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White matter fractional anisotropy is inversely related to anxious symptoms in older adults with atherosclerosis

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Abstract

Objective—Clinical anxiety disorders are associated with white matter hyperintensities and diffusion abnormalities measured using diffusion tensor imaging (DTI). However, it is not known if this association extends into individuals with mild anxious symptoms without formal diagnosis, in those who are older, or in those who have atherosclerosis. The current study explored whether white matter integrity and/or organization significantly associates with anxious symptoms in older adults with and without atherosclerosis.

Methods—We recruited older adults (ages 55–90); 35 with clinically diagnosed atherosclerotic vascular disease (AVD) and 22 without AVD. Anxious symptoms were measured using the validated Symptom Checklist-90-Revised. Fractional anisotropy (FA), a proxy for white matter organization and health, was measured in the white matter globally, by lobe, and in several smaller regions of interest suggested by the literature. Partial correlations between anxious symptoms and FA were calculated, controlling for significant covariates.

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Conflicts of Interest:

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Results—Participants with and without AVD did not differ in severity of anxious symptom endorsement. There was a unique inverse relationship between white matter health and anxious symptoms in the AVD participants, but not in healthy comparisons. Significant relationships were observed in the superior longitudinal fasciculus ($r=-.476$, $df=32$, $p=.004$), as well as the cingulum bundle, the frontal lobes, and the parietal lobes.

Conclusions—Anxiety symptoms uniquely correlated with low fractional anisotropy in older adults with atherosclerosis. These findings may have implications for future research on the topic of anxiety in aging and vascular disease and warrant replication.

Keywords

diffusion tensor imaging; anxiety; uncinate; cingulum; longitudinal fasciculus

Introduction

Even moderate anxiety, in the absence of a clinical diagnosis of an anxiety disorder, is associated with a 25–30% elevation in risk for cardiovascular events (Roest et al., 2010). The neural underpinnings of anxiety in general and in the setting of vascular disease remain unclear.

While the literature remains inconsistent with regards to the neural circuitry underlying anxiety as a whole, specific anxiety disorders including social anxiety disorder (Phan *et al.*, 2009), generalized anxiety disorder (Nitschke *et al.*, 2009), post-traumatic stress disorder (Shin *et al.*, 1997) and trait anxiety (Kim and Whalen, 2009), involve two anatomical areas in particular: the amygdala and the prefrontal cortex (PFC) (Rauch *et al.*, 1997; Charney, 2003). These findings are consistent with previous literature suggesting the PFC inhibits the fear responses generated by the amygdala, and damage to the PFC may result in heightened anxiety in a rat model (Morgan *et al.*, 1993).

Studies of the neural correlates of anxiety disorders in human samples have primarily focused on gray matter structures (Nitschke *et al.*, 2009; Rauch *et al.*, 1997; Charney, 2003; Shin *et al.*, 1997), while the underlying white matter has, until recently, received far less attention. One study assessed the relationship between trait anxiety, as measured by the State Trait Anxiety Inventory, and white matter health measured by Diffusion Tensor Imaging (DTI) in 20 non-psychiatric young adults (Kim & Whalen, 2009). DTI measures were reported in terms of fractional anisotropy (FA), the most common outcome measure from DTI studies. Anisotropy refers to the degree to which diffusion is directionally constrained, and is typically high in healthy white matter because water tends to diffuse parallel to fiber bundles. FA depends on microstructural components of the tissue being measured, including the integrity of cell membranes and the organization of fiber tracts (Basser, 1994). Individual differences in trait anxiety scores were found to be significantly and inversely related to fractional anisotropy (FA), in the uncinate fasciculus, an identified pathway connecting the amygdala with the ventromedial prefrontal cortex (VMPC). Results from that study suggested that greater integrity and/or organization of the connection between the amygdala and the VMPC may facilitate communication between these two structures and may predict lower levels of anxiety. Another case-control study using DTI found abnormal white matter organization or health (indicated by lower FA) near the orbital PFC in participants with social anxiety disorder (Phan *et al.*, 2009). That study also found aberrant fronto-amygdala structural connectivity in the uncinate fasciculus through an exploratory analysis. Previous studies in participants with atherosclerotic vascular disease (AVD) have shown that there are significant relationships of anxious symptoms with cognitive function

(Stillman *et al.*, 2012) as well as with resistance vessel dilator function, an indicator of vascular health (data not presented).

