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Co-Occurrence of Vascular Risk Factors and Late-Life White Matter Integrity Changes

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Abstract

Background—Hypertension, hyperlipidemia and diabetes are increasingly prevalent with advancing age and have been shown to cause white matter (WM) injury which may contribute to dementia risk. However, cumulative and over time effects of these medical illnesses have not been systematically examined.

Methods—121 cognitively normal old participants received comprehensive clinical evaluations and brain diffusion tensor imaging on two occasions. Clinical history and medical treatment of diabetes, hypertension and hyperlipidemia were assessed at both evaluations. We examined whether exposure to a greater number of vascular risk factor (VRF) was associated with greater rate of WM integrity change using longitudinal differences in fractional anisotropy (FA).

Results—Compared to individuals with no VRF, individuals with 1 VRF did not exhibit significantly different change in FA. However, those with 2 VRFs or more had greater decrease in FA within multiple WM regions including the splenium of the corpus callosum.

Conclusions—The accumulation of VRF increasingly affected WM integrity, particularly in areas known to be injured in patients with mild cognitive impairment and dementia.

Keywords

Diffusion tensor imaging; Diabetes; Hypertension; Hyperlipidemia; Aging; White matter

Introduction

Hypertension (HTN), hyperlipidemia (HLD) and diabetes mellitus type II (DM) are medical illnesses common to individuals older than 60 years of age (Crawford, et al., 2010,Go, et al.,

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2013). Besides being major risk factors for heart disease and mortality(Alexander, et al., 2003,Chobanian, et al., 2003), the presence of these medical illnesses in middle-life are significantly associated with increased risk for later-life dementia (Kivipelto, et al., 2001a, Kivipelto, et al., 2001b, Luchsinger, et al., 2005, Whitmer, et al., 2005). While the exact cause for this association remains incompletely understood, each of these medical illnesses is also a risk factor for subclinical cerebral vascular brain injury such as white matter hyperintensities, MRI infarcts (Das, et al., 2008, Jeerakathil, et al., 2004, Prabhakaran, et al., 2008) and accelerated brain atrophy (Moran, et al., 2013, Seshadri, et al., 2004, Swan, et al., 1998). Moreover, there is pathological evidence that vascular risk factors increase the risk for later-life dementia through the additive effect of cerebrovascular to Alzheimer's disease brain injury (Arvanitakis, et al., 2006, Schneider, et al., 2007a, Schneider, et al., 2007b, Schneider, et al., 2004, Schneider, et al., 2003). Consistent with this hypothesis, longitudinal observational studies find that white matter hyperintensities (WMH) increase in volume over time and are associated with decline in performance on both memory and executive tasks even among individuals who remain cognitively normal (Debette, et al., 2011, Maillard, et al., 2012) and the presence of extensive WMH or MRI infarcts are significantly associated with increased risk for future mild cognitive impairment and dementia (Debette, et al., 2010).

However, more recent research utilizing diffusion tensor imaging (DTI) finds that WMH are only the extreme manifestation of a more diffuse process of cerebral white matter injury (Maillard, et al., 2014). DTI is a relatively recently developed MR imaging technique that allows *in vivo* study of tissue microstructure. DTI is sensitive to the diffusion of water molecules in the brain. When hampered by axons and their myelin sheaths, diffusion becomes anisotropic. DTI provides multiple imaging metrics, including fractional anisotropy (FA), a normalized measure of anisotropy. While diffusion MRI technology is evolving quickly, the resolution of current DTI sequences are lower than their more conventional counterparts, and the relatively low signal-to-noise and imaging artifacts caused by the echo planar acquisition protocol require caution when interpreting images. Indeed, one critical factor that limits the sensitivity to detect changes in any longitudinal study is the reproducibility of repeated measures. Obtaining reproducible quantitative results from DTI data is not trivial given that the final results are sensitive to a large number of acquisition and analysis factors (Jones and Cercignani, 2010). In addition, DTI typically require longer acquisition times and/or specialized MRI sequences and is not routinely performed, particularly when involving older adult participants.

Despite these limitations, recent cross-sectional DTI studies find that vascular risk factors (VRFs) are associated with subtle reductions in measures of white matter (WM) integrity (Hsu, et al., 2012, Kodl, et al., 2008) even in the absence of obvious vascular brain injury including WMH (O'Sullivan, et al., 2001). Moreover, reduced white matter integrity often surrounds WMH and predicts future development and progression of WMH (Maillard, et al., 2013, Maillard, et al., 2011, Maillard, et al., 2014). In fact, recent research suggests that longitudinal DTI measures are a more sensitive and specific measure of progressive white matter injury than quantitative WMH measures from FLAIR imaging (Maillard, et al., 2014).

