Published in final edited form as:
Psychiatry Res. 2013 December 30; 214(3): 389–394. doi:10.1016/j.pscychresns.2013.07.011.

Characterizing white matter health and organization in atherosclerotic vascular disease: a diffusion tensor imaging study

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Abstract

Atherosclerotic vascular disease (AVD) is endemic to the developed world, with known negative outcomes for cognition and brain health. The effects of AVD on the white matter fibers of the brain have not yet been studied using diffusion tensor imaging (DTI). This study examined differences in fractional anisotropy (FA) between AVD and healthy comparison (HC) participants, and described the regional patterns of FA in each group. AVD participants were hypothesized to

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have lower FA than HC participants, indicating abnormalities in white matter health or organization. 1.5 tesla diffusion tensor imaging was performed in 35 AVD and 22 HC participants. Mean FA measures were calculated for the white matter of the whole brain, as well for individual lobes. Globally and in every brain region measured except the temporal lobes, there were significant effects of group where AVD participants had lower FA values than their HC counterparts. Group differences in FA remained significant when controlled for white matter hyperintensity (WMH) volume, suggesting that FA detects white matter abnormality above and beyond what is measurable using the older WMH technique. These findings suggest a likely neural substrate underlying the changes in cognition and mood reported in atherosclerotic vascular disease patients.

Keywords

diffusion-weighted imaging; atherosclerosis; leukoaraiosis; MRI; white matter disease

1. Introduction

Atherosclerosis, or the build-up of atherosclerotic plaques in the vasculature, is implicated in roughly half of all deaths in the developed world (Mitchell and Schoen, 2010). Atherosclerosis poses many risks, including plaque rupture (leading to thrombosis or embolism), obstruction of blood flow, and reduction of the vascular dilation and constriction functions necessary to maintain hemodynamically stable tissue perfusion. Relentless and prolonged hypoperfusion of the brain produces incomplete white matter infarction, a condition histologically similar to that observed in the penumbra of large cerebral infarcts (Pantoni et al., 1996). It is proposed that brain areas irrigated by short-penetrating arteries can better tolerate hypotension and hypoperfusion, explaining the relative sparing of the cortex, subcortical arcuate fibers, and the corpus callosum (Moody et al., 1990). The effects of atherosclerosis on the vessels are reported to be most prominent in the frontal lobes (Mitchell and Schoen, 2010), and localization studies have found that the frontal lobes, frontal subcortical areas, and frontostriatal pathways are particularly vulnerable to vascular injury in older adults (Raz et al., 2007). Ischemic damage to the white matter in these areas is the suspected neural substrate for changes in cognition and emotional regulation observed in vascular disease (Boone et al., 1992; Pantoni et al., 1996).

While a certain extent of white matter lesion development is expected in the course of normal aging (Awad et al., 1986), white matter lesions are notably more severe among individuals with vascular disease and hypertension (Fazekas et al., 1987; Taylor et al., 2003). Damage to the white matter is posited to be driven by endothelial dysfunction in the blood vessels (Hoth et al., 2007). Ischemic damage to white matter appears on T2 and fluid-attenuated inversion recovery (FLAIR) MRI imaging as bright areas, or “hyperintensities,” in the midst of normal-appearing white matter. These white matter hyperintensities (WMH) are the most common neuroradiological finding in participants with vascular disease (Pantoni et al., 1996). The vast majority of research studies on white matter health in vascular disease to date have focused on measures of white matter hyperintensities. However, studies of white matter hyperintensities are limited by reliance on the physical

properties of the damaged tissue to reach the threshold for appearing hyperintense. This means that white matter hyperintensity studies may not accurately detect subtle changes to white matter tissue, which are known to take place upstream and downstream of the areas that appear hyperintense.