The aims of the current study were to characterize the range of anxious symptoms experienced by older adults with and without diagnosed atherosclerotic vascular disease (AVD), and to examine the relationship of anxious symptoms with measures of white matter health globally and in a variety of subregions in the brain. Very little is known about the relationship between anxiety and white matter health in participants with vascular disease and in older adults. Given this lack of knowledge, we primarily intended the current study to be of an exploratory, hypothesis-generating nature.

Methods

Participants

As a part of a parent study (Moser *et al.*, 2007), older adults were recruited into two groups: an atherosclerotic vascular disease (AVD) group, recruited primarily from the University of Iowa Heart and Vascular Care clinic and a healthy comparison (HC) group, recruited primarily from print advertisements. Participants were additionally recruited to both groups from the Seniors Together in Aging Research (STAR) registry. 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, placement of coronary artery stent, or peripheral vascular disease (claudication). Exclusion criteria include coronary artery bypass grafting, valve replacement, carotid endarterectomy, stroke, head injury with a loss of consciousness >30 minutes, other neurological or systemic illness unrelated to vascular disease that is likely to affect cognition, focal neurological signs, diagnosed dementia, or severe and uncontrolled psychiatric illness (current or past). HC participants were required to be between 55 and 90 years old and have none of the AVD group diagnoses. The criteria for exclusion from the AVD group were applied to the HC group as well.

Since 2003 approximately 1,750 potential AVD participants have been contacted about the study. Approximately 25% of patients with AVD that were approached were interested in participation. Of those interested, approximately 20% completed all three baseline study visits. Of those that complete all study visits, approximately 40% chose to participate in neuroimaging as well.

All study procedures were conducted in accordance with the ethical standards of the University of Iowa Institutional Review Board and the Declaration of Helsinki, and all participants provided informed consent.

Demographics

All participants were asked to complete a brief demographic questionnaire and their medical records were examined for use of antidepressant or anxiolytic medications.

Psychological measure

The Symptom Checklist 90-Revised (SCL-90-R) (Derogatis and Melisaratos, 1983) was used to assess psychological symptoms. The SCL-90-R is an established self-report measure that asks participants to indicate the extent to which they have been distressed by specific psychological and related symptoms over the past seven days on a scale from 0 (not at all) to 4 (extremely). It provides an overall severity index T-score reflecting the level of general psychological distress (Global Severity Index) as well as T-scores for nine individual

symptom domains including anxiety. T-scores on the SCL-90-R are based on the participant's raw score adjusted for sex norms. Several studies have shown the Anxiety Scale of the SCL-90-R to be a valid indicator of anxious symptoms (Koeter, 1992; Steer and Ranieri, 1993; Cameron and Hudson, 1986; Schmitz *et al.*, 1999).

Imaging Measures

A subset of the participants in the parent study participated in neuroimaging, which included anatomical (T1, T2, and FLAIR) and diffusion-weighted imaging using Siemens Avanto 1.5T magnetic resonance scanner (Erlangen, Germany). Diffusion weighted imaging (DWI) data were gathered on 56 slices (TE=94ms, TR=9500ms, field of view=256×256, slice thickness/gap= 2.5/0.0mm, matrix=128×128, flip angle=90 degrees, pixel bandwidth=1347, frequency 63.623624MHz), using 12 gradient directions and a b-value of 1000.

