneous and may reflect axonal loss caused by ischemia and demyelination as well as neuronal loss, microglial, and endothelial activation (Wardlaw et al., 2015). Although WMH are a frequent occurrence on neuroimaging among cognitively normal older adults and were once thought to reflect benign changes in aging, it is now well established that they are related to an increased risk of cognitive impairment (Bangen et al., 2020; Bangen et al., 2018; Brickman et al., 2012; Brickman et al., 2015; Lee et al., 2016). A previous study involving participants with autosomal dominant genetic mutations for AD showed increased WMH volume, particularly in posterior regions, among mutation carriers up to 22 years prior to expected clinical symptom onset, suggesting that cerebrovascular disease (CVD) plays a role in the biology of AD rather than being simply a comorbidity (Lee et al., 2016). Similarly, elevated WMH, particularly in posterior regions, have been shown among individuals with Down syndrome who develop AD by their 5th

decade (Lao et al., 2020). Previous research has also shown that regional WMH volume predicts progression of clinical symptoms in MCI (Bangen et al., 2020). However, regional WMH have not been previously investigated in relation to Obj-SCD status.

In the current study we examined the association between regional WMH and Obj-SCD status in a well-characterized sample of older adults without dementia or stroke from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We hypothesized that (1) individuals with Obj-SCD would have greater WMH volume relative to CU participants and lower WMH volume than MCI participants and, (2) consistent with previous research of individuals at risk for AD (Brickman et al., 2012; Lao et al., 2020; Lee et al., 2016; Rizvi et al., 2021), the Obj-SCD and MCI groups would show higher WMH volumes in posterior regions relative to those with normal cognition.

2. Material and methods

2.1. ADNI

The data prepared for this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was led by Michael W. Weiner, MD in 2003 as a public private partnership. The objective of ADNI was to determine whether positron emission tomography, biological markers, clinical and neuropsychological assessment, and serial MRI can be combined to quantify the progression of MCI and early AD.

2.2. Participants

Participants included within ADNI were between 55 and 90 years of age, had at least 6 years of education, were English or Spanish speakers, were free of any significant systemic illness or neurological disease, had modified Hachinski Ischemic Scale scores less than 5, and had Geriatric Depression Scale (GDS) score less than 6 (possible range of 0-15) (Sheikh and Yesavage, 1986). The current study included participants who were free of dementia, clinical stroke, and brain infarcts on MRI and had available neuropsychological, lobar WMH volume, and apolipoprotein E (APOE) genotype ε4 data at baseline (n = 559). ADNI criteria for dementia include subjective memory complaint by participant or study partner that is verified by study partner; and abnormal memory function demonstrated by scoring below an education adjusted cutoff on the Wechsler Memory Scale – Revised (WMS-R) Logical Memory II subscale; and meets National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease with Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score of 20-26 (inclusive) and Clinical Dementia Rating scale (CDR) (Morris, 1993) score of 0.5 or 1. This study was approved by a local institutional review board at each institution. Written informed consent was obtained from all participants or their authorized representative.

2.3. Cognitive groups

Participants were diagnostically classified as cognitively unimpaired (CU) or MCI utilizing an actuarial neuropsychological diagnostic method (Bondi et al., 2014; Jak et

al., 2009) applied to each participant's neuropsychological assessment data. The six neuropsychological measures used in this diagnostic classification were chosen because of their routine use in determining early cognitive changes in AD, they assessed multiple cognitive domains, and they have been used by numerous previous studies applying these criteria to diagnose MCI in ADNI (Bangen et al., 2016; Bondi et al., 2014; Edmonds et al., 2015a). The 6 measures included: Rey Auditory Verbal Learning Test (AVLT) 30-minute delayed free recall (number of words recalled) and Rey Auditory Verbal Learning Test recognition (number of words correctly recognized minus false-positive errors) in the episodic memory domain; Animal Fluency total score and 30-item Boston Naming Test total score in the language domain; and Trail Making Test, Parts A and B (times to completion) in the speed/executive functioning domain. None of the cognitive measures mentioned were used to determine the initial ADNI diagnostic classification. Each of these cognitive measures was transformed to an age-, education-, and sex-adjusted z-score based on a sample of participants who remained classified as cognitively unimpaired throughout their participation in the ADNI study.