A key limitation to prior studies that examined the relationship between various vascular risk factors such as hypertension and brain injury or cognition, however, is that they assessed the impact of each VRF on brain injury independently. There is strong evidence that a significant proportion of individuals late in life are exposed to two or more of these conditions simultaneously (de Sereday, et al., 2004, Go, et al., 2013) and that the effect of VRFs on dementia risk is cumulative (Luchsinger, et al., 2005, Whitmer, et al., 2005). In addition, while the individual impact of HTN, HLD and DM on cross-sectional measurements of brain injury is fairly well understood, published results of longitudinal DTI studies are limited (Jovicich, et al., 2014, Teipel, et al., 2010) and none have, to our knowledge, assessed the effects of HTN, HYP and DM on longitudinal DTI-based measures of WM integrity in older adult individuals. Consequently there is a gap in our knowledge related to how vascular risk factors impact the time course of white matter integrity.

The goal of this study, therefore, was to explore, in cognitively normal older individuals, associations between patterns of co-occurring HTN, HLD, and DM history and longitudinal change in WM integrity as measured by DTI. We assessed this goal by relating cumulative exposure of HTN, HLD, and DM history to the change in fractional anisotropy (FA), a DTI-derived measure, using a sample of 121 cognitively normal older adult individuals. We chose to study cognitively normal older individuals as differences in FA measures in certain brain regions are associated with Alzheimer's disease (Clerx, et al., 2012, Nir, et al., 2013, Teipel, et al., 2014) which might confound our understanding of the potentially subtle effects of vascular risk factors on white matter integrity.

Methods

Sample

225 community-dwelling individuals received comprehensive clinical diagnoses according to standardized criteria at the Alzheimer's Disease Center at the University of California, Davis (UCD ADC) and brain MRI including DTI on two occasions. The present sample included individuals participating in the UCD ADC longitudinal community diversity study (Hinton, et al., 2010) who were classified as cognitively normal at baseline and follow-up based on detailed medical history, neurological examination and neuropsychological testing using the Uniform Data Set battery (Morris, et al., 2006, Weintraub, et al., 2009), resulting in a sample of 121 individuals. The presence or absence of HTN, HLD or DM was assessed for each individual based on thorough review of the participant's medical history, medical records, and medications brought into the clinic at the time of both initial, follow-up and in between evaluations. After assessment, each individual was designated as belonging to one of 4 groups: 0, 1, 2 or 3 VRFs in accordance to their individual history of exposure to HTN, HLD or DM. Table 1 summarizes the participant characteristics.

The Institutional Review Boards at all participating institutions approved this study, and participants gave written informed consent.

Image acquisition and processing

All participants also received a standardized MRI scan of the brain at two different dates with a mean (SD) inter-scan interval of 3.4 (1.7) years. All brain imaging was performed at the University of California, Davis Imaging Research Center on a 1.5-T GE Signa Horizon LX Echospeed system. Three sequences were used: a 3-dimensional T1-weighted coronal spoiled gradient- recalled echo acquisition (3DSPGR, IR-prepped, TE = 1.9 ms, flip angle = 20°, field of view (FOV) = 24 cm, matrix = 256 × 256, 124 contiguous slices, slice thickness = 1.6 mm), an axial-oblique 2D FLAIR fast spin echo sequence (TE = 144 ms, TR = 11000 ms, TI = 2250 ms, flip angle = 90°, FOV = 22 cm, matrix = 256 × 192, contiguous slices, slice thickness = 3 mm) and DTI using the diffusion tensor weighted echo-planar sequence (TE = 94 ms, TR = 8000 ms, flip angle = 90°, FOV = 22 cm, matrix = 128 × 128, slice thickness = 5 mm). All image acquisition was performed according to previously reported methods (see Supplemental Methods). Diffusion weighted images were generated using gradients applied in six directions, repeated four times, given by (Gx,Gy,Gz) = (1,1,0), (1,−1,0), (1,0,1), (1, 0, −1), (0,1,1) (0,1,−1) with total gradient diffusion sensitivity measured at b=1000 s/mm^2. Two diffusion unweighted images were also acquired. Signal to noise ratio was estimated using the diffusion unweighted images (please see Supplementary Data). All procedures described below were performed using FSL software tools (Jenkinson, et al., 2012). DTI data were corrected for eddy current-induced distortions and participant movements. FA was calculated at each image from the 3 eigenvalues of the diffusing tensor. Baseline and follow-up FA maps were computed from DTI images, aligned and subtracted to provide FA change (ΔFA) maps. ΔFA maps were then warped using linear and nonlinear transformations to a common DTI template and finally normalized by the inter scan time interval (please see Supplementary Data). To ensure the reliability of ΔFA measures, we applied the same method to a subsample of 10 young healthy individuals (mean ± SD age: 24.4 ± 1.9) who underwent 2 DTI exams (mean ± SD inter-scan interval: 1.3 ± 0.6 months) and performed, at each voxel, a linear regression with ΔFA as the dependent variable, controlling for age and gender. No voxel exhibited significant change in FA, after correcting for multiple comparisons ($p<0.05$, data not shown).

