Biological Psychiatry: CNNI

Archival Report

Contributions of Cerebral White Matter Hyperintensities to Postural Instability in Aging With and Without Alcohol Use Disorder

Edith V. Sullivan, Natalie M. Zahr, Qingyu Zhao, Kilian M. Pohl, Stephanie A. Sassoon, and Adolf Pfefferbaum

ABSTRACT

BACKGROUND: Both postural instability and brain white matter hyperintensities (WMHs) are noted markers of normal aging and alcohol use disorder (AUD). Here, we questioned what variables contribute to the sway path–WMH relationship in individuals with AUD and healthy control participants.

METHODS: The data comprised 404 balance platform sessions, yielding sway path length and magnetic resonance imaging data acquired cross-sectionally or longitudinally in 102 control participants and 158 participants with AUD ages 25 to 80 years. Balance sessions were typically conducted on the same day as magnetic resonance imaging fluid-attenuated inversion recovery acquisitions, permitting WMH volume quantification. Factors considered in multiple regression analyses as potential contributors to the relationship between WMH volumes and postural instability were age, sex, socioeconomic status, education, pedal 2-point discrimination, systolic and diastolic blood pressure, body mass index, depressive symptoms, total alcohol consumed in the past year, and race.

RESULTS: Initial analysis identified diagnosis, age, sex, and race as significant contributors to observed sway path–WMH relationships. Inclusion of these factors as predictors in multiple regression analyses substantially attenuated the sway path–WMH relationships in both AUD and healthy control groups. Women, irrespective of diagnosis or race, had shorter sway paths than men. Black participants, irrespective of diagnosis or sex, had shorter sway paths than non-Black participants despite having modestly larger WMH volumes than non-Black participants, which is possibly a reflection of the younger age of the Black sample.

CONCLUSIONS: Longer sway paths were related to larger WMH volumes in healthy men and women with and without AUD. Critically, however, age almost fully accounted for these associations.

https://doi.org/10.1016/j.bpsc.2024.03.005

Postural instability is a common marker of acute alcohol intoxication [e.g., (1)], and long-term effects from chronic alcohol use disorder (AUD) are seen even with sustained sobriety (2,3). Although neuroimaging studies have established a pontocerebellar substrate of postural instability and ataxia of gait in AUD (4–8) with support from histological studies indicating cerebellar pathology in AUD cases with manifest signs of imbalance in life (9–11), additional evidence suggests that disturbance of cortical white matter integrity could also contribute to imbalance (12–14). Early computed tomography (15,16) and magnetic resonance imaging (MRI) (17,18) studies revealed areas of hyperintense signal that are commonly seen on the periphery of the lateral ventricles and in deep white matter locations. Greater presence and size of these white matter hyperintensities (WMHs) in periventricular or deep white matter were predictive of postural instability or falls in normal aging (12,17,19–23) and neurodegenerative and psychiatric conditions, such as Alzheimer's disease (24), Parkinson's disease (25) [but see (26)], mild stroke (27–29), small cerebrovascular disease (30,31), and depression (32). Among WMH studies in AUD, a few (33,34) have reported larger volumes in AUD than in control groups; however, none thus far have studied the relationship between WMH volumes and balance instability. Nonetheless, studies using diffusion tensor imaging have reported greater AUD-related compromise of white matter microstructure (i.e., fractional anisotropy and high diffusivity) in anterior regions of the centrum semiovale (35,36) and segments of the corpus callosum (37). These 2 diffusion tensor imaging studies found that poorer balance on a test of ataxia correlated with microstructural white matter compromise in men and women with AUD, whereas greater postural instability was associated with deterioration of the sensorimotor and parietal segments of the corpus callosum (37). To the extent that WMH volumes are related to diffusion tensor imaging metrics (38) and volumetric measures of white matter (39), exploration of the relationships between postural instability and WMH location and size has foundation.

In our recent MRI study, we reported that aging accelerated WMH volume enlargement at similar rates in control participants and participants with AUD, although the AUD group had consistently larger WMH volumes than the control group (34).

 ISSN: 2451-9022

Because most participants in that study had posturography testing (40) concurrent with neuroimaging, we were able to pose the following questions in the current analysis. First, does evidence for postural instability measured as sway path length correlate with WMH volumes in normal aging and AUD? Second, does the balance-brain relationship vary by AUD and control group and WMH location? Third, what demographic and physiological variables contribute to the observed sway path–WMH relationship? We explored salient variables as potential contributors to sway path or WMH presence taken from prior studies: age (34,40); sex (34,41); socioeconomic status (SES) (42); education (43,44); pedal 2-point discrimination (40,45); systolic and diastolic blood pressure as indices of hypertension (46–49) and age-related cerebral small vessel disease (cSVD) (27,48,50–56); body mass index (BMI) as a possible risk factor for WMHs [(57,58), but see (59)]; depressive symptoms (60); alcohol consumption (33,61); and race in the context of evidence for heightened risk of hypertension (62) and cSVD (42,63,64) in the Black community.

METHODS AND MATERIALS

Participants

The data comprised 404 balance platform testing sessions, yielding sway path length and MRI (Table 1) acquired cross-sectionally or longitudinally from 102 control participants and 158 participants with AUD, who were ages 25 to 80 years at study entry. Balance sessions were typically conducted on the same day (mean = 0.80, median = 0, SD = 11.9 days in between) as MRI fluid-attenuated inversion recovery (FLAIR) acquisitions, which allowed for WMH volume quantification. Although most of the balance (40) and FLAIR (34) data were reported previously, those data were never combined to examine the relationship between sway and WMH volumes. In addition, the current analysis included an expanded data sample collected from October 12, 2006, to July 21, 2023 (Table 2). Participants were recruited from local alcohol and drug recovery centers, postcard mailings, recruitment flyers, and word of mouth.

The mainstay of the data acquisition and analysis methods have been described previously (34,40). These studies were approved by the institutional review boards of SRI International and Stanford University School of Medicine and were carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Table 1. Number of Participants With MRI and Balance Data

	Control Group, n = 102	AUD Group, n = 158
No. of Path+FLAIR Sessions		
1	58	120
2	26	20
3	8	12
4	4	4
5	5	1
6	1	1
Total No. of Path+FLAIR Sessions	181	223

AUD, alcohol use disorder; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

After obtaining written informed consent from study participation, all volunteers were administered the Structured Clinical Interview for DSM-IV-TR (65) to determine diagnoses of alcohol dependence/abuse and DSM-5 diagnoses of AUD (66). Interviews included structured health questionnaires and a semistructured timeline follow-back interview to quantify lifetime alcohol use (67). Principal exclusion criteria at study entry were a history of schizophrenia, bipolar disorder, or neurological disorders. Substance use dependence/abuse (current or in remission) for illicit drugs was common and involved cocaine, amphetamines, opiates, and cannabis (although the latter is now legal in California). All participants also completed metal screening to ensure MRI safety. At the beginning of each study day, participants underwent breathalyzer testing for recent alcohol consumption. Participants whose breathalyzer reading exceeded 0.0 were not tested on that day and were asked to return when they had refrained from drinking.

Balance, Sensory, and Physiological Testing

Balance platform data acquisition and analysis. Participants wore rubber-soled socks and stood still on a force plate with feet together and arms relaxed at their side. The test comprised three 30-second trials in each of 2 conditions: eyes open and then eyes closed. The microcomputer-controlled force plate (model 9284; Kistler) has multiple transducers and analog-digital converters and sampled data at 1000 Hz to produce sway paths for each trial of each condition. Raw data were center-of-pressure displacements (x-y pairs) subjected to a 10-Hz low-pass filter (99 terms, −50 dB Gibbs). Sway path length was expressed as the line integral (cm) (7) (equation 1). Examples of sway paths are shown in Figure 1A.

$$P = \sum_{i=1}^{N-1} \sqrt{(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2} \quad (1)$$

Sensory Testing: 2-Point Discrimination. Starting with the dominant side determined from handedness, the examiner touched the sole of 1 foot with 1 or 2 points of a 3-point aesthesiometer, and the participant (with eyes closed) responded "1" or "2." Testing avoided calloused skin and proceeded with descending limits (starting at 50 mm distance between points); the threshold was the shortest distance at which fewer than 3 errors were made (68). Thus, high scores were in the impaired direction. The procedure was repeated with the other foot. The score was the mean of the left and right thresholds.

Blood Pressure. Sitting blood pressure was collected twice. The mean of each of the 2 diastolic and systolic measures was used in multiple regression analyses described below.

Falls Questionnaire. About one-third of participants in each group (33 of 102 controls and 55 of 158 participants with AUD) completed a simple falls questionnaire (69) and were asked how many times they had fallen to the ground during the past year. The range was 0 to 6 occasions.