Individuals were classified as MCI if any one of the following three criteria were met: (1) an impaired score, defined as > 1 SD below the demographically-adjusted normative mean, on both measures within at least one cognitive domain (i.e., memory, language, or speed/executive function), (2) one impaired score, defined as > 1 SD below the demographically-adjusted normative mean, in each of the three cognitive domains sampled, or (3) a score on the Functional Assessment Questionnaire (FAQ) ≥ 6 indicating dependence in three or more daily activities (Teng et al., 2010). Participants who did not meet the actuarial neuropsychological MCI criteria were classified into either the Obj-SCD or CU group.

Consistent with our previous work (Thomas et al., 2018a; Thomas et al., 2020b; Thomas et al., 2020c), Obj-SCD status was determined based on: (1) an impaired total test score (>1 SD below demographically-adjusted mean) in 2 different cognitive domains (memory, language, speed/executive functioning), or (2) two impaired neuropsychological process scores (>1 SD below demographically-adjusted mean) from the AVLT, or (3) 1 impaired total test score and 1 impaired process score. Total test scores were the six neuropsychological variables described previously for determining MCI diagnosis. Three process scores from the AVLT were also used in the classification of Obj-SCD including AVLT learning slope ([list A trial 5–list A trial 1]/5), retroactive interference (list A trial 6/list A trial 5), and total intrusion errors (total number of extra-list intrusion errors across all recall trials). Previously, these process scores were shown to differ between those who progressed to MCI within 5 years of participation in ADNI and CU participants who remained stable (Thomas et al., 2018b). Consistent with the neuropsychological total scores, process scores were demographically-adjusted (age, sex, education) z scores determined using regression coefficients from a sample of CU participants in ADNI who did not progress to MCI based on ADNI's diagnostic classification for the duration of their study participation. Using this diagnostic classification process, 170 CU, 83 Obj-SCD, and 306 MCI participants were included. Of the 83 of participants classified as Obj-SCD, 31 had an impaired total test score in 2 different cognitive domains, 26 had two impaired neuropsychological process scores from the AVLT, and 26 had 1 impaired total test score and 1 impaired process score.

2.4. Image acquisition

MRI data was acquired as part of the ADNI-1 study. An in-depth description of ADNI MR imaging data acquisition can be located online at www.loni.usc.edu. A standardized, validated protocol for MR image acquisition was applied across ADNI sites and platforms (Jack et al., 2008). All scans were acquired on 1.5 Tesla systems. A 3D T1-weighted magnetization prepared rapid gradient echo sequence (MP-RAGE) was acquired in the sagittal orientation. For white matter hyperintensity quantification, a proton density/T2-weighted fast spin echo sequence (FSE) was acquired in the axial orientation. All imaging sites included in the ADNI were required to pass phantom-based monitoring and scanner validation tests (Jack et al., 2008).

2.5. Image analysis

Processed MR data was obtained from ADNI. An in-depth description of ADNI MRI data processing can be located online at www.loni.usc.edu. T1-weighted structural scans were motion corrected and parcellated and segmented using an analysis pipeline based on FreeSurfer to derive measures of total brain volume and total intracranial volume (Holland et al., 2009). WMH volumes were detected by an automated method previously described using co-registered T1-, T2-, and PD-weighted images (Carmichael et al., 2010; Schwarz et al., 2009). The T1-weighted image was stripped of nonbrain tissue and nonlinearly aligned to a minimum deformation template (Kochunov et al., 2001; Rueckert et al., 1999). T2- and PD-weighted images were also stripped of nonbrain tissue and warped to the space of the minimum deformation template based on the T1 alignment and warping parameters. Based on image intensities of the PD, T1, and T2 images combined with a spatial prior (i.e., the prior probability of WMH occurring at a given voxel) and a contextual prior (i.e., the conditional probability of WMH occurring at a given voxel based on the presence of WMH at neighboring voxels), WMH were detected in minimum deformation template space. WMH volumes quantified with the previously mentioned protocol agreed strongly with WMH volumes estimated in a diverse sample of older adults on fluid attenuated inversion recovery (FLAIR) MR images (Schwarz et al., 2009). WMH volumes of the frontal, temporal, parietal, and occipital lobes were obtained using an *a priori* lobar atlas (DeCarli et al., 2005). The development of the atlas and detailed descriptions of the boundaries of the lobes has been previously published (DeCarli et al., 2005). Labeled WMH voxels were summed and multiplied by voxel dimensions to yield volumes in cm^3.