Segmentation of WMH was performed by a semiautomated procedure using a set of in-house computer algorithms and programs previously described (DeCarli, et al., 2005) and which demonstrate high inter-rater reliability (Carmichael, et al., 2012). Total cranial volume based on FLAIR was quantified using the Quanta 2 package of software routines according to a previously reported analysis protocol (DeCarli, et al., 2005) and was used to correct cerebral brain and WMH volumes for differences in head size.

Statistical analysis

Descriptive statistics of participant characteristics—Continuous and categorical variables were compared using Student t-test and Chi-squared tests respectively and, when significant ($p<0.05$), posthoc pairwise comparisons corrected for multiple comparisons using Bonferroni correction were performed between groups when comparing (1) 0 vs. 1; (2) 1 vs. 2 and (3) 2 vs. 3 VRFs.

Voxel-based analyses—The primary goal of the statistical analysis was to determine if, at the voxel level, exposure to a greater number of risk factors was associated with greater annual rate of white matter integrity change as indicated by ΔFA. To achieve this goal, we investigated group differences between individuals with (1) 0 and 1 VRF; (2) 1 and 2 VRF and (3) 2 and 3 VRF. At each voxel we performed linear regressions with ΔFA as the dependent variable and number of VRF as the independent variable of interest, with age, gender, education, smoking status (non-, former or current smoker), body mass index and baseline FA as additional nuisance covariates.

The second goal was to determine if, at the voxel level, exposure to a greater number of risk factors was associated with lesser white matter integrity at baseline as measured by baseline FA. To achieve this goal we used linear regressions with measures of baseline FA as the dependent variable and VRF group membership as described above as the independent variable of interest, with age, gender, education, smoking status and body mass index as additional nuisance covariates.

Main associations from overall multivariate models between baseline FA and ΔFA with each of the variables are illustrated in the Supplemental Figure 2 (see Supplementary Data). The T-maps obtained for longitudinal and cross sectional analyses were evaluated for statistical significance using threshold free cluster enhancement (TFCE) at the $p<0.05$ level and corrected for multiple comparison using permutation-based correction (please see Supplementary Data).

We then overlaid the permutation corrected T-maps onto the Johns Hopkins University probabilistic fiber map atlas (Zhang, et al., 2010), warped to the DTI template space, to provide a *post hoc* description of the WM tracts to which the various clusters of significant voxels most likely belonged.

In addition, because body mass index (BMI) may be associated with increased risk of the medical illnesses studied, we investigated whether BMI modulated the relationship between VRF group and FA within WM regions in which lower FA and larger annual FA losses were found associated with increasing number of VRFs. To measure this effect, we calculated the corresponding mean ΔFA and baseline FA and conducted linear regressions with baseline FA and ΔFA as the dependent variables and number of VRFs and body mass index as the independent variables of interest, as well as the interaction between the two variables, controlling for age, gender, education and smoking status for each cluster of significant voxels.

Finally, we explored whether medication treatment affected FA measures within each VRF group. Analyses revealed effects of treatments on ΔFA or baseline FA only in punctuate WM regions that did not alter the results reported below (see Supplemental Figure 3 in the Supplemental Data for these findings).

Statistical analyses were performed using R version 2.10.0 (*R* Development Core Team, 2009, Vienna, Austria).

Results

Demographics

The age of the sample ranged from 60 to 92 years and the majority of the participants were female with a high school education. The cohort is racially and ethnically diverse by design (Hinton, et al., 2010) and 80% of the participants suffered with one or more VRFs. Consistent with the literature, Hispanic and African American participants were more likely to have multiple VRFs as compared to Whites, particularly when comparing the prevalence of 2 VRFs versus 3 VRFs (48.8 vs. 18.4% respectively, p=0.016). There were no significant differences between the four groups under study (0, 1, 2 or 3 VRFs among HTN, HLD and DM) in terms of age, sex, smoking status, body mass index, years of education, episodic memory and executive scores, mean FA, brain matter volume, WMH volume (see Supplemental Figure 4 for an illustration of WMH spatial distribution according to VRF groups), and race. Medication use differed in the expected direction (p values <0.01, see Tables 1 and 2 in the Supplemental Data for more detailed description of medication usage).