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). This software performs automatic AC-PC alignment, image alignment, standardization of image intensity, tissue classification, brain extraction, and automatic labeling of brain regions based on the Talairach and Tournoux atlas (Talairach and Tournoux, 1988). Only T1 and T2-weighted images are considered in the tissue classification algorithm, so white matter lesions were initially classified as gray matter. In order to correct this artifact, FLAIR and tissue-classified images were consulted and a human rater manually defined the lesions. Voxels corresponding to lesion were added as a separate tissue class and removed from the gray matter volume. All white matter tissue was included in the DTI analysis regardless of whether it was categorized as “lesioned” or not.

In the current study, the DWI data were first processed using GTRACT software (Cheng *et al.*, 2006). Each DWI volume was co-registered to its baseline to eliminate motion. Once the images were co-registered, tensor images were estimated and scalar maps including fractional anisotropy (FA) were generated. The FA maps were then aligned with each subject's anatomical scan. Each participant's neuroimaging data were subsequently visually inspected for quality to verify that the co-registration of DTI data to anatomical scans was appropriate, as well as to check for artifacts such as head motion, table vibration, RF noise, and susceptibility artifacts. White matter was segmented using tissue classification (Harris *et al.* 1994). Measures of FA were then obtained in each Talairach-defined region (frontal, temporal, parietal, occipital, subcortical and total cerebrum) in white matter defined by the white matter plus lesion mask in voxels where the FA was greater than 0.1 (to exclude regions of susceptibility artifact or regions that were clipped based on the number of slices acquired).

Atlas-based analyses utilized the white matter atlas developed by Mori and colleagues at Johns Hopkins University (Mori *et al.*, 2005). The Mori Atlas was registered to the anatomical images and scalar maps generated by the GTRACT software and FA values were generated for a variety of white matter tracts throughout the brain. Regions of interest for the current study were the uncinate fasciculus and the cingulum bundle, given the literature reporting relationships in these regions in patients with diagnosed anxiety disorders (Kim and Whalen, 2009; Phan *et al.*, 2009). Additionally, we included the superior longitudinal fasciculus (SLF) as a comparison region, anticipating there would not be any relationships between FA in the SLF and anxious symptoms (see Figure 1 for coverage of regions of interest)

Analyses

Correlational analyses were used to determine whether there were relationships between structural variables of interest and anxiety. We used an alpha level $< .05$ for determination of statistical significance for all comparisons between groups and in the primary correlational analyses. Comparisons were made across multiple brain regions in these exploratory analyses for the purpose of hypothesis generation for future studies.

Demographic comparisons used Student's t-tests and chi-square tests to examine group differences in age, education, and sex. Because of the low frequency of ambidexterity in handedness measures, Fisher's exact test was used. Visual inspection of the histograms of DTI data revealed relatively normal distributions in all measures. Levene's test for equality of variances during means comparisons in the DTI data showed non-significant differences in variance between groups. However, visual inspection of anxiety data revealed a skewed distribution and Levene's test for equality of variances between groups was significant ($F = 4.18, p = .046$). After log-transforming the anxiety data to control for the non-normality of distributions, partial correlations were used to assess the relationships among DTI measures and SCL-90-R Anxiety Scale scores while controlling for significant covariates. Given previous research showing significant relationships between age and FA (Pfefferbaum *et al.*, 2005), we controlled for age in all correlations. Previous research also suggested an effect of sex on FA in the frontal lobes (Hsu *et al.* 2008); however, inclusion of sex as a covariate in the correlation of frontal FA with anxiety did not alter the significance of the original findings. Previous research with the current sample (Stillman *et al.*, 2011) suggested there was a high correlation between anxiety and depressive symptoms, so partial correlations were re-calculated including depressive symptoms as a covariate for comparison purposes.