Neuroimaging Acquisition and Analysis

Protocols and Parameters. Scanning was conducted at SRI International on a GE 3T MR750 system with array spatial sensitivity encoding technique for parallel and accelerated

Table 2. Study Entry Demographics at Baseline

	Control, n = 102	AUD, n = 158	Simple Effects Statistics		
			Group	Sex	Age
Age, Years	53.51 (14.36)	51.13 (10.75)	$t = -1.52$, $p = .130$	$t = 0.090$, $p = .928$	–
Sex, Female/Male	42/60	43/115	$\chi^2_2 = 5.49$, $p = .019$[a]		
Education, Years	16.21 (2.47), n = 99	13.47 (2.41), n = 154	$t = -8.364$, $p = 4.36 \times 10^{-15}$[a]	$t = -1.457$, $p = .146$	$t = 4.653$, $p = 5.31 \times 10^{-6}$[a]
Socioeconomic Status[b]	24.86 (12.05), n = 100	41.26 (15.36), n = 158	$t = 8.550$, $p = 1.17 \times 10^{-15}$[a]	$t = 1.909$, $p = .574$	$t = -3.119$, $p = .002$[a]
Body Mass Index	25.97 (4.41), n = 100	27.10 (4.40), n = 153	$t = 2.019$, $p = .045$[a]	$t = -0.631$, $p = .529$	$t = 0.292$, $p = .771$
Diastolic Blood Pressure	75.99 (11.41), n = 86	78.91 (10.78), n = 144	$t = 2.153$, $p = .032$[a]	$t = 0.049$, $p = .961$	$t = 1.676$, $p = .095$
Systolic Blood Pressure	126.60 (18.84), n = 86	128.92 (16.95), n = 144	$t = 1.028$, $p = .305$	$t = 2.782$, $p = .006$[a]	$t = 2.137$, $p = .034$[a]
Global Assessment of Functioning	84.32 (6.70), n = 99	67.20 (10.62), n = 152	$t = -13.987$, $p = <2 \times 10^{-16}$[a]	$t = 0.039$, $p = .969$	$t = 1.293$, $p = .197$
2-Point Pedal Discrimination	18.17 (9.37), n = 95	20.28 (10.23), n = 149	$t = 2.827$, $p = .005$[a]	$t = 0.639$, $p = .524$	$t = 9.364$, $p = <2 \times 10^{-16}$[a]
Beck Depression Inventory II	2.69 (3.75), n = 96	9.39 (8.07), n = 155	$t = 7.803$, $p = 1.07 \times 10^{-13}$[a]	$t = -1.856$, $p = .065$	-0.431, $p = .667$
Lifetime Alcohol Consumption, kg	40.47 (66.66), n = 101	1236.57 (988.58), n = 158	$t = 12.290$, $p = <2 \times 10^{-16}$[a]	$t = 2.900$, $p = .004$[a]	$t = 3.667$, $p = .0003$[a]
Total Alcohol in Past Year, kg	1.00 (0.61), n = 99	30.88 (31.18), n = 158	$t = 9.079$, $p = <2 \times 10^{-16}$[a]	$t = 2.306$, $p = .022$[a]	$t = -0.460$, $p = .646$
Age at AUD Diagnosis, Years	–	25.42 (9.55), n = 152	–	–	–
Number of Falls in Past Year, 0/1/2/3/4/5/6	14/11/6/0/1/1/0, n = 33	26/8/7/4/3/2/5, n = 55	$\chi^2_6 = 9.58$, $p = .134$		
Race, Asian/Black/Other/White[c]	25/18/6/53, n = 102	5/60/22/71, n = 158	$\chi^2_4 = 37.38$, $p < .0001$		

Values are presented as mean (SD) or n.
AUD, alcohol use disorder.
[a]p Values meeting significance with correction for multiple comparisons.
[b]A lower socioeconomic score indicates higher status.
[c]Other includes mixed, other, and don't know.

imaging on an 8-channel head coil. Detection and localization of WMHs used 3 MRI acquisition protocols: 1) T1-weighted (T1-w) MRI for anatomical localization: 3-dimensional axial inversion-recovery prepared, spoiled gradient recalled; repetition time = 6.5 ms, echo time = 1.54 ms, thickness = 1.25 mm, locations (loc) = 124, skip = 0; 2) T2-weighted MRI merged with T1 data for skull stripping: 3-dimensional isotropic fast spin echo (GE name = CUBE); repetition time = 2500 ms, effective echo time = 99 ms, echo train length = 100 ms, thickness = 1 mm, loc = 150, field of view = 256 mm^2, xy_matrix = 256 × 256, resolution = 1 × 1 × 1 mm^3; and 3) FLAIR imaging for estimates of WMH volumes: 2-dimensional axial, repetition time = 9000 ms, echo time = 82.5 ms, inversion time = 2200 ms, thickness = 2.5 mm, loc = 65.

MRI Structural Analysis. T1-w and T2-weighted MRI data were corrected for noise (70) and field inhomogeneity via N4ITK (71). T2-weighted images were then aligned to T1-w images via CMTK (72). The SRI24 atlas (73) was nonrigidly aligned to T1-w images via ANTS (74), and the SRI24 mask was used to refine inhomogeneity correction of both modalities. Next, an improved brain mask was created by majority voting (75) across maps extracted by FSL BET (76), AFNI 3dSkullStrip (77), FreeSurfer mri_gcut (78), and the robust brain extraction method (79). Atropos generated brain tissue segmentations (gray matter, white matter, and cerebrospinal fluid) (80). Regarding majority voting, a voxel is labeled inside the brain if a majority of masks agrees; otherwise, the voxel is labeled outside the brain. The resulting probabilistic label maps of each time point were overlaid with the SRI24 atlas to define cortical and subcortical regions in each brain lobe.

WMH Quantification. WMH analysis of FLAIR data was accomplished with the UBO Detector, a freely available, cluster-based, fully automated pipeline for extracting and calculating WMH volume on a voxel basis (81,82). The UBO Detector was validated on longitudinal data and gold-standard Fazekas ratings (83). This procedure yielded voxel maps of total, periventricular (PVWMH) and deep (DWMH) WMHs (Figure 1B) and DWMH volumes in each of 4 lobar regions. Analysis required that FLAIR and T1-weighted data be transformed into Montreal Neurological Institute space prior to nonrigid transformation into standard atlas space. This was necessary for accurate placement of anatomical locations to enable comparisons across individuals and imaging modalities on a voxelwise basis without the need for further correction for intracranial volume.

Statistical Analysis

Statistical analysis was performed using R 3.5.1 (R Core Team, 2019). Taking advantage of the fact that several participants had multiple data sets across time (84), the primary statistic was a linear mixed-effects model (lmer) applied separately to test the relationship between balance platform condition (i.e., eyes open or closed) and each WMH volume (i.e., total,

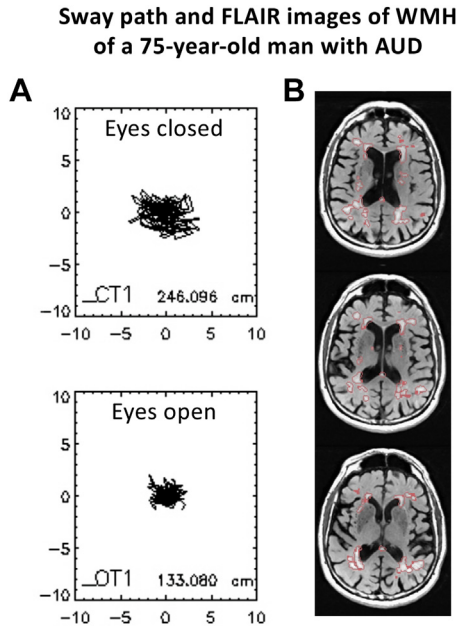

Figure 1. **(A)** Examples of sway paths of a 75-year-old man with alcohol use disorder (AUD). The top sway path (246.1 cm long) occurred while trying to stand still with eyes closed, and the bottom sway path (133.1 cm long) occurred with eyes open. **(B)** Axial images from fluid-attenuated inversion recovery (FLAIR) data of the man with AUD. His white matter hyperintensities (WMHs) are delineated in red outlining.

periventricular, deep) as a function of group (control, AUD) + age^2. Previously, we found that the relationship of path length (40) and WMH volumes (34) to age were best fit with an age^2 function; thus, age^2 was used in all analyses herein. Because of the heteroscedasticity of WMH volumes across individuals, their values were square root transformed before statistical analysis. The WMH analysis proceeded in a hierarchal fashion: initial comparisons were based on total WMH volume, PVWMH, and DWMH volumes; the whole brain was then divided into 4 cortical lobes (frontal, temporal, parietal, and occipital) for regional analysis of DWMH volumes.

To account for differences in demographic characteristics and variables that have been reported to correlate with WMH size, linear mixed-models multiple regression analysis included diagnosis, age^2, sex (self-identified), SES, number of years of education, 2-point pedal discrimination, systolic and diastolic blood pressure, BMI, depressive symptoms (Beck Depression Inventory-II score), amount of alcohol consumed in the past year, and race (Black vs. non-Black, self-identified). Analyses were repeated after eliminating variables that did not contribute significantly to the main effect. The model outputs for group differences produced t and p values. Within-group analysis examined relationships between WMH volumes and sway path lengths while accounting for the demographic variables noted above that were significant contributors in the multiple regression analyses. Familywise Bonferroni correction was applied to correct for multiple comparisons in each primary analysis as noted in the tables.