2.6 Additional covariates and descriptive variables

Vascular risk factors were assessed though clinical interview, physical and neurological exams, and/or review of medical records. The modified Hachinski Ischemic Scale was completed by a clinician familiar with the study participant's medical history with the study partner. Possible scores for the modified Hachinski Ischemic Scale ranged from 0 to 12 with higher scores indicating greater likelihood of cerebrovascular (rather than neurodegenerative) etiology although ADNI excluded potential participants with a score of 5 or higher on screening. Given that vascular risk factors tend to cluster and history of multiple vascular risk factors relates to the presence of cerebrovascular pathology among individuals with autopsy-confirmed AD (Bangen et al., 2015) as well as evidence that the etiology of

WMH may be heterogeneous (e.g., Wardlaw et al., 2015), the modified Hachinski Ischemic Scale score was included as a covariate in secondary analyses to determine whether group differences in WMH volume persist above and beyond general vascular risk. To further characterize our sample and determine whether cognitive groups differed, common individual vascular risk factors were also assessed. History of hypertension was determined as part of the modified Hachinski Ischemic Scale and defined as blood pressure >150/95 for 6 months. Brachial artery blood pressure measures were obtained while the participant was seated. Pulse pressure (systolic – diastolic blood pressure), a proxy measure for arterial stiffness that it thought to serve as an index of vascular aging, was calculated. History of type 2 diabetes was defined based on self-reported history, use of glucose lowering medication, and/or or fasting blood glucose ≥126 mg/dL. High cholesterol was defined as total cholesterol level ≥240 mg/dL. Fifteen participants (1 CU, 4 Obj-SCD, 10 MCI) were missing cholesterol data.

2.7. Statistical analyses

Analysis of variance (ANOVA) or Chi-squared ($\chi 2$) tests examined differences in demographic and clinical characteristics by cognitive group (CU, Obj-SCD, MCI). Post hoc pairwise comparisons were performed if the omnibus test was significant. To correct for head size and to be consistent with previous studies (e.g., Bangen et al., 2018; DeCarli et al., 1999; DeCarli et al., 2005), regional WMH volumes were divided by total intracranial volume. The distribution of both raw WMH volumes and WMH volumes divided by total intracranial volume were highly positively skewed for all regions, so a log-transformation was used. The WMH variable that was divided by total intracranial volume and log transformed was used in all analyses.

A 3 (cognitive group) x 4 (lobe) repeated measures analysis of covariance (ANCOVA) compared groups on regional WMH adjusting for age, sex, and APOE ε4 allele frequency (0, 1, 2). Region/lobe was treated as a within-subjects factor to determine whether the pattern of regional differences across groups was significant. Mauchly's test was used to assess deviations from sphericity and, if significant, a Huynh-Feldt correction was applied to analyses. To assist in interpreting the results from the repeated measures model, additional ANCOVAs compared groups on WMH. Post hoc pairwise comparisons were performed if the omnibus test was significant. To address potential inflation of type I error resulting from multiple comparisons, we applied the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) to the post-hoc pairwise comparisons of regional WMH volume. We assessed results when the false discovery rate (FDR) was controlled at 0.05. Finally, we performed secondary analyses in which we re-ran our primary analyses additionally adjusting for modified Hachinski Ischemic Scale score to determine whether group differences in regional WMH persist above and beyond general vascular risk.

3. Results

3.1. Participant characteristics

Descriptive data for clinical and demographic characteristics of the sample by cognitive group (CU, Obj-SCD, MCI) are shown in Table 1. There were no group differences in age,

years of education, or vascular risk burden (i.e., modified Hachinski Ischemic Scale score; pulse pressure; or history of hypertension, diabetes, and high cholesterol). The CU group had a higher proportion of women than the Obj-SCD and MCI groups who did not differ from each other. The MCI group had a higher proportion of APOE ε4 carriers relative to the CU and Obj-SCD groups, and the Obj-SCD group had a higher proportion of APOE ε4 carriers relative to the CU group. As expected, the MCI group had lower performance relative to the CU and Obj-SCD groups on each of the 6 individual cognitive measures. The Obj-SCD group had lower scores than the CU group on both language and both memory measures but not on either of the executive functioning/processing speed measures. The MCI group had lower total brain volume (normalized by estimated total intracranial volume) compared to the CU and Obj-SCD groups which did not differ from each other.