Diffusion tensor scans passed initial quality control for overt head motion, resonance frequency noise, table vibration, and susceptibility artifacts. However, one AVD participant's scan was later deemed unsuitable for DTI analyses because of subtle warping of the brain shape in the posterior parietal and occipital lobes, and was excluded from analysis. Power analysis for means comparison showed that our sample of 35 AVD and 22 HC participants had 44% power to detect a medium-sized effect (Cohen's $d = 0.5$) and 82% power to detect a large-sized effect (Cohen's $d = 0.8$). For correlational analyses, power analysis showed that the sample of AVD participants had 80% power to detect a medium-to-large correlation ($r = .453$), and the sample of healthy comparison participants 80% power to detect a large correlation ($r = 0.556$). In order to assess whether any relationship between anxiety and FA was mediated by variation in vascular risk factor burden, we added 2-year Framingham risk as a covariate (D'Agostino *et al.*, 2000).

Results

Among the participants with AVD, there were no significant differences between participants completing neuroimaging and those who did not in terms of age, education, sex, or handedness ($p > .05$ for each). In the HC group, there was a significant difference in the sex of the participants completing neuroimaging (54.5% women) compared to those who did not (86.2% women), though there were no other significant differences between these groups ($p > .05$ for age, education, handedness). Usable neuroimaging data were gathered on thirty-five AVD and 22 HC participants from the parent study. Participants who underwent neuroimaging did not differ significantly from the larger sample regarding age, education, sex, handedness, or SCL-90-R Anxiety Scale scores (p -values ranging from .308 to .761). Within the group of participants who underwent neuroimaging, there were no significant differences between AVD and HC groups in terms of age, sex, education, handedness, or SCL-90-R Anxiety Scale scores (Table 1). In the AVD group, ten participants took antidepressants and three took anxiolytics; in the HC group three participants took

antidepressants and two took anxiolytics. Comparison between groups revealed non-significant differences in medication use (antidepressant: $X^2=1.71$, $df=1$ $p=.191$; anxiolytic: $X^2=.641$, $df=1$ $p=.726$).

Analysis of the distribution of anxiety symptoms in AVD and HC participants showed scores in the broad normal range (SCL-90-R Anxiety Scale T-scores: AVD mean=47, SD=7; HC mean=47, SD=10). In our group of 35 AVD and 22 HC participants, two HC participants and zero AVD participants endorsed anxiety symptoms more than 1.5 standard deviations above the normative mean.

Exploratory partial correlations between fractional anisotropy and SCL-90-R anxiety scores were computed in the AVD and HC groups (AVD findings presented in Table 2). Partial correlations were calculated first controlling for age. Statistically significant partial correlations between FA and anxiety scores were seen in a variety of subregions including the frontal and parietal lobes, the superior longitudinal fasciculus (SLF), and the cingulum bundle in the AVD group. In light of previous research with the current sample having suggested a high correlation between anxiety and depressive symptoms (Stillman et al., 2011), partial correlations were re-calculated including both age and depressive symptoms on the SCL-90-R as covariates. Findings revealed that the previously strong correlations in the parietal lobes and the SLF remained significant (parietal: $r=-.370$, $DF=31$, $p=.034$; SLF: $r=-.387$, $DF=31$, $p=.026$), while the previous correlations in the frontal lobes and cingulum bundle became non-significant ($p>.05$ for each). In addition, a significant correlation between occipital lobe FA and anxious symptoms emerged when controlled for depression ($r=-.385$, $DF=31$, $p=.027$). Identical partial correlations between FA and anxiety symptoms were non-significant in the HC group under both sets of statistical controls (p -values ranging from .10 to .96). There was no change in the association between global FA and anxiety when additionally controlled for two-year Framingham risk (before: $r=-.319$, $p=.066$; after: $r=-.263$, $p=.139$).