A final set of analyses was used to follow up on variables that were found to contribute significantly to the relationship between sway path and WMHs in the multiple regression analyses. Because the resulting groups were of different ages, the sway path and WMH volumes of individuals were adjusted for age. Accordingly, within the control and AUD groups separately, the standardized residuals from the fixed effects of a linear mixed-model regression for balance scores and for WMH volumes were reduced to a single mean value for each participant, and the resulting age-adjusted balance and WMH values were compared using a simple linear regression analysis.

RESULTS

Comparison of Groups on Demographic Variables

The AUD and control groups were not statistically different in age or number of falls reported over the past year. Compared with the control group, the AUD group had fewer years of education, lower SES, lower Global Assessment of Functioning scores, higher BMI and diastolic blood pressure, more depressive symptoms (Beck Depression Inventory), and poorer 2-point pedal discrimination (Table 2). The AUD group had disproportionately more men than women and a larger Black representation than the control group. The AUD group had consumed significantly more alcohol than the control group over their lifetime, since their last visit, and during the year prior to testing. Given these group differences, multiple regression analyses were used to examine the influence of these variables in testing group differences and in conducting within-group correlations between sway path and WMH volumes.

Group Differences in Predicting Sway Path Length From WMH Volume

An omnibus linear mixed-model multiple regression of balance with eyes closed as a function of diagnosis with total WMH volume, age^2, sex, SES, education, pedal 2-point discrimination, systolic blood pressure, diastolic blood pressure, BMI, Beck Depression Inventory score, total alcohol consumed in the past year, and race (Black vs. non-Black) as covariates revealed significant contributions from age and race. The same pattern emerged for balance with eyes open (Table S1). Considering these significant contributing factors and inclusion of sex as a biological variable, subsequent analyses comparing balance between the AUD and control groups included diagnosis, WMH volume, age, sex, and race as potential contributors.

Both larger total WMH and PVWMH volumes predicted longer sway paths with eyes closed, with significant contributions from age and race and a modest contribution from sex. In regional lobar analyses, this pattern held for DWMH parietal volume. For sway path length with eyes open, the group effects for total, parietal, and occipital DWMH volumes remained after controlling for significant effects of age and sex and the nonsignificant contribution of race (i.e., not meeting correction for multiple comparisons) (Table 3).

Predicting Sway Path Length From WMH Volume Within Each Group

Initial analyses tested whether WMH volumes predicted sway path length without consideration of other potentially

contributing variables. Each of the 7 WMH total and regional volumes significantly correlated (with correction for multiple comparisons) with path length in the AUD and control groups separately in the eyes closed and eyes open conditions (Table 4; Figures 2 and 3; Figures S1 and S2).

Next, within-group multiple regression analyses controlling for age, sex, and race were used to examine whether the AUD and control groups differed in factors predicting sway paths over time. When adding these factors to WMH volume in the models predicting path length, the contribution from WMH volumes was attenuated and supplanted by age in both groups and for all WMH measures (Figures 2 and 3; Figures S1 and S2). In 6 instances, WMH volumes survived as a contributor to path length, but generally with marginal significance after correction for multiple comparisons: With eyes closed, total WMH and PVWMH volumes contributed to sway path in the control group, whereas parietal DWMH volume contributed to sway path in the AUD group; with eyes open, total WMH and parietal and occipital DWMH volume contributed to sway path in the AUD group. Sex was also a factor, albeit not meeting Bonferroni correction, in all comparisons in the eyes open condition in the AUD group. Race was a significant factor (meeting Bonferroni correction) in all comparisons in both sway path conditions in the AUD group (Table 4).

Effects of Sex and Race on Sway Path Length and WMH Volume

To discern the effects of sex and race on sway path length, the control and AUD groups were divided first by sex and then by race (Table 5 and Figure 4, top). On average, women, irrespective of group and race, had shorter sway paths than men in the eyes closed ($t_{196.64}$ = 2.787, p = .006) and eyes open ($t_{183.75}$ = 2.838, p = .005) conditions. Black participants, irrespective of group and sex, had significantly shorter sway paths than non-Black participants with eyes closed ($t_{172.99}$ = −2.235, p = .027) and nonsignificantly shorter paths with eyes open ($t_{219.84}$ = −1.856, p = .065).

When considering the effects of sex and race on total WMH volumes (Table 5 and Figure 4, bottom), the combined group of Black participants, irrespective of diagnostic group or sex, had nonsignificantly larger WMH volumes than non-Black participants ($t_{124.87}$ = 1.917, p = .057), although the mean total WMH volumes of the Black men and women with AUD were larger than those of the Black control men and women. By contrast, the combined groups of men and women did not differ in total WMH volumes ($t_{134.50}$ = −1.082, p = .281). The same set of comparisons did not yield any significant differences for DWMH volumes for race ($t_{138.43}$ = 0.579, p = .564) or sex ($t_{142.66}$ = −0.792, p = .430).

DISCUSSION

The results of the current study provided answers to questions posed and raised additional questions. First, regarding answers, postural instability measured as longer sway path length was significantly correlated with larger WMH volumes in normal aging and AUD. Second, the observed balance-brain relationships were similar in the AUD and control groups by WMH location and in both balance vision conditions. Third and most critically, testing of 12 demographic and physiological variables identified age as the strongest factor in tempering direct balance-WMH relationships, with additional contributions from sex and race.

WMH is a neuroimaging feature associated with cSVD and commonly taken as evidence for microvascular rarefaction in

Table 3. The Effects of Group, WMH Volume, Age, Sex, and Race on Sway Path Length

	Group		WMH volume		Age		Sex		Race (Black vs. Non-Black)	
Sway and WMH Condition	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Eyes Closed										
Total WMH	2.959	.003[a]	2.915	.004[a]	5.317	.000[a]	2.385	.018[b]	−3.149	.002[a]
PVWMH	2.733	.007[a]	3.066	.002[a]	6.005	.000[a]	2.343	.020[b]	−3.175	.002[a]
DWMH	2.077	.038[b]	3.077	.002[a]	5.864	.000[a]	2.244	.026[b]	−2.921	.004[a]
Frontal	0.988	.324	3.294	.001[a]	7.050	.000[a]	2.121	.035[b]	−2.955	.003[a]
Temporal	1.323	.187	3.350	.001[a]	7.219	.000[a]	2.199	.029[b]	−2.916	.004[a]
Parietal	2.711	.007[a]	2.979	.003[a]	5.865	.000[a]	2.273	.024[b]	−2.941	.004[a]
Occipital	0.885	.377	3.384	.001[a]	7.111	.000[a]	2.117	.035[b]	−2.845	.005[a]
Eyes Open										
Total WMH	2.291	.023[b]	3.163	.002[a]	7.247	.000[a]	2.842	.005[a]	−2.635	.009[b]
PVWMH	1.435	.152	3.371	.001[a]	8.135	.000[a]	2.749	.006[a]	−2.579	.011[b]
DWMH	3.063	.002[a]	3.067	.002[a]	7.087	.000[a]	2.840	.005[a]	−2.477	.014[b]
Frontal	0.906	.365	3.448	.001[a]	8.774	.000[a]	2.653	.008[b]	−2.498	.013[b]
Temporal	0.911	.363	3.524	.001[a]	9.048	.000[a]	2.697	.007[a]	−2.443	.015[b]
Parietal	2.859	.005[a]	3.101	.002[a]	7.487	.000[a]	2.814	.005[a]	−2.490	.014[b]
Occipital	2.792	.005[a]	3.402	.001[a]	8.267	.000[a]	2.714	.007[a]	−2.312	.022[b]

Regressions are based on 404 observations in 102 control and 158 AUD participants.

AUD, alcohol use disorder; DWMH, deep WMH; PVWMH, periventricular WMH; WMH, white matter hyperintensity.

[a]Bonferroni correction for 7 comparisons (2-tailed, α = 0.05) requires $p \leq .007$.

[b]$p \leq .05$ uncorrected.