Measures of white matter hyperintensities have demonstrated varying degrees of sensitivity to the effects of vascular disease on the brain; however, a more complete understanding of these effects may be gained by analysis using diffusion tensor imaging (DTI). DTI is used to quantify the molecular motion of water in the brain, which is constrained by neuron and myelin integrity (Basser et al., 1994; Beaulieu, 2002). A variety of measures can be generated by diffusion tensor imaging, though the most commonly utilized is fractional anisotropy (FA). Anisotropy refers to the degree to which diffusion is directionally constrained, typically being high in white matter because water tends to diffuse parallel to organized fiber bundles. The degree of anisotropy depends on the microstructural tissue components such as the integrity of cell membranes and the organization of fiber tracts (Beaulieu, 2002). Standardization studies have shown that areas of white matter hyperintensity have decreased FA, and normal-appearing white matter outside of hyperintense areas frequently show FA abnormalities as well (Taylor et al., 2007). Other, complementary measures of diffusion sometimes used in DTI analyses include mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). MD is taken to represent overall density and organization of tissue, while research suggests radial diffusivity may be more sensitive to specific alterations of myelin, and axial diffusivity is more specific to axonal degeneration (Alexander et al., 2007).

Remarkably, DTI findings remain unreported in atherosclerotic vascular disease (AVD). DTI analysis is the ideal follow-up to studies that have examined white matter hyperintensities because of the tremendous sensitivity of DTI to white matter damage and its ability to examine the white matter dimensionally rather than dichotomously (i.e. damaged vs. not damaged). The use of DTI in the current study is well suited to produce a clearer picture of white matter dysfunction in AVD than has been previously reported.

Studies examining the relationships of demographic variables with DTI measures of white matter have produced clear results with regards to age, but less clear results with respect to sex, education, and handedness. For example, age-related changes in FA in the frontal lobes and corpus callosum have been reported in a variety of studies (Buckner, 2004). Examinations of sex differences in DTI measures have produced mixed results depending on participant group and brain region examined (Abe et al., 2002; Sullivan and Pfefferbaum, 2003; Oh et al., 2007). Studies specifically examining the relationship between education level and DTI measures have not yet been reported, though one study reported a significant relationship of childhood IQ with current measures of FA in 83-year-old adults in a Scottish longitudinal birth cohort study (Deary et al., 2006).

The aims of the current study were three-fold. First, we aimed to examine FA measures for effects of sex, age, education, and handedness. After determining the relationship of these demographic variables with FA, we aimed to compare the participants with AVD to healthy comparisons (HC) in terms of white matter integrity globally, by hemisphere, and by lobe.

Third, we aimed to characterize regions of vulnerability to white matter damage separately in each group of participants. We hypothesized that FA would be lower (as a function of poorer white matter organization or health) in older participants and in participants with AVD, compared to younger and HC participants respectively. Based on existing literature, we made no *a-priori* hypotheses about the effects of sex, education, or handedness because these effects have not been thoroughly examined in DTI analyses with any population to date. Studies have previously reported vulnerability of the frontal white matter to damage in vascular disease, so we expected to see the lowest FA values in that region in the AVD group.

2. Methods

2.1 Participants

As a part of the parent study, “Aging, Vascular Disease, and Cognition” (grant number RO1AG030417-01A2 from the National Institute on Aging), elderly individuals were recruited from University of Iowa Heart and Vascular Care clinic (AVD participants) and from newspaper and magazine advertisements (healthy comparisons). All participants were between 55 and 90 years old. Participants in the AVD group were required to have an unequivocal diagnosis of atherosclerotic vascular disease and a history of one or more of the following: angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty (PCTA), placement of coronary artery stent, or peripheral vascular disease (claudication). Participants were excluded from the study if they had a history of stroke, coronary artery bypass grafting, valve replacement, carotid endarterectomy, head injury with a loss of consciousness >30 minutes, other neurological or systemic illness unrelated to vascular disease that was likely to affect cognition, focal neurological signs, diagnosis of dementia, or severe and uncontrolled psychiatric illness (current or past) (Moser et al., 2007). The AVD group had an average duration of cardiovascular disease of 9.6 years (9.2 SD), including 12 people with prior diagnosed myocardial infarction, 5 with diagnosed unstable angina, 28 with a history of PCTA and/or stent placement, 5 with diagnosed peripheral vascular disease, and 3 with a history of cerebrovascular disease. Those with cerebrovascular disease included two with transient ischemic attack (carefully examined to exclude stroke), and one with Amaurosis Fugax (transient monocular vision loss).