Discussion

Partial correlation analyses showed significant relationships between anxiety symptoms and white matter FA in the superior longitudinal fasciculus, as well as suggestive relationships in the frontal and parietal lobes and the cingulum bundle in older adults with atherosclerosis. Some of these relationships appear to be explained by depressive symptoms or more broadly, by negative affectivity. However there remained strong correlations in the AVD group even after statistical control for depressive symptoms. By comparison, there were no significant relationships identified between white matter health and anxiety scores in the older adults without atherosclerosis. This suggests that there may be specific relationships of white matter health with anxiety symptoms in older adults with vascular disease. SCL-90-R Anxiety Scale scores were within broad normal limits in both participant groups, suggesting that the current findings are unlikely to reflect effects of severe or diagnosable anxiety disorders. The findings in the current study suggest for the first time that there is a relationship between white matter health and anxious symptoms even in the absence of clinically diagnosable anxiety disorders.

Previous studies by Phan *et al.* (2009) and Kim and Whalen (2009) used DTI to show white matter relationships with diagnosed anxiety disorders in the uncinate fasciculus and immediately adjacent structures. The current study extends these previous findings to include anxious symptoms that fall within broad normal limits in vascular disease participants who are much older than previous studies have included. Due to the exploratory nature of the current study and the use of multiple comparisons, these findings need replication in a hypothesis-driven analysis.

The current study was limited by basic experimental issues including the use of a 1.5 Tesla MRI scanner, a limited participant sample, relatively few diffusion sensitizing gradients, and a relatively gross measure of anxious symptoms. The current study was also limited by its potential for confounding by other unmeasured attributes that could contribute significantly to the variance in anxious symptom manifestation. Future studies of this topic should aim to remedy the neuroimaging and measurement shortcomings of the current study and to assess the long-term effects of anxious symptoms on white matter and cardiovascular health through the use of a longitudinal design. However, experimental issues in the current study are much more likely to bias our findings toward the null hypothesis rather than leading to spurious significant findings.

The current study is well-situated to shed light on the relationship of white matter health with anxious symptoms for several reasons. First, individuals with vascular disease are known to have damage to white matter structures, (Pantoni, Garcia, & Gutierrez, 1996; Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987; Taylor et al., 2003), so there may be a greater range of FA values in this population than in others. Second, the current study examines anxiety as a continuous variable measured by the SCL-90-R, rather than defining groups based on the presence or absence of clinically diagnosed anxiety disorders. This technique may lend more sensitivity (though less specificity) to the analysis. Third, there have been no prior studies of anxious symptoms and white matter health in older adults with atherosclerosis. Studies of this type are critical because anxious symptoms are frequently overlooked in the elderly (Beekman et al., 1998), despite the fact that anxiety independently predicts future risk of cardiovascular events (Roest et al., 2010).

The causality of the observed relationship between anxiety and white matter health cannot be unequivocally established in the current study. It is possible that damage to white matter fibers causes miscommunication among the anxiety-controlling regions of the brain and the subsequent failure of multiple neurotransmitter systems (Kaloupek and Nutt, 1996; Malizia et al., 1998; Argyropoulos et al., 2004). However, it is also possible that the experience of anxiety over the lifetime triggers elevated sympathetic nervous system activation, increasing the risk for vascular disease and subsequent damage to white matter. The current findings of significant relationships only in participants with definitive atherosclerosis could be interpreted to support the latter possibility. We speculate that perhaps control participants without atherosclerosis were somewhat protected from the deleterious vascular effects of anxiety, and so do not exhibit the consequent damage to white matter. Further, the relationship between anxiety and white matter integrity was not altered by controlling for vascular risk factor burden using two-year Framingham risk, suggesting any damage to white matter due to anxiety may not be mediated through worsened vascular risk factors such as smoking, diabetes, hypertension, or dyslipidemia. However, larger and longitudinal studies of the relationship between anxiety and white matter health are necessary to clarify the direction of any causal relationships.