Table 4. Simple Regressions Between Sway Path Length and WMH Volumes and Multiple Regressions Predicting Sway From WMH Volumes Controlling for Age, Sex, and Race

		Simple Regressions		Multiple Regressions							
		WMH Volume		WMH Volume		Age		Sex		Race	
Sway Condition	Group	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Eyes Closed											
Total WMH	Control	6.289	.000[a,b]	2.597	.010[a]	3.750	.000[a,b]	1.547	.125	0.108	.914
	AUD	3.634	.000[a,c]	1.847	.066	3.887	.000[a,c]	1.670	.097	−3.463	.001[a,c]
PVWMH	Control	5.841	.000[a,b]	2.716	.007[a,b]	4.504	.000[a,b]	1.468	.145	0.212	.833
	AUD	3.057	.003[a,c]	1.653	.100	4.216	.000[a,c]	1.662	.098	−3.496	.001[a,c]
DWMH	Control	4.436	.000[a,b]	0.820	.413	5.057	.000[a,b]	1.271	.207	0.273	.786
	AUD	3.944	.000[a,c]	1.692	.092	3.915	.000[a,c]	1.591	.114	−3.276	.001[a,c]
Frontal	Control	3.210	.002[a,b]	0.846	.399	5.796	.000[a,b]	1.260	.210	0.228	.820
	AUD	2.280	.024[c]	0.335	.738	4.742	.000[a,c]	1.521	.130	−3.325	.001[a,c]
Temporal	Control	2.284	.024[b]	-0.245	.807	6.431	.000[a,b]	1.145	.255	0.377	.707
	AUD	2.963	.003[a,c]	1.752	.081	4.554	.000[a,c]	1.705	.090	−3.356	.001[a,c]
Parietal	Control	4.008	.000[a,b]	0.589	.557	5.326	.000[a,b]	1.247	.215	0.289	.774
	AUD	4.632	.000[a,c]	2.604	.010[c]	3.735	.000[a,c]	1.551	.123	−3.248	.00[a,c]
Occipital	Control	3.246	.001[a,b]	0.062	.950	5.960	.000[a,b]	1.163	.247	0.368	.714
	AUD	2.528	.012[c]	0.869	.386	4.807	.000[a,c]	1.562	.120	−3.267	.001[a,c]
Eyes Open											
Total WMH	Control	5.918	.000[a,b]	1.358	.177	5.493	.000[a,b]	1.656	.101	0.235	.815
	AUD	3.885	.000[a,c]	1.679	.095	4.791	.000[a,c]	2.122	.035[c]	−2.919	.004[a,c]
PVWMH	Control	4.937	.000[a,b]	0.953	.342	6.339	.000[a,b]	1.569	.120	0.308	.759
	AUD	2.969	.003[a,c]	1.105	.270	5.262	.000[a,c]	2.083	.039[c]	−2.898	.004[a,c]
DWMH	Control	5.279	.000[a,b]	1.105	.271	5.958	.000[a,b]	1.624	.108	0.247	.806
	AUD	5.124	.000[a,c]	2.616	.010[c]	4.384	.000[a,c]	2.071	.040[c]	−2.721	.007[a,c]
Frontal	Control	3.342	.001[a,b]	0.526	.600	7.060	.000[a,b]	1.529	.130	0.277	.782
	AUD	2.784	.006[a,c]	0.456	.649	5.542	.000[a,c]	1.985	.049[c]	−2.796	.00[a,c]
Temporal	Control	2.555	.012[b]	−0.530	.597	7.697	.000[a,b]	1.438	.154	0.391	.697
	AUD	3.032	.003[a,c]	1.576	.117	5.482	.000[a,c]	2.160	.032[c]	−2.806	.006[a,c]
Parietal	Control	4.838	.000[a,b]	0.926	.356	6.192	.000[a,b]	1.618	.109	0.242	.809
	AUD	4.866	.000[a,c]	2.511	.013[c]	4.643	.000[a,c]	2.022	.045[c]	−2.722	.007[a,c]
Occipital	Control	4.322	.000[a,b]	0.734	.464	6.837	.000[a,b]	1.497	.138	0.368	.714
	AUD	4.279	.000[a,c]	2.615	.010	5.274	.000[a,c]	2.077	.039[c]	−2.659	.009[c]

Regressions are based on 181 observations in 102 controls and on 223 observations in 158 AUD participants.
AUD, alcohol use disorder; DWMH, deep WMH; PVWMH, periventricular WMH; WMH, white matter hyperintensity.
[a]Bonferroni correction for 7 comparisons (2-tailed, $\alpha = 0.05$) requires $p \leq .007$.
[b]$p \leq .05$ uncorrected for the control group.
[c]$p \leq .05$ uncorrected for the AUD group.

normal aging (48,50–54) and disease (85) including AUD (86,87) and often considered a substrate of cognitive and motor declines (27). Relationships between WMH volumes and motor performance may be mediated by WMH size and location (88–91). Factors that we tested in the current study that were previously known as potential contributors to the observed balance-WMH relationship were systolic and diastolic blood pressure (34), 2-point pedal discrimination (40,69), BMI (38), depressive symptoms (34), and recency and amount of alcohol consumption (2). Although we previously found that older age of AUD onset, systolic and diastolic blood pressure, and more depressive symptoms were each modest predictors of larger WMH volumes in participants with AUD, none of these factors made adequate contributions to the balance-WMH relationships in either diagnostic group in the current study; thus, none was strong enough to warrant inclusion in multiple regressions in our principal analysis. Factors that did make greater contributions to the balance-WMH relationships were age, sex, and race.

Of all the variables that were tested, age had by far the greatest effect on the balance-WMH relationship. Age almost fully accounted for the correlations between longer sway paths and larger WMH volumes in both the AUD and control groups. Attenuation of the sway path–WMH volume correlations with age indicated that the relationship between increasing instability and enlarging of WMH volumes occurred principally because they advanced together with age and thereby provided weak support for speculations regarding WMH presence, size, or location as potential causal factors in postural instability in either the control or

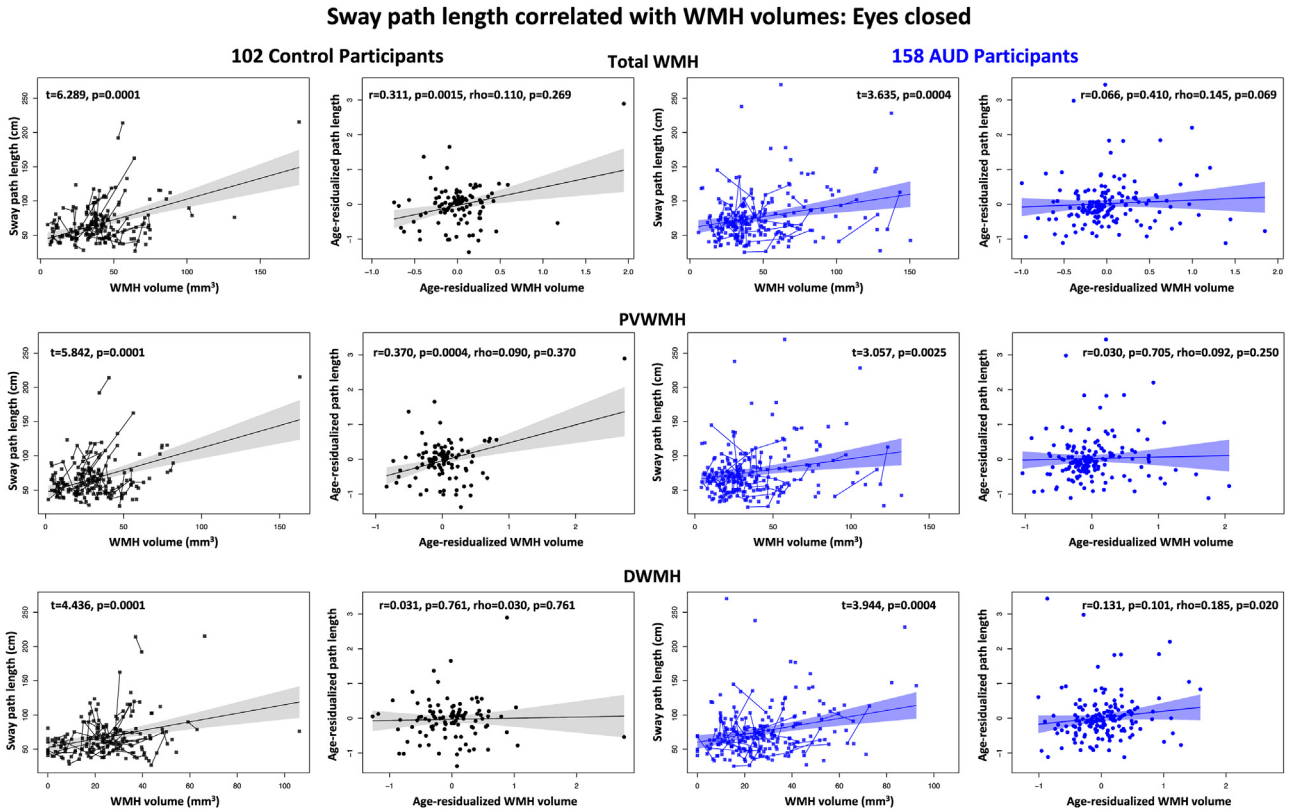

Figure 2. Correlations between sway path length (eyes closed condition) and white matter hyperintensity (WMH) volume for total, periventricular WMH (PVWMH), and deep WMH (DWMH) regions for 102 control participants (gray) and 158 participants with alcohol use disorder (AUD) (blue). Participants with multiple pairs have their data points connected as shown in the spaghetti plots (first and third images across each line). The second and fourth images are age-residualized values for both WMH volumes and sway path lengths (of mean values of individual with multiple test points) adjusted for age. Also plotted are the mean regression lines and 95% CIs. Without age adjustment, all correlations were significant. With age adjustment, all correlations were diminished, yielding only 1 marginally significant correlation in the AUD group (sway with eyes closed and DWMH volume).

the AUD group. This conclusion is consistent with that of a longitudinal study of 59 normal older people examined annually for 8 to 10 years (19). Specifically, observations of age-related decreases in vestibular, visual, auditory, and somatosensation and worse WMH ratings correlated with slowed gait and advancing postural instability, but all variables combined accounted for <30% of the gait and balance declines.