HC participants were required to meet none of the AVD inclusion or exclusion criteria and to meet the age requirement previously described. Therefore, none of the HC participant group had prior diagnosed myocardial infarction, unstable angina, peripheral vascular disease, cerebrovascular disease, aortic aneurysm, or PCTA and/or stent placement. 36 AVD and 22 HC participants participated in neuroimaging; structural magnetic resonance and diffusion-weighted scans were acquired. All of these scans passed initial quality control; however, one AVD participant's scan was later assessed to be unsuitable for DTI analyses because of subtle warping of the brain shape in the posterior parietal and occipital lobes. Participants provided informed consent for all aspects of the current research, as required by the University of Iowa Institutional Review Board and the Declaration of Helsinki.

2.2 Demographics

Participants were asked to fill out a brief demographic questionnaire asking them to identify their current age, highest level of educational attainment, sex, and handedness (dominant left- or right-handedness or ambidextrous) (see Table 1). Participants additionally were interviewed about their medical history, the results of which were reviewed to confirm group membership.

2.3 Imaging Measures

Participants underwent anatomical and diffusion tensor imaging using a Siemens Avanto 1.5T scanner (Erlangen, Germany). The anatomical images collected included a 3D T1 weighted scan, 2D T2 weighted scan, and a 2D FLAIR scan. The 3D T1 weighted images were collected in the coronal plane using a FLASH sequence (TE=4.7ms, TR=25ms, flip angle=30°, field of view=260×260×192mm, matrix=256×256×128, averages=2, bandwidth=130 Hz/pixel). The T2 weighted images were acquired in the coronal plane using a fast spin-echo sequence (TE=95ms, TR=9750ms, field of view=260×260mm, matrix=256×256, slice thickness/gap=3.0/0.0mm, averages=2, bandwidth=130 Hz/pixel, echo train length=20). The FLAIR images were collected in the axial plane (TE=110ms, TR=9600ms, TI=2500ms, field of view=260×260mm, matrix=256×256, slice thickness/gap=3.0/0.0mm, averages=2, bandwidth=130 Hz/pixel, echo train length=15). DTI data were gathered on 56 slices (TR/TE = 9500/94ms, field of view=256× 256mm, matrix=128×128, slice thickness/gap=2.5/0.0mm, 12 gradient directions, b-value=1000, flip angle=90, pixel bandwidth=1347Hz, imaging frequency=63.623624 MHz).

Automated processing of the T1, T2, and FLAIR images was performed using BRAINS2 (Brain Research: Analysis of Images, Networks, and Systems) software (Magnotta et al., 2002). The BRAINS2 software includes automated AC-PC alignment, image alignment, image intensity standardization, tissue classification, brain extraction, and automated labeling based on the Talairach atlas (Talairach and Tournoux, 1988). The BRAINS2 method for white matter segmentation has shown reliability with manual raters and adequately addresses concerns of partial volume contamination (Harris et al., 1999). Only the T1 and T2 weighted images were considered in the tissue classification and thus the brain lesions were initially classified as gray matter. To correct this artifact, the FLAIR and tissue classified images were consulted and a human rater manually defined the brain lesions. Voxels corresponding to the brain lesion were added as a separate class and removed from the gray matter label. This step allowed for comparison of white matter lesion volumes as well. It was determined that all white matter tissue should be included in the DTI analysis regardless of whether it was categorized as “lesioned” or “unlesioned”.

The diffusion tensor data were first processed using GTRACT software, which performs motion correction, co-registration, tensor decomposition, and calculation steps (Cheng et al., 2006). DTI scalar maps (FA, RD, AD, MD) were then clipped to include only the white matter based on the tissue classification step from BRAINS2. DTI measures are reported in white matter defined by a white matter plus lesion mask in voxels where the FA was greater than 0.1, in order to exclude regions with susceptibility artifacts, those with imprecise registration, and those with inappropriate clipping based on the number of slices acquired.

Each participant's neuroimaging data were subsequently visually inspected for co-registration and to check for artifacts such as head motion, table vibration, RF noise, and susceptibility artifacts. Measures of FA, MD, RD, and AD were then obtained in each Talairach-defined lobe, using an automated tool within the BRAINS2 software. The Talairach-defined subcortical box region is also reported in the current study, though this region comprises only a small amount of white matter contained within the basal ganglia complex (Andreasen et al., 1996).