Distribution of hypertension, hyperlipidemia and diabetes history and medication use across VRFs groups

Upon review of this categorization scheme, we noted that hypertension was the most common vascular risk in isolation, i.e within the group with 1 VRF (63%). The group with 2 VRFs was mostly composed of individuals with a combined history of hypertension and hyperlipidemia (90%, see Table 1). Interestingly, this distribution of VRFs corresponds to the most frequent profile for older and cognitively normal individuals reported in the literature (Davis, et al., 2011, Fryar, et al., 2010). Among individuals with 0 VRFs, two were found to use medications that would affect blood pressure without history or evidence of hypertension suggesting an alternative use for these medications. Among individuals with 1 VRF, 9 were treated neither for hypertension, hyperlipidemia nor diabetes, and 13 were under treatment for hypertension. Of the 41 individuals with 2 VRFs, 21 were treated for both hypertension and hyperlipidemia and 11 for hypertension only. Finally, 23 of the 38 individuals with a history of hypertension, hyperlipidemia and diabetes received treatments for all 3 medical conditions (see Table 1 and Table 2 in the Supplemental Data for more detailed description of medication use).

0 vs. 1 vascular risk factor

Compared to controls, individuals with a history of single VRF differed in FA values at baseline in only areas areas (see Figures 1 and 2) covering 0.06 mL of the WM and located mostly in the corpus callosum (CC) region (see Table 2). Those with 1 VRF also had greater FA decline over time (see Figures 1 and 2) in similarly small regions covering only 0.9 mL of the WM (see Table 2).

1 vs. 2 vascular risk factors

Individuals with 2 VRFs showed lower FA values at baseline in a larger (22.72 mL) volume of cerebral WM (see Figures 1 and 2) compared to those with 1 VRF. The CC and thalamic radiations were the most heavily involved WM tracts in this comparison (6.26 and 5.59 mL

respectively, see Table 2). Those with 2 VRFs also had greater FA reductions over time (see Figures 1 and 2) within voxels covering 6.01 mL of the WM. Again, the CC was the most heavily involved tract (2.14 mL, equivalent to 36% of significant voxels, see Table 2).

2 vs. 3 vascular risk factors

Compared to individuals with 2 VRFs, those with an additional VRF had lower FA values at baseline (see Figures 1 and 2) within voxels covering 2.07 mL of the WM including 1.61 mL of the CC (see Table 2). These individuals also experienced greater reduction in FA values over time within voxels that covered 31.9 mL of the WM (see Figures 1 and 2). The CC was particularly prone to greater FA reductions in this group (12.81 mL, equivalent to 40% of significant voxels, see Table 2).

Interaction between VRFs number and body mass index

The associations between both baseline FA and ΔFA and increased number of VRFs were not found to be modulated by the body mass index except in the CC and the superior longitudinal fasciculus regions where the association between an increase in VRF number from 1 to 2 was found to be accentuated with increasing body mass index ($p=0.027$ and $p=0.035$ respectively, see Supplemental Table 3).

Discussion

Our results reveal three important findings. First, among cognitively healthy older adult individuals with generally average exposure to various VRFs, a prior history of only one VRF among hypertension (approximately 60%), hyperlipidemia (approximately 35%), or diabetes was associated with extremely mild exacerbation of age-related WM integrity loss. Second, as compared with individuals with only one VRF, additional VRFs were associated with greater WM integrity loss over time within a substantial portion of the WM. Third, while we had limited power to assess the impact of medical treatment on baseline and longitudinal change in FA, results showed only small differences that suggested lower FA integrity for those being treated. From these findings we concluded that medical treatment may be an indicator of worse severity as suggested by the literature (Wolf, et al., 1991). Taken together, these longitudinal findings strengthen evidence that greater VRF exposure is associated with poorer trajectories of brain health late in life (Luchsinger, et al., 2005, Whitmer, et al., 2005). These results also emphasize the fact that VRFs often occur in conjunction (Davis, et al., 2011, Fryar, et al., 2010) and that it is this co-occurrence that is likely to have the greatest impact on brain structure and function (Luchsinger, et al., 2005, Whitmer, et al., 2005), particularly when diabetes is present (Luchsinger, et al., 2005).

Because progression of WM injury is accompanied by concomitant decline in cognitive performance (Maillard, et al., 2012), it is crucial to determine how VRFs impact WM integrity and may be differentially associated with accelerated WM degeneration. The present work revealed that a prior history of only one VRF explained only limited variability in microstructural WM integrity. This finding may reflect the fact that our subgroup with one VRF, mostly consisting of isolated HTN, had either relatively mild hypertension or a relatively limited duration of exposure, or both. We base this conclusion on data from prior

reports which show that older adult individuals who experience prolonged exposure to HTN (such as those with a history of midlife HTN) show significantly poorer brain structure and function (Swan, et al., 1998).