Regardless of diagnostic group, the men in this study had longer sway paths than the women, which is consistent with our earlier study based on a larger sample from which the current group was drawn (40). In an earlier study, we also found longer sway paths in healthy women than in men, but longer sway paths correlated with larger WMH volumes in women but not men (39). Further complicating the sex effects in the context of aging and WMH size, another study found that postmenopausal women had longer sway paths, faster age-related acceleration, and more WMHs than premenopausal women and men of similar ages; notably, the longer sway paths of postmenopausal women were not related to use of hormone replacement treatment (41). When considering sex and postural instability in AUD, we have consistently observed greater imbalance in men than women with AUD, whether using force platform (92) or simple ataxia (8) testing. Although the extent of imbalance in AUD has been related selectively to cerebellar volume deficits in men with AUD (7) or anomalous frontocerebellar connectivity (5), neither our studies nor those of others had identified relationships between postural instability and WMH volumes in AUD.

The combined group of self-identified Black participants, irrespective of diagnostic group or sex, tended to have shorter sway paths but larger WMH volumes than the non-Black participants. This paradoxical combination may have some foundation in the age differences between our Black control participants and their White counterparts, who were about 10 years older on average than the Black participants in the current study. Nonetheless, in light of epidemiological studies showing greater prevalence in middle-age Black individuals of cSVD that are considered a leading cause of WMHs (93), we found race to be a moderator of the WMH-balance relationship.

Limitations

On average, Black participants in the current study were about a decade younger than non-Black participants, which

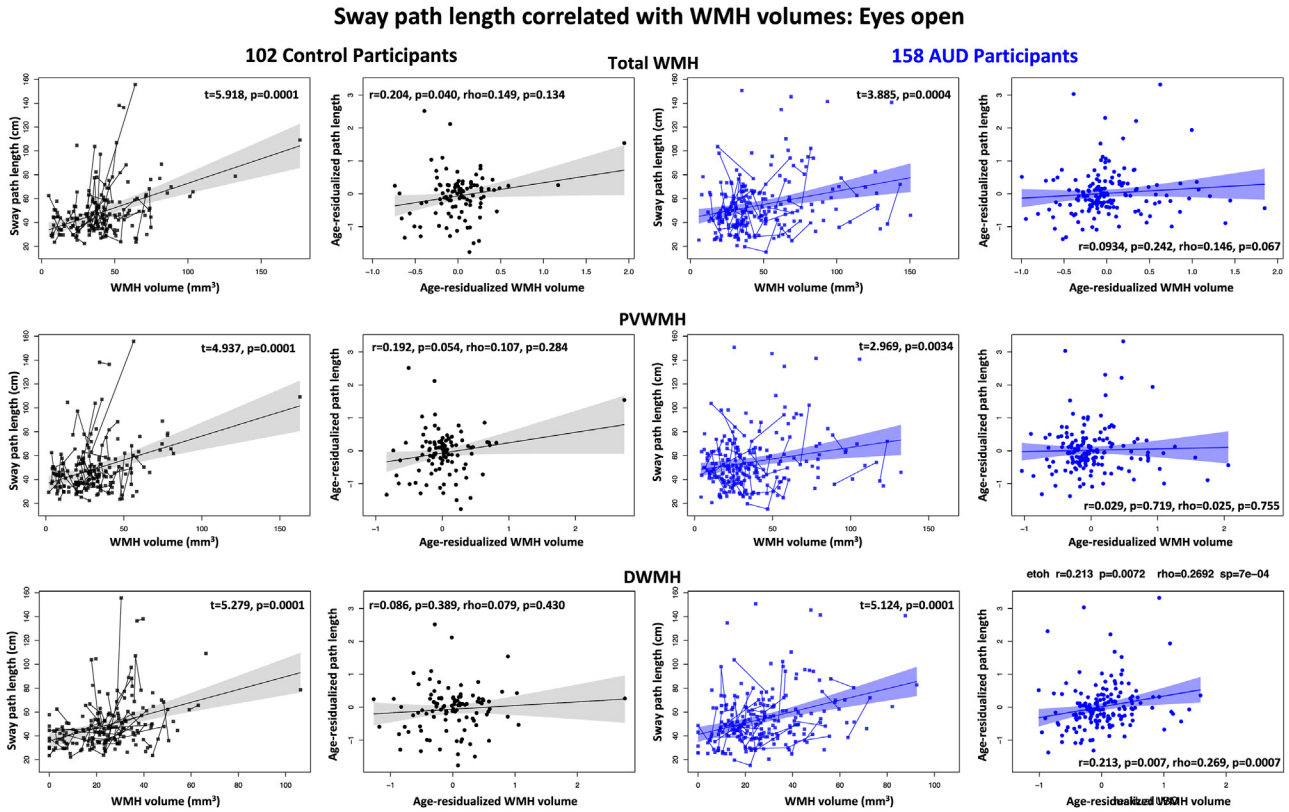

Figure 3. Correlations between sway path length (eyes open condition) and white matter hyperintensity (WMH) volume for total WMH, paraventricular WMH (PVWMH), and deep WMH (DWMH) regions for 102 control participants (gray) and 158 participants with alcohol use disorder (AUD) (blue). Participants with multiple pairs have their data points connected as shown in the spaghetti plots (first and third images across each line). The second and fourth images are age-residualized values for both WMH volumes and sway path lengths (of mean values of individual with multiple test points) adjusted for age. The mean regression lines and 95% CIs are also plotted. Without age adjustment, the correlations were significant. With age adjustment, all correlations were diminished, yielding only 1 significant correlation in the AUD group (sway with eyes open and DWMH volume).

necessitated the use of age-adjusted sway path length and WMH volume in statistical comparisons. These post hoc analyses indicated that the Black participants with AUD had shorter sway paths despite larger total WMH volumes (adjusted for age) than the non-Black participants with AUD. To the extent that WMHs, especially those in deep cortical regions, are typically associated with cSVD (94) and with higher prevalence in Black than White groups (93), it was surprising that our results were not consistent with earlier findings. The lack of agreement may be due, at least in part, to the limited sample sizes and significant age differences in our sample. Despite these shortcomings, objectively observed, race-based differences indicate a need to incorporate race as a variable in biologically based research. However, to do so calls for mindful consideration of race-based disparities that emerge insidiously and serve to bias the outcome and interpretation of results from comparisons of racially defined groups [cf., (95)]. Fair comparisons require adequate power,

Table 5. Sway Path Length and WMH Volumes Adjusted for Age Divided by Sex and Race

	Black				Non-Black			
	Control		AUD		Control		AUD	
	Men, *n* = 13	Women, *n* = 5	Men, *n* = 43	Women, *n* = 17	Men, *n* = 47	Women, *n* = 37	Men, *n* = 72	Women, *n* = 26
Age, Years, Mean (SD)	40.40 (10.21)	38.81 (14.13)	52.86 (8.21)	48.29 (9.28)	57.15 (12.57)	55.48 (14.37)	50.20 (12.80)	52.68 (8.78)
Eyes Closed, Mean (SD)	52.80 (11.02)	60.58 (14.44)	67.47 (35.78)	62.64 (18.87)	76.09 (30.79)	64.85 (32.01	87.89 (40.42)	71.54 (30.47)
Eyes Open, Mean (SD)	37.69 (8.36)	41.94 (10.20)	50.61 (20.48)	46.38 (12.59)	54.79 (22.66)	47.15 (17.87)	60.93 (26.04)	51.12 (25.42)
Total WMH, Mean (SD)	30.12 (14.19)	34.22 (23.77)	50.50 (29.68)	56.58 (36.31)	43.69 (20.77)	49.44 (32.77)	46.88 (27.63)	48.61 (30.93)
DWMH, Mean (SD)	16.54 (14.74)	22.68 (17.03)	27.69 (15.77)	29.30 (20.25)	25.25 (13.21)	29.20 (19.81)	29.27 (17.26)	28.66 (18.35)

AUD, alcohol use disorder; DWMH, deep WMH; WMH, white matter hyperintensity.