3.2 Total WMH Volume by Cognitive Group

Adjusting for age, sex, and APOE ε4 frequency, there was a main effect of cognitive group on total WMH volume ($F_{2, 553} = 6.23$, $p = .002$). Post-hoc pairwise comparison tests showed that the MCI and Obj-SCD groups both had higher total WMH volume relative to the CU group (MCI vs CU: $p < .001$, Obj-SCD vs CU: = .032) although they did not differ from each other (MCI vs Obj-SCD: $p = .679$). The statistical significance for these post-hoc pairwise comparisons was retained using a 0.05 FDR.

3.3 Regional WMH Volume by Cognitive Group

The repeated measures ANCOVA model showed that, adjusting for age, sex, and APOE ε4 frequency, mean WMH volume differed across groups and the magnitude of group differences varied across the lobes (cognitive group by lobe interaction: $F_{(5.12, 1417.82)} = 2.23$, $p = 0.048$; main effect of cognitive group: $F_{(2, 553)} = 10.34$, $p < 0.001$). Note that for the repeated measures ANCOVA model, Mauchly's test of sphericity was significant ($p < 0.05$) and so the Huynh-Feldt correction was applied.

Post hoc univariate pairwise comparisons showed that: (1) the Obj-SCD group had greater WMH volume relative to the CU group in temporal ($F(1, 248) = 6.03$, $p = 0.015$, $\eta_p^2 = 0.024$), occipital ($F(1, 248) = 4.62$, $p = 0.033$, $\eta_p^2 = 0.018$), and frontal lobes ($F(1, 248) = 6.65$, $p = 0.010$, $\eta_p^2 = 0.026$), with no difference for the parietal lobe ($F(1, 248) = 2.61$, $p = 0.108$, $\eta_p^2 = 0.010$) and (2) the MCI group had greater WMH volume compared with the CN group across all regions including temporal ($F(1, 471) = 23.27$, $p < 0.001$, $\eta_p^2 = 0.047$), parietal ($F(1, 471) = 9.76$, $p = 0.002$, $\eta_p^2 = 0.020$), occipital ($F(1, 471) = 19.64$, $p < 0.001$, $\eta_p^2 = 0.040$), and frontal lobes ($F(1, 471) = 10.01$, $p = 0.002$, $\eta_p^2 = 0.021$). There were no differences in regional WMH volume between the Obj-SCD and MCI groups (all p's > 0.05; temporal: $p = 0.232$, $\eta_p^2 = 0.004$; parietal: $p = 0.312$, $\eta_p^2 = 0.003$; occipital: $p = 0.217$, $\eta_p^2 = 0.004$; frontal: $p = 0.993$, $\eta_p^2 < .001$). All models adjusted for age, sex, and APOE ε4 frequency. Statistical significance of these post hoc pairwise comparisons was retained using a 0.05 FDR. See Fig. 1.

3.4 Analyses Additionally Adjusting for Vascular Risk Burden

In secondary analyses, we re-ran our primary models additionally adjusting for vascular risk burden (i.e., modified Hachinski Ischemic Scale). All results remained qualitatively and

statistically similar. That is, the repeated measures ANOVA showed a significant lobe x group interaction ($F_{(5.19, 1574.78)} = 2.25$, $p = 0.045$). Univariate pairwise tests for each lobe showed a qualitatively and statistically similar pattern compared to the primary models.

4. Discussion

We found that both global and regional WMH volumes vary across cognitive groups. Compared to the CU group, the Obj-SCD group had higher temporal, occipital, and frontal WMH whereas the MCI group had larger WMH increases affecting all regions, which is in line with the greater severity of cognitive impairment in the MCI group. Previous research showed increases in regional WMH volume in clinical stages of MCI and AD dementia compared to CU individuals (Bangen et al., 2020; Brickman et al., 2012). Our current study extends these results to a pre-MCI phase using the Obj-SCD classification.