2.4 Analyses

Power analysis showed 43.9% power to detect subtle (Cohen's $d = 0.5$) mean differences and 82.3% power to detect strong ($d = 0.8$) differences in means with the current sample. Because the demographic data showed relative normality of distribution and equality of variances, parametric statistical analyses were used (e.g., Student's *t*-tests). One notable exception was the comparison of lesion volumes (Table 1), which were not normally distributed and were therefore examined using a Mann-Whitney *U* Test. To follow up on the observed differences between AVD and HC participants in rates of diagnosed diabetes and anti-hypertensive medication use (Table 1), we calculated t-tests across all participants (AVD and HC alike) to examine whether stratification on either variable was related to significant differences in whole brain FA. Analyses of covariance were used to examine the effects of relevant covariates on the structural variables of interest. Main effects and interaction terms were calculated using univariate general linear models with each region as a dependent variable, group (AVD vs. HC) as a fixed factor, and demographic variables as covariates. Interaction terms were calculated for age*group and sex*group in the context of the full statistical model. Main effects reported in Table 2 were calculated after removing the non-significant main effects and interactions from the model. Unadjusted p-values are presented in Table 2 and marked with asterisks to identify values that remained significant after adjustment for the false discovery rate (Benjamini and Hochberg, 1995). Analysis of covariance was used to examine whether the difference in FA between experimental groups remained significant when additionally controlled for white matter hyperintensity volume. Analyses of covariance were also used to examine the main effects of group, age, and sex on alternative measures of white matter health (MD, RD, and AD), again using group as a fixed factor and demographic variables as covariates.

Non-parametric Friedman's one-way ANOVA was used to assess the vulnerability of different cortical regions to FA changes, by ranking the FA values for each brain region (frontal, temporal, parietal, occipital, and subcortical) within each participant from lowest FA (ranked 1) to highest FA (ranked 5). Then, the mean ranking for each cortical region was calculated within the AVD group and the HC group, and the pattern of mean ranks was tested for statistical significance. This analysis was used to test the hypothesis that in AVD participants, the frontal lobes may be more vulnerable to white matter damage and therefore show lower FA values than other areas of the brain. In the current study, Friedman's one-way ANOVA is used as a qualitative assessment and it should be noted that there was no statistical comparison between participant groups or individual regions. All analyses used two-tailed tests of significance with an alpha level < 0.05.

3. Results

Statistical comparison of the AVD and HC groups on their demographic characteristics revealed no significant differences in age, education, sex, handedness, or ethnicity (Table 1). Groups were additionally compared on potentially meaningful clinical characteristics including diabetes history, resting systolic and diastolic blood pressures, use of antihypertensive medications, and total white matter hyperintensity volume. AVD participants were found to have significantly more frequent diagnoses of diabetes and more frequent usage of antihypertensive medication than healthy controls (Table 1). However, neither diagnosed diabetes nor use of antihypertensives was found to be related to any abnormality in FA in the current sample (diabetes: $t = -0.333$, $df = 55$, $p = 0.740$; antihypertensive use: $t = 1.527$, $df = 55$, $p = -0.133$).

Significant main effects of age and sex on mean FA were initially observed (Table 2), though the main effect of sex did not remain significant under statistical control for false discovery. Main effects of age (i.e. older participants tended to have lower FA) were detected globally in the whole cerebrum, as well as in specific lobes including the frontal, temporal, and parietal lobes. Main effects of education, as well as interaction effects (sex * group and age * group) were non-significant (data not shown). Student's *t*-tests comparing left-handers to right-handers showed no significant differences in global FA between groups (data not shown).

A significant main effect of group membership was observed when examining global FA values during ANCOVA analysis (Table 2). Lobar analyses of covariance revealed significant main effects of group, where AVD participants had lower FA than HC participants in every single brain region measured, with the exception of the temporal lobes (Table 2). All of these main effects remained statistically significant after adjustment for false discovery rate.