Unlike isolated HTN, the co-occurrence of two VRFs appears to have a strong negative effect on WM integrity. Individuals in this subgroup predominantly had a prior combined history of HTN and HLD (90%, see Table 1). Like HTN, HLD is independently associated with elevated risk of cognitive decline, dementia and Alzheimer's disease (Anstey, et al., 2008, Blom, et al., 2013). Our data suggests that in the context of HTN, HLD appears to have especially serious effects on WM integrity. This finding parallels findings of previous observational prospective studies that did not find a consistent relationship between cholesterol levels and incidence of stroke, except in individuals with risk factors for cardiovascular disease (including hypertension) (Borghi, 2002). While this interaction between HLD and HTN is poorly understood in the context of small cerebral vessels thought to be involved in WM injury, much more is known about their effects on larger cerebral vessels. Briefly, the mechanisms of interaction between HLD and HTN may contribute to increased vessel wall shear stresses, resulting in endothelial dysfunction and increased oxidative stress of the intrarenal renin-angiotensin system (Singh and Mehta, 2003). Such endothelial dysfunction represents a key early step in the development of atherosclerosis, with elevated cholesterol representing another key contributor (Hadi, et al., 2005). Additional work is needed to understand WM vulnerability related to HLD-HTN co-occurrence highlighted in the present work.

Because the frequency of individuals with DM history in the group with 2 VRFs was extremely low (n=4 out of 41), we presumed that differences observed between this group and that combining the triad of HTN, HLD and DM history (n=38) was explained predominantly by the additional effect of DM. It is widely recognized that DM is associated with increased risk for cerebrovascular disease and mortality (Go, et al., 2013) and recent studies suggested that arterial stiffness may play an important role in linking diabetes with CVD (de Oliveira Alvim, et al., 2013, Stehouwer, et al., 2008). Complementary to two recent cross-sectional DTI studies suggesting that DM may injure WM in restricted brain regions (Hsu, et al., 2012, Yau, et al., 2013) among individuals in their fifth and sixth decades of life, the present study suggests that, ten to twenty years later in the lifespan, individuals with a history of DM may exhibit ongoing decrements in WM integrity in large areas of the CC, and may support previous findings that reported an association between DM and cognition only in individuals of 60 years of age and older (Biessels, et al., 2008, Xu, et al., 2009). Interestingly, the main effect of DM in the context of combined HLD and HTN was to extend the spatial extent of WM damage, but not to increase the magnitude of change in regions that were damaged in individuals who, for the most part, exhibited the combination of HLD and HTN. DM may enhance arterial stiffness through pathological changes in the vascular bed, such as reduced nitric oxide bioavailability, chronic low-grade inflammation, increased sympathetic tone and changes in type or structure of elastin and/or collagen in the arterial wall (de Oliveira Alvim, et al., 2013). The diabetic state is also typified by an increased tendency for oxidative stress and high levels of oxidized lipoproteins, especially the so-called small, dense low-density lipoprotein (Hadi, et al., 2005). DM, when combined with HTN and HLD, likely worsens the effects on endothelial

adhesiveness and its consequences. Additional studies are needed to understand the chronology and factors linking the combined effects of these risk factors on arterial aging, microvascular damage and WM injury.

We found that compared to other WM pathways, the CC was differentially vulnerable to the effects of co-occurring VRFs. This structure has a unique myelination pattern that includes small diameter fibers most frequent in the anterior CC (genu) which myelinates much later in normal development, in conjunction with fibers of large diameter, especially in the splenium that myelinate early in development. Several cross-sectional studies have found an association between altered diffusivity measures in CC with global cognitive function, AD and MCI (Chua, et al., 2008), emphasizing the need of understanding the biological mechanisms that result in associations between VRFs and microstructural integrity of CC most specifically. Importantly, our findings of preferential impact in posterior white matter tracts is consistent with recent cortical thickness studies that find reduced thickness due to VRFs in regions vulnerable to the AD process (Villeneuve, et al., 2014).

Study Limitations

Our study, however, is not without some limitations. First, we examined only the cumulative impact of HTN, HDL and DM and did not include co-occurring vascular disease such coronary artery disease or stroke which can accompany these medical illnesses. In addition, we did not measure potential modifying behaviors such as exercise, diet or weight control. While the present study aimed to focus on biological rather than behavioral measures, including such measures may be of interest for future studies with larger sample sizes. In addition, while medication use was collected at each visit, we did not have the number of participants in this study to effectively examine the impact of medication, isolated or in combination, on white matter integrity measures across VRFs groups, with the exception of individuals with 1 VRF treated or not for hypertension and individuals with 2 VRFs treated for both hypertension and hyperlipidemia or for hypertension only (see Supplemental Data). Finally, although supported by visual inspection, the superposition with JHU map indicated that CC appears to be the WM region the most implicated in the associations but only provided a *posthoc* quantitative description that highly relies on the warping process. To bypass this limitation and comfort the present findings, further studies may use tractography which, although relying on registration of specific *a priori* regions of interest or specific tracts into the subject DTI space, uses the more anisotropic tensors to form streamlines of tensors leading to estimations of white matter fiber tracts.