Relative to the CU group, individuals classified as Obj-SCD had higher WMH volumes in occipital regions which is consistent with several previous reports which have shown a propensity toward a posterior distribution of WMH among individuals at increased risk for AD (Lao et al., 2020; Lee et al., 2016; Rizvi et al., 2021). In addition, the Obj-SCD group in the present study showed higher temporal and frontal WMH relative to the CU group, which is consistent with their subtle deficits in episodic memory, which is subserved by medial temporal lobe functions, and their susceptibility to intrusion errors and retroactive interference, which have both been linked to frontal lobe deficits (Daum and Mayes, 2000; Dewar et al., 2007).

We previously showed that regional WMH volumes discriminate among cognitively normal older adults and MCI subgroups (amnestic, nonamnestic) and that regional measures of WMH may be more sensitive relative to global WMH in identifying those at increased risk of developing AD and predicting decline in everyday functioning (Bangen et al., 2020). In another previous study we found that older adults with Obj-SCD had higher global WMH compared to CU participants, although this was not a significant difference (Thomas et al., 2020c). Of note, in this previous study, we did not examine regional WMH volumes and the subsample of Obj-SCD participants was substantially smaller relative to the current study (i.e., 31 versus 83 participants) (Thomas et al., 2020c). Previously published work by others shows that WMH predict cognitive decline (Carmichael et al., 2010; Tosto et al., 2014); are elevated among AD autosomal dominant mutation carriers approximately 22 years prior to estimated symptom onset, which is thought to be around the same time that changes in CSF $ptau_{181}$ and amyloid occur (Lee et al., 2016); and are more reliably associated with neurodegeneration than measures of Aβ (Guzman et al., 2013). Although WMH are pathologically heterogeneous and have been linked to demyelination, axonal loss due to ischemia or neuronal death, microglia and endothelial activation, and cerebral amyloid angiopathy (Wardlaw et al., 2015), growing evidence consistently demonstrates their impact on cognitive functioning across the aging spectrum. Future research linking radiological white matter abnormalities to neuropathology is needed to further elucidate how WMH evolve and progress (Lee et al., 2016).

In addition to their role in both AD (Lee et al., 2016) and non-AD forms of cognitive impairment (Gorelick et al., 2011), WMH are also common in normal aging (DeCarli et al., 2005), reflecting an acceleration of cerebrovascular disease with advancing age, and it is worth noting that our cognitive groups did not differ in terms of mean age. While the ADNI sample is selected to have low vascular risk burden, in order to examine individuals with subclinical or relatively mild CVD, we also excluded potential participants with MRI defined brain infarct(s) and reported history of clinical stroke. In addition, in secondary analyses adjusting for vascular risk burden, we found quantitatively and statistically similar results. Findings suggest that our Obj-SCD criteria may reflect subclinical brain changes including relatively mild cerebrovascular changes. Notably, findings may have differed in a sample including individuals with more severe vascular risk and/or WMH burden.

Strengths of the current study include a large and well-characterized sample of older adults, quantification of lobar rather than solely global WMH volume, and the use of actuarial Obj-SCD and MCI classifications. Although there is no consensus regarding how to operationalize SCD, a growing body of work using process scores to classify Obj-SCD shows that Obj-SCD status predicts faster progression to MCI/dementia, Aβ and tau accumulation, entorhinal atrophy, altered cerebral blood flow, elevated plasma neurofilament light, (Bangen et al., 2021; Cui et al., 2021; Thomas et al., 2020a; Thomas et al., 2020b; Thomas et al., 2020c; Thomas et al., 2018a; Thomas et al., 2018b) – and now elevated regional WMH volume. Like all studies using ADNI data, our study is somewhat limited in its generalizability beyond the mostly white, highly educated, and generally healthy sample. In addition, previous research has shown that ADNI participants have greater rates of hippocampal volume loss than those observed in a population-based sample (Mayo Clinic Study of Aging) and may have a more pure and aggressive disease phenotype (Whitwell et al., 2012). The ADNI cohort may be more representative of clinical populations rather than the more general population. Our study is also limited by its cross-sectional design. Replication of our results in larger, more diverse samples with higher cerebrovascular disease burden that may better represent the general population and include more individuals classified as Obj-SCD as well as expansion to a longitudinal study are important future directions. We analyzed data from the ADNI-1 MRI protocol which acquired data primarily on 1.5T scanners and did not include acquisition of FLAIR scans. Although WMH volumes quantified with the current method agreed strongly with WMH volumes estimated based on FLAIR scans in individuals with normal cognition, MCI, and dementia (Schwarz et al., 2009), future studies should incorporate FLAIR scans and higher field MR scanners. In addition, we focused on lobar WMH volume and future studies should examine deep versus periventricular WMH volume. Additional research is also needed to clarify the link between small-vessel cerebrovascular disease and early stages of AD, particularly in light of evidence that cerebrovascular changes may precede, initiate, and exacerbate neurodegenerative processes (Bell et al., 2012; Zlokovic, 2011). Findings add to growing evidence of associations between Obj-SCD and imaging biomarkers, providing support for utility of our criteria to capture subtle biologically based changes.