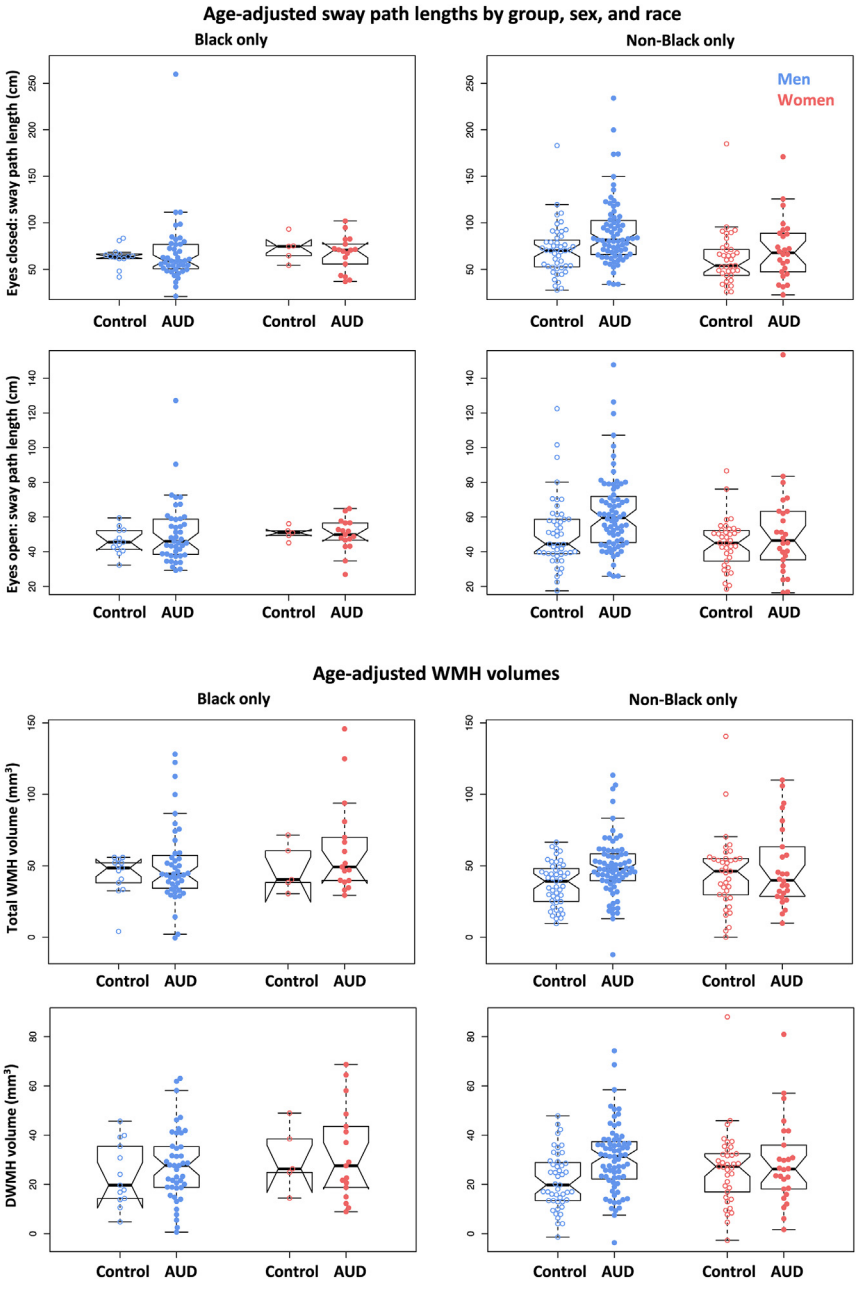

Figure 4. Box plots overlaid on bee swarm scatterplots of each participant, men in blue and women in red. All values are adjusted for age. For participants with more than 1 observation, the mean values for path length and white matter hyperintensity (WMH) volume were computed and plotted so that each participant had only 1 value per metric. The top set of 4 figures divided the groups by race (Black and non-Black) to illustrate the effect of race on sway path length. The bottom 4 figures also divided the groups by race to show the effect of race on WMH volumes. The means ± SDs of these plots are given in Table 5. AUD, alcohol use disorder; DWMH, deep WMH.

appropriate control groups, and responsible research questions poised to identify environmental, biological, or other factors that may help explain a phenomenon, for example by furthering a mechanistic understanding of a neuropsychiatric disorder.

As we previously speculated (34), poor nutritional status, notably low vitamin D, may be a risk factor for greater WMH burden (96), whereas physical exercise may enhance central nervous system health (97), but these measures were not available in our study. A further shortcoming is the unequal sample size across groups. Although men and women were similarly represented in the control group, men outnumbered women in the AUD group, which is consistent with epidemiological data (98). Clearly, inclusion of larger groups, especially women of color, is warranted.

Conclusions

The results of this study provide evidence that longer sway paths are related to larger WMH volumes in healthy individuals and those with AUD. However, this finding needs to be considered in the context of aging given that age nearly fully

accounted for this relationship. Recognizing that WMH size as a neural substrate of imbalance and propensity for falls has been reported primarily in older adults and diagnostic groups, it may be fitting that the WMH-balance relationships observed herein were modulated primarily by age and thus do not necessarily occur in people who are in relatively good health or even in those with AUD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (Grants Nos. AA005965 [to AP, NMZ] and AA010723 [to EVS]) and the National Institute of Mental Health (Grant No. MH113406 [to KMP]), but funding officials were not involved in the conduct of the study.

We note in the Methods and Materials that the mainstay of the sway path and neuroimaging data was published separately, but the current analysis has repurposed those data to address questions regarding the potential predictive value of WMH volumes to postural instability in healthy aging and AUD.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, California (EVS, NMZ, KMP, SAS, AP); Center for Health Sciences, SRI International, Menlo Park, California (NMZ, SAS, AP); and Department of Radiology, Weill Cornell Medicine, New York, New York (QZ).

Address correspondence to Edith V. Sullivan, Ph.D., at edie@stanford.edu.

Received Jan 8, 2024; revised Feb 29, 2024; accepted Mar 22, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2024.03.005.