The current findings, if replicated, could have implications for both research and clinical practice. Future DTI studies in older adults with vascular disease should consider not only controlling for the effects of age, but also the possible effects of anxious symptoms and depressive symptoms, both of which appear to have strong relationships with white matter health and could represent significant sources of inter-participant variability. Clinically, anxiety and anxiety disorders have been associated with vascular disease, events, and mortality in observational studies (Fiedorowicz, et al., 2011; Moser et al., 2011; Roest, et al., 2010; Phillips et al., 2009, Davies et al., 2009). If anxiety is shown in future studies to cause damage to the vasculature, then there would be a strong rationale for better assessment of anxiety in primary care, as a part of cardiovascular risk stratification. Further clinical trials would be needed to test whether treatment of even subtle anxious symptoms could

significantly reduce the risk for these adverse cardiovascular outcomes as well as subsequent damage to the white matter.

In conclusion, we show for the first time that anxious symptoms within the normal range in older adults with atherosclerosis are associated with abnormalities in the cerebral white matter. Understanding of the mechanisms underlying anxious symptom manifestation in participants with vascular disease is critical, especially given the strong relationship of anxiety with elevated risk of adverse cardiovascular events. With greater understanding of these mechanisms, perhaps anxious symptoms can be identified and managed earlier, which in turn could improve cognition, brain health, and quality of life in individuals affected by vascular disease.

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Key points

- Anxious symptoms significantly correlate with white matter health and/or organization in participants with atherosclerosis, despite these participants' lack of diagnosed anxiety disorders.
- Significant relationships between anxious symptoms and fractional anisotropy were observed in the frontal lobes, parietal lobes, superior longitudinal fasciculus, and cingulum bundle.
- Relationships in the parietal lobes and superior longitudinal fasciculus remained significant after statistically controlling for depressive symptoms.

Figure 1.

Table 1

Demographics

	AVD Mean (SD)	HC Mean (SD)	DF	Statistic	p-value
Sample size	35	22			
Age	67.2 (7.4)	69.3 (7.4)	55	$t = 1.193$	.238
Education	14.8 (3.3)	14.0 (2.6)	55	$t = -1.061$	.293
Sex	40% F (14 f ; 21 m)	55% F (12 f ; 10 m) ⁺	1	$\chi^2 = 1.152$	.283
Handedness	(29 R ; 5 L ; 1 A) [*]	(18 R ; 3 L ; 1 A) [*]			Fisher's exact $p = 1.000$
SCL-90-R Anxiety	47 (7)	47 (10)	55	$t = -.191$	.849

Note: Age and education reported in years.

^{*} R = right handed, L = left handed, A = ambidextrous. Comparison of handedness uses Fisher's exact test. SCL-90-R Anxiety presented as sex-normed T-scores.

⁺ indicates significant difference on this parameter between the parent study and the subset of participants completing neuroimaging ($\chi^2 = 6.297$, $df = 1$, $p = .012$).

Table 2

Partial correlations of FA with Anxiety Scale Score from the SCL-90-R, in the AVD group.

Region	r	DF	p
Cerebrum	-.319	32	.066
Frontal	-.378	32	.028
Temporal	.137	32	.440
Parietal	-.398	32	.020
Occipital	-.296	32	.089
Superior Longitudinal Fasciculus	-.476	32	.004 *
Cingulum	-.367	32	.033
Uncinate Fasciculus	-.202	32	.252

Note: All partial correlations were statistically controlled for age and used two-tailed tests of significance. Non-significant correlations are presented for comparison purposes only. Anxiety data were first log-transformed to control for non-normality of distribution. FA values from bilateral cerebrum, frontal, and parietal regions were generated using GTRACT in-house software based on regions defined by Talairach and Tournoux (1988). FA values from SLF, Cingulum, and Uncinate regions were segmented using the Mori et al. (2005) white matter atlas.

AVD = atherosclerotic vascular disease group, HC = healthy comparison group, SLF = superior longitudinal fasciculus, Uncinate = uncinate fasciculus, DF = degrees of freedom. All FA measures presented include bilateral coverage of the region of interest.

* indicates comparisons that remain significant after adjustment for the false discovery rate (Benjamini and Hochberg, 1995).