Summary/Conclusions

This is one of very few studies of longitudinal DTI change in the older adults. It is unclear whether differences in microstructural WM trajectories associated with hypertension, hyperlipidemia and diabetes are preventable, but the current study emphasizes the importance of early management of these medical illnesses as a possible preventive strategy against white matter integrity loss in late life, in addition to the recognized benefits of treatment on cardio- and cerebrovascular events (Chobanian, et al., 2003, Collins, et al., 2004).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- We explore effects of vascular risk factors (VRFs) on white matter integrity change
- VRFs include hypertension, hyperlipidemia and diabetes mellitus type II
- Diffusion tensor imaging derived measure is used to describe white matter integrity
- Accumulation of VRFs affect both baseline and change in white matter integrity
- Injured regions are known to be involved in mild cognitive impairment and dementia

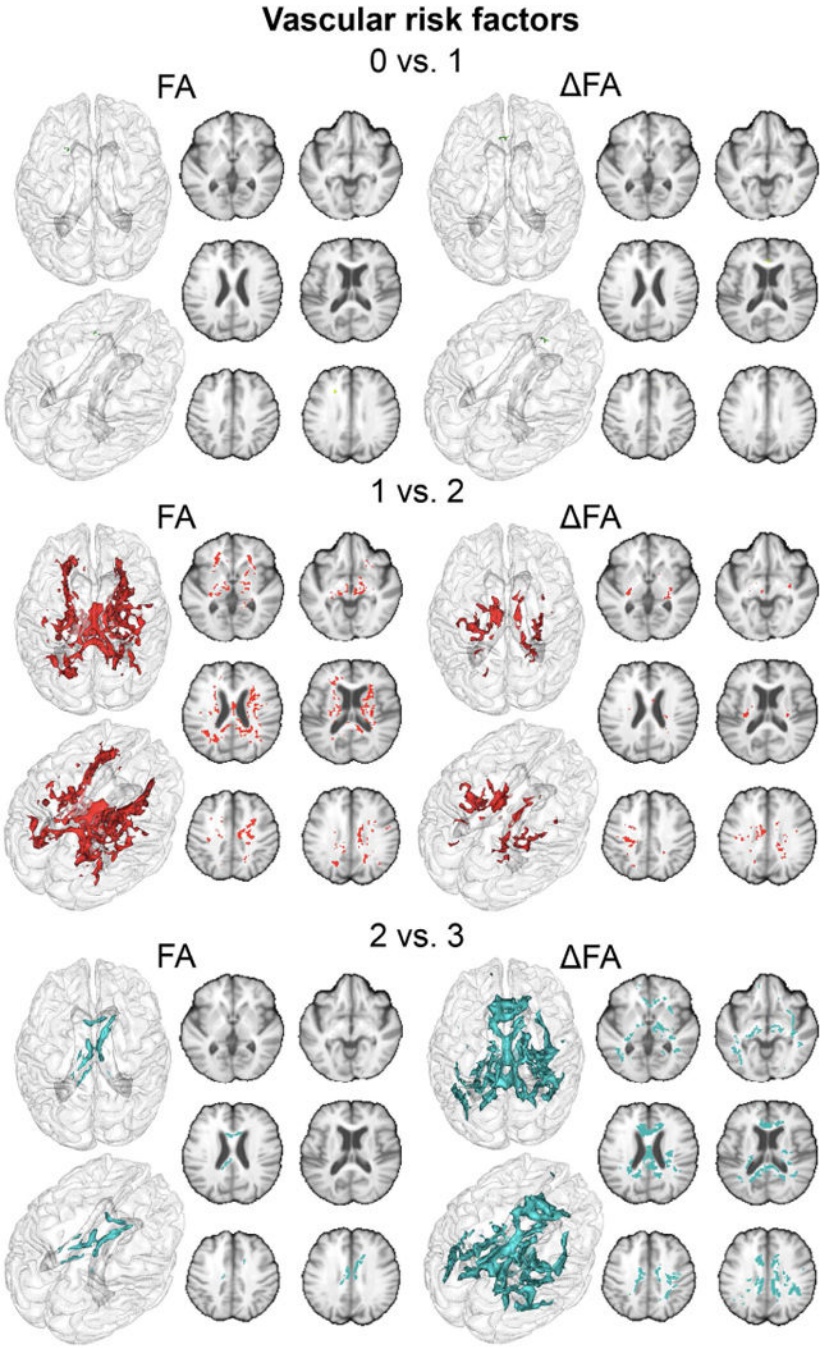

Figure 1.

Regions of the cerebral white matter in which lower FA and larger annual FA losses are significantly associated with increasing number of vascular risks (VRFs) (green: 0 vs. 1 VRF, red: 1 vs. 2 VRFs and blue: 2 vs. 3 VRFs).