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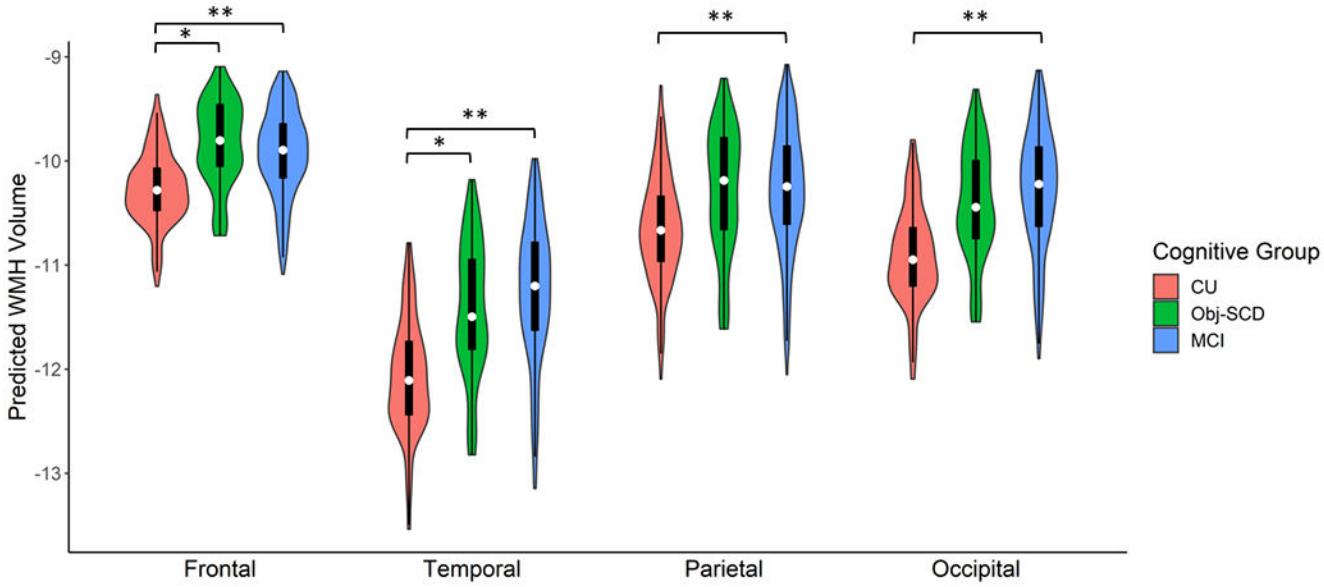

Fig. 1.

Violin plots demonstrating model predicted mean regional white matter hyperintensity (WMH) volume for cognitively unimpaired (CU), objective subtle cognitive decline (Obj-SCD) and mild cognitive impairment (MCI) groups. ANCOVA models adjusted for age, sex, and APOE ε4 frequency and examined WMH normalized by estimated total intracranial volume and log-transformed. * $p < 0.05$, ** $p < 0.01$