Next, ANCOVA was used to examine whether the observed differences in FA remained significant when controlled for the volume of white matter hyperintensities. Results from this analysis indicated that the main effect of group remained statistically significant when controlled for WMH volume ($F = 4.142$, $df = 1$, $p = 0.047$). This result is even more impressive when considering that FA and WMH are very tightly correlated (Pearson's $r = -0.450$, $df = 57$, $p < 0.001$). This suggests that analysis of FA is sensitive to white matter abnormalities above and beyond what is detectable with white matter hyperintensity analysis.

Significant main effects of group membership were additionally observed when examining global MD and AD values in ANCOVA analyses (MD: $F = 5.045$, $df = 1$, $p = 0.029$; AD: $F = 7.130$, $df = 1$, $p = 0.010$), though non-significant effects of group were observed in the RD data ($F = 3.524$, $df = 1$, $p = 0.066$). All three of these measures, MD, AD, and RD showed significant main effects of age ($p < 0.001$ for each) and non-significant main effects of sex on ANCOVA analysis.

Friedman's one-way ANOVA was used to test for a significant pattern of FA values across cortical regions (Table 3). This analysis revealed identical, significant patterns in both the

AVD and the HC groups, where the occipital lobe was ranked lowest (meaning lowest FA) in every participant in both groups, while the subcortical box was ranked highest (meaning highest FA) in every participant.

The current findings support the hypothesis that AVD participants have widespread abnormalities in the white matter compared with healthy comparison participants; however, the Friedman's one-way ANOVA failed to support the hypothesis that the frontal lobes would be uniquely vulnerable to the effects of vascular disease.

4. Discussion

The current study sought to examine the effects of demographic variables and vascular disease status on white matter health and/or organization using FA measures from DTI. In addition, the current study assessed whether the frontal lobes were particularly vulnerable to the adverse effects of vascular disease. There were significant effects of age on FA, indicating that older participants tended to have lower FA in a variety of brain regions. In addition, significant effects of group membership (AVD vs. HC) were detected globally and in every brain region measured except the temporal lobes. Significant effects of group were also found when considering two other measures of diffusion; mean diffusivity and axial diffusivity. The overall landscape of FA values in the brain, as described for each group individually (using Friedman's one-way ANOVA), showed that AVD and HC participants displayed essentially identical patterns of anisotropy across lobes. The occipital lobe consistently showed the lowest FA, followed by the temporal, frontal, and parietal lobes, and the subcortical white matter consistently showed the highest FA values.

The main effect of age was significant in the global measure of FA as well as in the frontal, temporal, and parietal lobes. The test of interaction between age and group (AVD and HC) was non-significant, suggesting that the relationship of lower FA with older age was not specific to the AVD condition. Previous studies have reported declines in FA values in all regions of the brain, though the largest age-related changes in the white matter have been observed in the frontal lobes and anterior corpus callosum (Buckner, 2004). The significant relationship of lower FA with older age is an established finding that underscores the necessity to adequately control for the effects of age in studies of the white matter.

A trend toward a main effect of sex was detected in the frontal lobes, though this effect did not remain statistically significant after adjustment for the false discovery rate (Benjamini and Hochberg, 1995). No effects of sex were found in any other brain region or in the global measure of white matter (cerebrum). There was no significant sex by group interaction, suggesting the effect is not likely specific to AVD participants. Reports of sex differences in DTI measures have been mixed. For example, one study reported that men had significantly higher FA than women in a global measure of corpus callosum, while women had significantly higher FA than men in smaller regions of interest in the rostrum, genu, and splenium of the corpus callosum (Oh et al., 2007). However, reports of non-significant differences between sexes have also been made (Abe et al., 2002; Sullivan and Pfefferbaum, 2003). The reasons for these inconsistencies include differences in sample sizes, DTI

methodologies, and the possibility that other demographic characteristics are more strongly related to FA than sex.