REFERENCES

1. Diener HC, Dichgans J, Bacher M, Hülser J, Liebich H (1983): Mechanisms of postural ataxia after intake of alcohol. Z Rechtsmed 90:159–165.
2. Smith S, Fein G (2011): Persistent but less severe ataxia in long-term versus short-term abstinent alcoholic men and women: A cross-sectional analysis. Alcohol Clin Exp Res 35:2184–2192.
3. Sullivan EV, Rosenbloom MJ, Lim KO, Pfefferbaum A (2000): Longitudinal changes in cognition, gait, and balance in abstinent and relapsed alcoholic men: Relationships to changes in brain structure. Neuropsychology 14:178–188.
4. Gilman S, Adams K, Koeppe RA, Berent S, Kluin KJ, Modell JG, *et al.* (1990): Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with positron emission tomography. Ann Neurol 28:775–785.
5. Müller-Oehring EM, Schulte T, Pfefferbaum A, Sullivan EV (2022): Disruption of cerebellar-cortical functional connectivity predicts balance instability in alcohol use disorder. Drug Alcohol Depend 235:109435.
6. Sullivan EV, Deshmukh A, Desmond JE, Lim KO, Pfefferbaum A (2000): Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. Neuropsychology 14:341–352.
7. Sullivan EV, Rose J, Pfefferbaum A (2006): Effect of vision, touch and stance on cerebellar vermian-related sway and tremor: A quantitative physiological and MRI study. Cereb Cortex 16:1077–1086.
8. Sullivan EV, Rohlfing T, Pfefferbaum A (2010): Pontocerebellar volume deficits and ataxia in alcoholic men and women: No evidence for "telescoping". Psychopharmacology 208:279–290.
9. Victor M, Adams RD, Mancall EL (1959): A restricted form of cerebellar degeneration occurring in alcoholic patients. Arch Neurol 1:579–688.
10. Torvik A, Lindboe CF, Rogde S (1982): Brain lesions in alcoholics. A neuropathological study with clinical correlations. J Neurol Sci 56:233–248.
11. Harper CG (1998): The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J Neuropathol Exp Neurol 57:101–110.
12. Sullivan EV, Rohlfing T, Pfefferbaum A (2010): Quantitative fiber tracking of lateral and interhemispheric white matter systems in normal aging: Relations to timed performance. Neurobiol Aging 31:464–481.
13. Sullivan EV, Zahr NM, Rohlfing T, Pfefferbaum A (2015): Cognitive demands during quiet standing elicit truncal tremor in two frequency bands: Differential relations to tissue integrity of corticospinal tracts and cortical targets. Front Hum Neurosci 9:175.
14. Zhao Q, Sullivan EV, Honnorat N, Adeli E, Podhajsky S, De Bellis MD, *et al.* (2021): Association of heavy drinking with deviant fiber tract development in frontal brain systems in adolescents. JAMA Psychiatry 78:407–415.
15. Hachinski VC, Potter P, Merskey H (1986): Leuko-araiosis: An ancient term for a new problem. Can J Neurol Sci 13(suppl):533–534.
16. Goto K, Ishii N, Fukasawa H (1981): Diffuse white-matter disease in the geriatric population. A clinical, neuropathological, and CT study. Radiology 141:687–695.
17. Starr JM, Leaper SA, Murray AD, Lemmon HA, Staff RT, Deary IJ, Whalley LJ (2003): Brain white matter lesions detected by magnetic resonance [correction of resosnance] imaging are associated with balance and gait speed. J Neurol Neurosurg Psychiatry 74:94–98.
18. Tell GS, Lefkowitz DS, Diehr P, Elster AD (1998): Relationship between balance and abnormalities in cerebral magnetic resonance imaging in older adults. Arch Neurol 55:73–79.
19. Baloh RW, Ying SH, Jacobson KM (2003): A longitudinal study of gait and balance dysfunction in normal older people. Arch Neurol 60:835–839.
20. Taylor ME, Lord SR, Delbaere K, Wen W, Jiang J, Brodaty H, *et al.* (2019): White matter hyperintensities are associated with falls in older people with dementia. Brain Imaging Behav 13:1265–1272.
21. Willey JZ, Moon YP, Dhamoon MS, Kulick ER, Bagci A, Alperin N, *et al.* (2018): Regional subclinical cerebrovascular disease is associated with balance in an elderly multi-ethnic population. Neuroepidemiology 51:57–63.
22. Zheng JJ, Lord SR, Close JC, Sachdev PS, Wen W, Brodaty H, Delbaere K (2012): Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: A prospective cohort study. J Gerontol A Biol Sci Med Sci 67:1085–1091.
23. Blahak C, Baezner H, Pantoni L, Poggesi A, Chabriat H, Erkinjuntti T, *et al.* (2009): Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: Cross sectional results from the LADIS study. J Neurol Neurosurg Psychiatry 80:608–613.
24. Ogama N, Sakurai T, Shimizu A, Toba K (2014): Regional white matter lesions predict falls in patients with amnestic mild cognitive impairment and Alzheimer's disease. J Am Med Dir Assoc 15:36–41.
25. Pozorski V, Oh JM, Okonkwo O, Krislov S, Barzgari A, Theisen F, *et al.* (2019): Cross-sectional and longitudinal associations between total and regional white matter hyperintensity volume and cognitive and motor function in Parkinson's disease. NeuroImage Clin 23:101870.
26. Carvalho de Abreu DC, Pieruccini-Faria F, Sarquis-Adamson Y, Black A, Fraser J, Van Ooteghem K, *et al.* (2023): White matter hyperintensity burden predicts cognitive but not motor decline in Parkinson's disease: Results from the Ontario Neurodegenerative Diseases Research Initiative. Eur J Neurol 30:920–933.
27. Hua M, Ma AJ, Liu ZQ, Ji LL, Zhang J, Xu YF, *et al.* (2023): Arteriolosclerosis CSVD: A common cause of dementia and stroke and its association with cognitive function and total MRI burden. Front Aging Neurosci 15:1163349.
28. Chen K, Jin Z, Fang J, Qi L, Liu C, Wang R, *et al.* (2023): The impact of cerebral small vessel disease burden and its imaging markers on gait, postural control, and cognition in Parkinson's disease. Neurol Sci 44:1223–1233.

29. Dai S, Piscicelli C, Lemaire C, Christiaens A, Schotten MT, Hommel M, *et al.* (2022): Recovery of balance and gait after stroke is deteriorated by confluent white matter hyperintensities: Cohort study. Ann Phys Rehabil Med 65:101488.
30. Ibitoye RT, Castro P, Cooke J, Allum J, Arshad Q, Murdin L, *et al.* (2022): A link between frontal white matter integrity and dizziness in cerebral small vessel disease. NeuroImage Clin 35:103098.
31. Pinter D, Ritchie SJ, Doubal F, Gattringer T, Morris Z, Bastin ME, *et al.* (2017): Impact of small vessel disease in the brain on gait and balance. Sci Rep 7:41637.
32. Cahn DA, Malloy PF, Salloway S, Rogg J, Gillard E, Kohn R, *et al.* (1996): Subcortical hyperintensities on MRI and activities of daily living in geriatric depression. J Neuropsychiatry Clin Neurosci 8:404–411.
33. Fein G, Shimotsu R, Di Sclafani V, Barakos J, Harper C (2009): Increased white matter signal hyperintensities in long-term abstinent alcoholics compared with nonalcoholic controls. Alcohol Clin Exp Res 33:70–78.
34. Pfefferbaum A, Zhao Q, Pohl KM, Sassoon SA, Zahr NM, Sullivan EV (2024): Age-accelerated increase of white matter hyperintensity volumes is exacerbated by heavy alcohol use in people living with HIV. Biol Psychiatry 95:231–244.
35. Pfefferbaum A, Adalsteinsson E, Sullivan EV (2006): Supratentorial profile of white matter microstructural integrity in recovering alcoholic men and women. Biol Psychiatry 59:364–372.
36. Pfefferbaum A, Adalsteinsson E, Sullivan EV (2006): Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. Neurobiol Aging 27:994–1009.
37. Pfefferbaum A, Rosenbloom MJ, Fama R, Sassoon SA, Sullivan EV (2010): Transcallosal white matter degradation detected with quantitative fiber tracking in alcoholic men and women: Selective relations to dissociable functions. Alcohol Clin Exp Res 34:1201–1211.
38. Shen X, Raghavan S, Przybelski SA, Lesnick TG, Ma S, Reid RI, *et al.* (2022): Causal structure discovery identifies risk factors and early brain markers related to evolution of white matter hyperintensities. NeuroImage Clin 35:103077.
39. Sullivan EV, Rose J, Rohlfing T, Pfefferbaum A (2009): Postural sway reduction in aging men and women: Relation to brain structure, cognitive status, and stabilizing factors. Neurobiol Aging 30:793–807.
40. Sullivan EV, Zahr NM, Sassoon SA, Pfefferbaum A (2021): Disturbed sensory physiology underlies poor balance and disrupts activities of daily living in alcohol use disorder. Addict Biol 26:e12966.
41. Lohner V, Pehlivan G, Sanroma G, Miloschewski A, Schirmer MD, Stöcker T, *et al.* (2022): Relation between sex, menopause, and white matter hyperintensities: The Rhineland study. Neurology 99:e935–e943.
42. Morris EP, Turney IC, Palms JD, Zaheed AB, Sol K, Amarante E, *et al.* (2023): Racial and ethnic differences in the relationship between financial worry and white matter hyperintensities in Latinx, non-Latinx Black, and non-Latinx White older adults. Neurobiol Aging 129: 149–156.
43. Jokinen H, Melkas S, Madureira S, Verdelho A, Ferro JM, Fazekas F, *et al.* (2016): Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease. J Neurol Neurosurg Psychiatry 87:1296–1302.
44. Petersen KJ, Lu T, Wisch J, Roman J, Metcalf N, Cooley SA, *et al.* (2023): Effects of clinical, comorbid, and social determinants of health on brain ageing in people with and without HIV: A retrospective case-control study. Lancet HIV 10:e244–e253.
45. Zahr NM, Pohl KM, Pfefferbaum A, Sullivan EV (2019): Central nervous system correlates of "objective" neuropathy in alcohol use disorder. Alcohol Clin Exp Res 43:2144–2152.
46. Hisamatsu T, Tabara Y, Kadota A, Torii S, Kondo K, Yano Y, *et al.* (2024): Alcohol consumption and cerebral small- and large-vessel diseases: A Mendelian randomization analysis. J Atheroscler Thromb 31:135–147.
47. Stewart CR, Stringer MS, Shi Y, Thrippleton MJ, Wardlaw JM (2021): Associations between white matter hyperintensity burden, cerebral blood flow and transit time in small vessel disease: An updated meta-analysis. Front Neurol 12:647848.
48. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al.* (2013): Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12:822–838.
49. Wartolowska KA, Webb AJS (2021): Blood pressure determinants of cerebral white matter hyperintensities and microstructural injury: UK Biobank cohort study. Hypertension 78:532–539.
50. Li Q, Yang Y, Reis C, Tao T, Li W, Li X, Zhang JH (2018): Cerebral small vessel disease. Cell Transplant 27:1711–1722.
51. Debette S, Markus HS (2010): The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. BMJ 341:c3666.
52. Cai J, Sun J, Chen H, Chen Y, Zhou Y, Lou M, Yu R (2022): Different mechanisms in periventricular and deep white matter hyperintensities in old subjects. Front Aging Neurosci 14:940538.
53. Murray KD, Uddin MN, Tivarus ME, Sahin B, Wang HZ, Singh MV, *et al.* (2021): Increased risk for cerebral small vessel disease is associated with quantitative susceptibility mapping in HIV infected and uninfected individuals. NeuroImage Clin 32:102786.
54. Sargurupremraj M, Suzuki H, Jian X, Sarnowski C, Evans TE, Bis JC, *et al.* (2020): Cerebral small vessel disease genomics and its implications across the lifespan. Nat Commun 11:6285.
55. Su T, Wit FW, Caan MW, Schouten J, Prins M, Geurtsen GJ, *et al.* (2016): White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy. AIDS 30:2329–2339.
56. Jochems ACC, Arteaga C, Chappell F, Ritakari T, Hooley M, Doubal F, *et al.* (2022): Longitudinal changes of white matter hyperintensities in sporadic small vessel disease: A systematic review and meta-analysis. Neurology 99:e2454–e2463.
57. Busby N, Newman-Norlund R, Wilmskoetter J, Johnson L, Rorden C, Gibson M, *et al.* (2023): Longitudinal progression of white matter hyperintensity severity in chronic stroke aphasia. Arch Rehabil Res Clin Transl 5:100302.
58. Taylor-Bateman V, Gill D, Georgakis MK, Malik R, Munroe P, Traylor M, International Consortium of Blood Pressure (ICBP) (2022): Cardiovascular risk factors and MRI markers of cerebral small vessel disease: A Mendelian randomization study. Neurology 98:e343–e351.
59. Han YP, Tang X, Han M, Yang J, Cardoso MA, Zhou J, Simó R (2021): Relationship between obesity and structural brain abnormality: Accumulated evidence from observational studies. Ageing Res Rev 71: 101445.
60. Fleischman DA, Arfanakis K, Leurgans SE, Zhang S, Lamar M, Han SD, *et al.* (2023): Late-life depressive symptoms and white matter structural integrity within older Black adults. Front Aging Neurosci 15:1138568.
61. McEvoy LK, Fennema-Notestine C, Elman JA, Eyler LT, Franz CE, Hagler DJ Jr, *et al.* (2018): Alcohol intake and brain white matter in middle aged men: Microscopic and macroscopic differences. NeuroImage Clin 18:390–398.
62. Bogoian HR, Barber SJ, Carter SE, Mingo C, Rosano C, Dotson VM (2024): Association of white matter hyperintensities and clinical vascular burden with depressive symptoms in Black older adults. Int J Geriatr Psychiatry 39:e6052.
63. Brickman AM, Schupf N, Manly JJ, Luchsinger JA, Andrews H, Tang MX, *et al.* (2008): Brain morphology in older African Americans, Caribbean Hispanics, and Whites from northern Manhattan. Arch Neurol 65:1053–1061.
64. Brothers RM, Fadel PJ, Keller DM (2019): Racial disparities in cardiovascular disease risk: Mechanisms of vascular dysfunction. Am J Physiol Heart Circ Physiol 317:H777–H789.
65. American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR) Washington, DC: American Psychiatric Association.
66. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorder (DSM-V). Washington, DC: American Psychiatric Association.
67. Skinner HA (1982): Development and Validation of a Lifetime Alcohol Consumption Assessment Procedure. Toronto, Canada: Addiction Research Foundation.
68. Corkin S, Milner B, Rasmussen T (1970): Somatosensory thresholds—Contrasting effects of postcentral-gyrus and posterior parietal-lobe excisions. Arch Neurol 23:41–58.