Table 1

Demographics and clinical characteristics by cognitive status

Variable	Cognitively Unimpaired n = 170		Objective Subtle Cognitive Decline n = 83		Mild Cognitive Impairment n = 306		F or X^2	p
	Mean	SD	Mean	SD	Mean	SD		
Age, years	75.63	5.63	75.59	6.66	74.46	7.02	F= 2.16	0.117
Education, years	16.04	2.87	16.16	2.85	15.53	3.10	F= 2.35	0.096
Sex, % female	47.65%		33.73%		37.91%		X^2= 6.02 *ab*	**0.049**
Race (%)							X^2= 2.43	0.965
White	93.53%		93.98%		91.50%			
Black	4.71%		3.61%		5.56%			
Asian	1.76%		2.41%		2.29%			
American Indian/Alaska Native	0.00%		0.00%		0.33%			
More than one	0.00%		0.00%		0.33%			
APOE ε4 frequency, %							X^2= 35.15 *bc*	**<0.001**
0	69.41%		65.06%		45.42%			
1	25.88%		33.73%		41.83%			
2	4.71%		1.20%		12.75%			
Vascular Risk								
Pulse Pressure, mmHg	59.01	14.32	59.17	15.07	60.68	16.34	F= 0.75	0.473
HIS *	0.55	0.64	0.58	0.59	0.58	0.69	F= 0.09	0.916
Hypertension, %	44.12%		53.01%		47.06%		X^2= 1.77	0.413
Diabetes, %	10.00%		7.23%		11.44%		X^2= 1.28	0.527
High cholesterol, %	17.16%		13.92%		14.86%		X^2= 0.60	0.742
Cognitive Function								
Animal Fluency, z-score **	0.16	0.97	−0.40	0.98	−1.00	0.90	F= 85.09 *abc*	**<0.001**
Boston Naming Test, z-score **	0.15	0.81	−0.41	1.14	−1.58	2.01	F= 67.12 *abc*	**<0.001**
Trails A, z-score **	0.20	0.76	−0.18	1.05	−1.16	2.11	F= 39.25 *bc*	**<0.001**
Trails B, z-score **	0.21	0.72	−0.11	1.04	−1.39	1.96	F= 64.62 *bc*	**<0.001**
AVLT Delayed Recall, z-score **	0.31	0.80	−0.68	0.82	−1.41	0.83	F= 241.78 *abc*	**<0.001**

Variable	Cognitively Unimpaired n = 170		Objective Subtle Cognitive Decline n = 83		Mild Cognitive Impairment n = 306		F or X^2	p
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
AVLT Recognition, z-score **	0.38	0.71	−0.41	0.85	−1.74	1.41	F= 190.46 *abc*	**<0.001**
MRI Markers								
Total Brain Volume ***	0.68	0.03	0.68	0.03	0.67	0.03	F= 16.35 *bc*	**<0.001**
	Median	**Interquartile range**	**Median**	**Interquartile range**	**Median**	**Interquartile range**		
WMH Volume, cm^3 ****								
Total	0.18	0.36	0.24	0.47	0.28	0.59	F= 6.23 *ab*	**.002**
Frontal	0.05	0.12	0.07	0.14	0.09	0.20	Group F= 10.34 Group x region F= 2.23	**<.001**
Temporal	0.01	0.04	0.02	0.11	0.03	0.10		
Parietal	0.03	0.11	0.05	0.11	0.05	0.17		**.048**
Occipital	0.03	0.09	0.04	0.20	0.06	0.21		

SD = standard deviation; APOE = apolipoprotein E; mmHg = millimeters of mercury; HIS = modified Hachinski Ischemic Scale; AVLT = Rey Auditory Verbal Learning Test.

F statistic reported for one-way ANOVAs, $\chi 2$ statistic report for chi-square tests. Data are summarized as mean and standard deviation, unless otherwise indicated. Significant group differences ($p < 0.05$) appear in bold font.

a significant differences between CU and Obj-SCD;

b significant differences between CU and MCI;

c significant difference between Obj-SCD and MCI

* HIS possible scores ranged from 0 to 12 with higher scores indicating greater likelihood of vascular (rather than degenerative) etiology although ADNI excluded potential participants with a score of 5 or higher on screening

** Each of the cognitive measures was transformed to an age-, education-, and sex-adjusted z-score based on a sample of participants who remained classified as cognitively unimpaired throughout their participation in the ADNI study.

*** Total brain volume was normalized by dividing whole brain volume by total intracranial volume.

**** Note that values reported here for total and regional WMH volumes are median and interquartile range for absolute volume in centimeters cubed (cm^3) although analyses were performed for absolute values divided by total intracranial volume in cm^3 and then log-transformed. These models are adjusted for age, sex, and APOE ε4 frequency. Absolute values were reported for interpretability and median and interquartile range were reported due to the significantly skewed distribution of the raw WMH volumes.