A significant main effect of group (AVD vs. HC) was found globally and in all regions except the temporal lobes, suggesting that AVD participants have significantly lower FA than HC participants in most brain regions. The finding of lower FA in AVD participants compared to HC participants is important and suggests a potentially useful and sensitive measure to examine the neural substrates for AVD-related cognitive and emotional dysfunction (Moser et al., 2007). The findings that MD and AD significantly differed between groups suggested that the white matter abnormality detected by FA analysis was not specific to the myelin, but rather perhaps reflected the overall breakdown of white matter fibers including the axons. Additionally, the current study showed that the main effect of group remained significant when controlled for white matter hyperintensity volumes, a result that is particularly striking given the strong relationship between FA and WMH. This finding suggests that FA is able to detect differences in white matter structure above and beyond what is captured by WMH analyses. Previous reports relating white matter hyperintensity volumes with cognitive variables have produced mixed results (Boone et al., 1992; Moser et al., 2001), perhaps due to lower sensitivity of white matter hyperintensity measures compared to DTI.

Findings from the within-groups Friedman's One-way ANOVA characterize a standard landscape of FA values that differs systematically across Talairach-defined regions, with the lowest FA being in the occipital lobes in every participant in both groups, and the highest FA in the subcortical box in every participant in both groups. This analysis was used to test the hypothesis that in AVD participants, the frontal lobes may be more vulnerable to white matter damage than other areas of the brain. If this hypothesis were true, we would have expected to see the frontal lobes ranked lower (lower mean FA across participants) than the other lobes in the AVD participants. In the current study, the frontal lobe was not ranked lowest in either experimental group and the pattern of regional FA values did not seem to differ between AVD and HC participants. These findings suggest that underlying regional differences in structure may exert a stronger effect on FA than any vascular disease process. There has been a great deal of variability in the literature with regards to the regional landscape of FA values, as well as in the absolute values of regional mean FA measures. For example, one study reported that the absolute values of mean FA by region ranged between 0.21 and 0.26 in older adults (Head et al., 2004). By comparison, another study in older adults reported global average FA to be 0.320, with regional mean FA values ranging from 0.26 to 0.33 (Grieve et al., 2007).

4.1. Limitations and Future Directions

The current study was limited by basic experimental issues such as moderately small sample sizes, lower MRI magnetic field strength (1.5 Tesla), and relatively few diffusion sensitizing gradients (12 directions). However, the use of a lower magnetic strength and fewer gradient directions is not likely to produce spurious significant findings, but rather would be likely to produce non-significant findings because of a lack of spatial sensitivity and low signal-to-noise ratio. Additionally, the specificity of FA measures remains a controversial topic, as

studies have shown reduced FA in edema, demyelination, gliosis, and inflammation (Assaf and Pasternak, 2008), none of which can be conclusively ruled out in the current sample. Furthermore, the characterization of all tissue within a given voxel as a single tensor (i.e. a three-dimensional vector) can be problematic for interpretation, especially at tissue interfaces (such as between gray and white matter) and in regions where multiple fiber systems converge or branch (Tuch et al., 2002).

While the medical profile of the participants recruited to the AVD group resembles that of a normative sample of patients with atherosclerosis, the current participants vary from the average population of people with atherosclerosis in terms of their willingness to participate in research, education level, ethnicity, and the fact that all are under close medical care. These issues are inherent recruiting biases that occur due to the geographical location of the study and the pragmatics of enrolling participants who have been identified as potential research participants via their recent contact with a cardiologist. Future studies including participants with AVD would do well to use alternative enrollment strategies to maximize their sampling of a more diverse group of participants.

4.2. Conclusions and implications

The current research has served to characterize for the first time the differences in white matter integrity between healthy older adults and their counterparts with atherosclerotic vascular disease. Findings of diffuse differences in white matter health and/or geometrical organization between the two groups may help explain the neuropsychological and emotional differences frequently noted between participants with vascular disease and healthy comparisons (Boone et al., 1992; Pantoni et al., 1996). This and future studies may be of further use in motivating clinical patients with atherosclerotic vascular disease to seek out appropriate treatments or interventions with the goal of attenuating or reverse these effects. With early resolution of vascular disease, perhaps white matter damage could be prevented and the development of cognitive and emotional dysfunction could be curtailed.

Acknowledgments

The authors would like to acknowledge the participants in the Aging, Vascular Disease, and Cognition study, without whose contributions of energy and time, none of the current research would have been possible. Financial support for the current study was provided to Dr. David J. Moser by the National Institutes on Aging (grant numbers: 1 K23 AG020649-01A1, RO1AG030417-01A2), as well as a grant from the National Center for Research Resources (grant number: UL1RR024979) made to the University of Iowa.