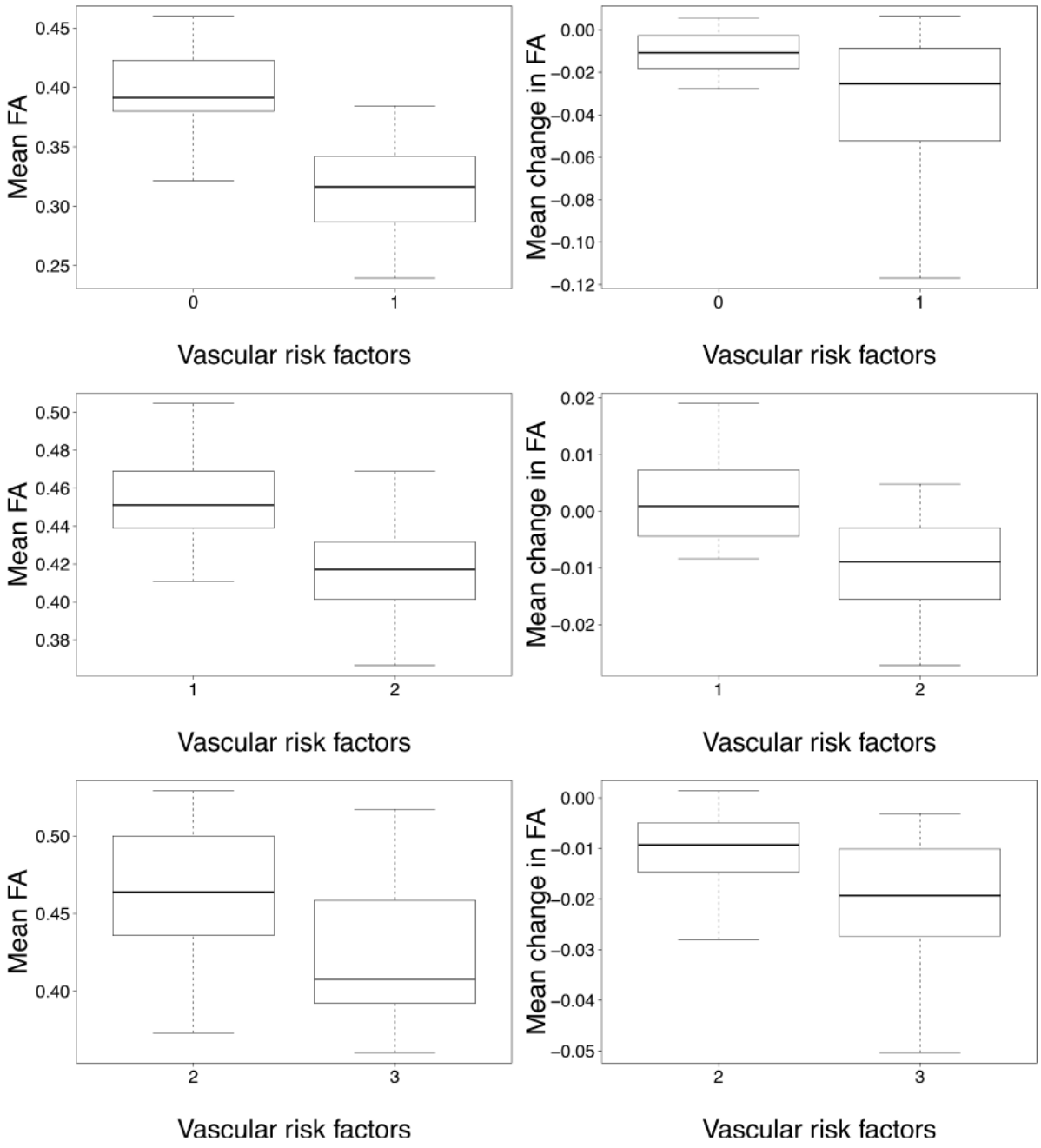

Figure 2.

Boxplot of mean FA and annual change in FA computed in regions significantly associated with increasing number of vascular risks (VRFs)

Table 1

Summary of participants' characteristics. Data presented as means ±SD for continuous data or #; % for categorical data.