69. Sullivan EV, Zahr NM, Sassoon SA, Pfefferbaum A (2022): Aging accelerates postural instability in HIV infection: Contributing sensory biomarkers. J Neuroimmune Pharmacol 17:538–552.
70. Coupe P, Yger P, Prima S, Hellier P, Kervrann C, Barillot C (2008): An optimized blockwise nonlocal means denoising filter for 3-D magnetic resonance images. IEEE Trans Med Imaging 27:425–441.
71. Tustison NJ, Avants BB, Cook PA, Zheng Y, Egan A, Yushkevich PA, Gee JC (2010): N4ITK: Improved N3 bias correction. IEEE Trans Med Imaging 29:1310–1320.
72. Rohlfing T, Maurer CR Jr (2003): Nonrigid image registration in shared-memory multiprocessor environments with application to brains, breasts, and bees. IEEE Trans Inf Technol Biomed 7:16–25.
73. Rohlfing T, Zahr NM, Sullivan EV, Pfefferbaum A (2010): The SRI24 multichannel atlas of normal adult human brain structure. Hum Brain Mapp 31:798–819.
74. Avants BB, Epstein CL, Grossman M, Gee JC (2008): Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 12:26–41.
75. Rohlfing T, Russakoff DB, Maurer CR Jr (2004): Performance-based classifier combination in atlas-based image segmentation using expectation-maximization parameter estimation. IEEE Trans Med Imaging 23:983–994.
76. Smith SM (2002): Fast robust automated brain extraction. Hum Brain Mapp 17:143–155.
77. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.
78. Sadananthan SA, Zheng W, Chee MW, Zagorodnov V (2010): Skull stripping using graph cuts. Neuroimage 49:225–239.
79. Iglesias JE, Liu CY, Thompson PM, Tu Z (2011): Robust brain extraction across datasets and comparison with publicly available methods. IEEE Trans Med Imaging 30:1617–1634.
80. Avants BB, Tustison NJ, Wu J, Cook PA, Gee JC (2011): An open source multivariate framework for n-tissue segmentation with evaluation on public data. Neuroinformatics 9:381–400.
81. Jiang J, Liu T, Zhu W, Koncz R, Liu H, Lee T, *et al.* (2018): UBO detector – A cluster-based, fully automated pipeline for extracting white matter hyperintensities. Neuroimage 174:539–549.
82. Jiang J, Paradise M, Liu T, Armstrong NJ, Zhu W, Kochan NA, *et al.* (2018): The association of regional white matter lesions with cognition in a community-based cohort of older individuals. NeuroImage Clin 19:14–21.
83. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA (1987): MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 149:351–356.
84. Bates D, Machler M, Bolker B, Walker S (2015): Fitting linear mixed-effects models using lme4. J Stat Softw 67:1–48.
85. van Dinther M, Voorter PH, Jansen JF, Jones EA, van Oostenbrugge RJ, Staals J, Backes WH (2022): Assessment of microvascular rarefaction in human brain disorders using physiological magnetic resonance imaging. J Cereb Blood Flow Metab 42:718–737.
86. Lewis JP, Suchy-Dicey AM, Noonan C, Blue Bird Jernigan V, Umans JG, Domoto-Reilly K, *et al.* (2021): Associations of binge drinking with vascular brain injury and atrophy in older American Indians: The Strong Heart Study. J Aging Health 33:51s–59s.
87. Schutte R, Smith L, Wannamethee G (2022): Alcohol – The myth of cardiovascular protection. Clin Nutr 41:348–355.
88. Gongvatana A, Cohen RA, Correia S, Devlin KN, Miles J, Kang H, *et al.* (2011): Clinical contributors to cerebral white matter integrity in HIV-infected individuals. J Neurovirol 17:477–486.
89. Lescure FX, Moulignier A, Savatovsky J, Amiel C, Carcelain G, Molina JM, *et al.* (2013): CD8 encephalitis in HIV-infected patients receiving cART: A treatable entity. Clin Infect Dis 57:101–108.
90. Nir TM, Jahanshad N, Busovaca E, Wendelken L, Nicolas K, Thompson PM, Valcour VG (2014): Mapping white matter integrity in elderly people with HIV. Hum Brain Mapp 35:975–992.
91. Mina Y, Wu T, Hsieh HC, Hammoud DA, Shah S, Lau CY, *et al.* (2021): Association of white matter hyperintensities with HIV status and vascular risk factors. Neurology 96:e1823–e1834.
92. Sullivan EV, Rose J, Pfefferbaum A (2010): Mechanisms of postural control in alcoholic men and women: Biomechanical analysis of musculoskeletal coordination during quiet standing. Alcohol Clin Exp Res 34:528–537.
93. Turney IC, Lao PJ, Rentería MA, Igwe KC, Berroa J, Rivera A, *et al.* (2023): Brain aging among racially and ethnically diverse middle-aged and older adults. JAMA Neurol 80:73–81.
94. Huo Y, Wang Y, Guo C, Liu Q, Shan L, Liu M, *et al.* (2023): Deep white matter hyperintensity is spatially correlated to MRI-visible perivascular spaces in cerebral small vessel disease on 7 Tesla MRI. Stroke Vasc Neurol 8:144–150.
95. Kuehn BM (2024): Citing harms, momentum grows to remove race from clinical algorithms. JAMA 331:463–465.
96. Schramm S, Schliephake L, Himpfen H, Caspers S, Erbel R, Jöckel KH, Moebus S (2021): Vitamin D and white matter hyperintensities: Results of the population-based Heinz Nixdorf Recall Study and 1000BRAINS. Eur J Neurol 28:1849–1858.
97. Kilgore CB, Strain JF, Nelson B, Cooley SA, Rosenow A, Glans M, *et al.* (2022): Cardiorespiratory fitness is associated with better white matter integrity in persons living with HIV. J Acquir Immune Defic Syndr 89:558–565.
98. White AM (2020): Gender differences in the epidemiology of alcohol use and related harms in the United States. Alcohol Res 40:01.