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1

Demographics comparison of AVD and HC participants.

	AVD Mean (SD)	HC Mean (SD)	Statistic	*DF*	*P-value*
Sample size	35	22			
Age	67.2 (7.4)	69.3 (7.4)	$t = 1.193$	55	0.238
Education	14.8 (3.3)	14.0 (2.6)	$t = -1.061$	55	0.293
Sex	40% F (14f:21m)	55% F (12f:10m)	$X^2 = 1.152$	1	0.283
Handedness	(29R:5L:1A)*	(18R:3L:1A)*			1.000
Ethnicity	100% Caucasian	95% Caucasian	$X^2 = 1.619$	1	0.203
Diabetes	23%	0%	$X^2 = 5.850$	1	0.016
Resting Systolic	133.2 (18.1)	126.7 (16.6)	$t = -1.361$	55	0.179
Resting Diastolic	71.7 (9.4)	74.8 (10.3)	$t = 1.166$	55	0.248
Antihypertensive	1.7 (1.1)	.4 (.8)	$t = -5.516$	53.8	< 0.000
Lesion Volume	11.4 (14.5)	6.3 (4.5)	$U = 292$	$n_1 = 35$ $n_2 = 22$	0.127

Note: Age and education reported in years.

Comparison of handedness used Fisher's exact test. “Diabetes” reflects a positive or negative medical history of diagnosis with diabetes mellitus. Resting systolic and diastolic blood pressures reflect millimeters Hg. “Antihypertensive” reflects the average number of discrete antihypertensive medications used per participant. Levene's test reflected inequality of variances on antihypertensive medication usage between AVD and HC, so the degrees of freedom have been adjusted accordingly. “Lesion volume” reflects cubic centimeters of white matter tissue appearing hyperintense on fluid-attenuated inversion recovery imaging, based on manual tracings. Comparisons of lesion volume used Mann-Whitney *U* test because of non-normality.

*R = right handed, L = left handed, A = ambidextrous.

2

Comparison of AVD to HC participants in terms of global and lobar FA.

Region	Mean FA(SD)		Main Effects (*P*-values)		
	AVD	*HC*	*Sex*	*Age*	*Group*
Cerebrum	0.253 (0.016)	0.261 (0.015)	0.208	0.003*	0.007*
Frontal	0.262 (0.020)	0.270 (0.017)	0.049	0.012*	0.023*
Temporal	0.251 (0.015)	0.255 (0.015)	0.590	<0.001*	0.103
Parietal	0.265 (0.019)	0.277 (0.017)	0.392	0.017*	0.004*
Occipital	0.194 (0.013)	0.203 (0.014)	0.253	0.066	0.008*
Subcortical	0.366 (0.023)	0.381 (0.022)	0.079	0.354	0.006*

Note: Samples included 35 AVD and 22 HC participants. Mean FA reflects average raw FA values in each participant group, presented for qualitative examination only. Analyses of covariance were used to examine the effects of relevant covariates on the structural variables of interest. Main effects and interaction terms were calculated using univariate general linear models with each region as a dependent variable, group (AVD vs. HC) as a fixed factor, age and sex as covariates. R^2 values for the general linear models used to test main effects and interactions ranged from .155 to .258 across all regions. Each test of main effects had one degree of freedom. Unadjusted *P*-values are presented and asterisks note values that remain significant after adjustment for the false discovery rate (Benjamini and Hochberg, 1995).

3

Friedman's within-groups one-way ANOVA.

AVD group		**HC group**	
Region	***Mean Rank***	***Region***	***Mean Rank***
Frontal	3.03	Frontal	3.18
Temporal	2.37	Temporal	2.09
Parietal	3.60	Parietal	3.73
Occipital	1.00	Occipital	1.00
Subcortical	5.00	Subcortical	5.00
Statistical Analysis		*Statistical Analysis*	
n	35	*n*	22
Chi-square	122.58	Chi-square	82.62
DF	4	*DF*	4
P-value	<0.001	*P*-value	<0.001

Note: Analyses used two-tailed tests of significance