		All	Vascular risk factors (VRF)				P value
			0	1	2	3	
Number		121	12	30	41	38	–
Baseline age, y		73.9±6.6	71.5±5.3	74.5±5.7	75.3±7.2	72.8±6.6	0.98
Years of Education		12.7±4.9	13.7±5.7	12.1±5.3	13.7±3.80	11.7±5.2	0.36
Inter-time scan interval		3.4±1.7	3.8±1.4	3.4±1.7	3.6±1.8	3.1±1.5	0.24
Sex (male)		32; 26.4	2; 16.7	13; 43.3	7; 17.1	10±26.3	0.077
Race	African American	25; 20.7	2; 16.7	4; 13.3	7; 17.1	12; 31.6	0.24
	Hispanic	46; 28.0	3; 25.0	10; 33.3	14; 34.1	19; 50.0	0.29
	White	50; 41.3	7; 58.3	16; 53.3	20; 48.8	7; 18.4	0.0067*
Hypertension		97; 80.2	0; 0	19; 63.3	40; 97.6	38; 100	–
Hyperlipidemia		86; 71.1	0; 0	10; 33.3	38; 95.0	38; 100	–
Diabetes mellitus		43; 35.5	0; 0	1; 3.3	4; 9.8	38; 100	–
Medication (yes)		96; 79.3	2; 16.7	21; 70.0	36; 87.8	37; 97.4	<0.001ζ
Body Mass Index		30.4±9.0	31.1±14.5	27.2±6.2	31.5±11.2	31.6±4.8	0.20
Smoking status	Non smoker	74; 61.2	7; 58.3	20; 66.7	26; 63.4	21; 55.3	0.78
	Former smoker	42; 34.7	3; 25.0	9; 30.0	14; 34.1	16; 42.1	0.63
	Current smoker	5; 4.1	2; 16.7	1; 3.3	1; 2.4	1; 2.6	0.15
Baseline episodic memory scores		102.7±13.1	101.2±9.7	104.0±16.5	104.4±14.3	100.2±9.8	0.57
Baseline executive function scores		102.8±13.9	103.4±13.7	106.5±16.3	104.0±13.1	98.6±12.8	0.12
Baseline brain matter volume (% ICV)		79.1±4.2	79.1±3.6	78.5±4.0	79.8±4.3	78.8±4.3	0.83
White matter hyperintensities volume (% ICV)		0.45±0.67	0.44±0.82	0.44±0.81	0.54±0.68	0.39±0.57	0.91

ζ, ψ and * respectively indicate significant (<0.05) difference for *post hoc* pairwise comparisons, corrected for multiple comparisons using Bonferroni correction, between groups with (1) 0 and 1 VRFs, (2) 1 and 2 VRFs and (3) 2 and 3 VRFs. Executive function and episodic memory measures were obtained using the Spanish and English Neuropsychological Assessment Scales (Mungas, et al., 2004, Mungas, et al., 2005, Mungas, et al., 2000). Baseline brain matter and white matter hyperintensities volumes are expressed as ratio of intracranial volumes (ICV). Please see Supplemental Data for more detailed description of medication use.

Table 2

Cross sectional and longitudinal associations between decreasing baseline fractional anisotropy (FA) and greater rate of FA loss (ΔFA) respectively with increasing number of vascular risk factors (VRFs). Data indicate volume (mL) of WM significantly different between comparison groups in given WM region and percentage of WM mask voxels that were significantly different between comparison groups in given WM region.

Groups	Design	Cerebral region	Volume (mL)	Percentage (%)	P value
0 vs. 1 VRF	Cross sectional	WM mask	0.06	100.00	<0.001
		CC	0.03	58.82	<0.001
		UNC	0.02	35.29	<0.001
	Longitudinal	WM mask	0.09	100.00	<0.001
		CC	0.08	85.71	0.0029
		ILF	0.01	7.14	<0.001
1 vs. 2 VRFs	Cross sectional	WM mask	22.72	100.00	<0.001
		CC	6.26	27.57	<0.001
		TH	5.59	24.60	<0.001
		SAF	3.74	16.48	<0.001
		CST	2.02	8.88	0.0020
		IFO	1.59	7.01	<0.001
		SLF	1.38	6.06	<0.001
		CGC	1.37	6.03	<0.001
		UNC	0.72	3.15	<0.001
		ILF	0.05	0.21	0.0071
	Longitudinal	WM mask	6.01	100	<0.001
		CC	2.14	35.60	<0.001
		CST	1.02	16.96	<0.001
		SAF	0.90	15.05	<0.001
		TH	0.78	12.91	<0.001
		CGC	0.70	11.62	0.0016
		SLF	0.25	4.21	<0.001
		IFO	0.12	2.08	<0.001

Groups	Design	Cerebral region	Volume (mL)	Percentage (%)	P value
		UNC	0.08	1.40	0.0014
		ILF	0.01	0.17	0.0048
2 vs. 3 VRFs	Cross sectional	WM mask	2.07	100.00	<0.001
		CC	1.61	77.65	<0.001
		CGC	0.46	22.35	<0.001
	Longitudinal	WM mask	31.91	100.00	<0.001
		CC	12.81	40.16	<0.001
		CGC	4.20	13.16	<0.001
		SAF	3.81	11.94	<0.001
		TH	3.50	10.96	<0.001
		SLF	2.73	8.55	<0.001
		CST	2.25	7.07	0.0015
		IFO	1.07	3.35	<0.001
		UNC	0.89	2.78	0.0014
		ILF	0.65	2.03	<0.001

CC: corpus callosum; SAF: short association fibers; TH: thalamic radiations; CST: corticospinal tracts; CGC: Cingulum; SLF: superior longitudinal fasciculus; IFO: inferior fronto-occipital tracts.