ORIGINAL ARTICLE

Linking an Anxiety-Related Personality Trait to Brain White Matter Microstructure

Diffusion Tensor Imaging and Harm Avoidance

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Context: Emotional, cognitive, and behavioral response patterns underlying temperament and personality are established early and remain stable from childhood. Anxiety-related traits are associated with psychiatric disease and represent predisposing factors for various affective disorders, including depression and anxiety. Emotional processing relies on the structural and functional integrity of distributed neuronal circuits. Therefore, anxiety-related personality traits and associated increased risk of psychiatric disease might be rooted in structural variability in large-scale neuronal networks.

Objective: To test the hypothesis that individuals with high scores on the harm avoidance (HA) subscale of the Temperament and Character Inventory show reduced white matter (WM) structural integrity in distributed brain areas, including corticolimbic pathways involved in emotional processing and reappraisal.

Design: Healthy participants completed the Temperament and Character Inventory and underwent diffusion tensor imaging. Tract-based spatial statistics were used to examine the associations between HA and WM integrity across the brain.

Setting: Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway.

Participants: A total of 263 healthy adults aged 20 to 85 years recruited through newspaper advertisements.

Main Outcome Measure: Neuroimaging diffusivity indexes of brain WM microstructure, including fractional anisotropy, mean and radial diffusivity, and their associations with HA.

Results: In line with our hypothesis, increased HA was associated with decreased fractional anisotropy and increased mean and radial diffusivity in major WM tracts, including pathways connecting critical hubs in a corticolimbic circuit. There was no evidence of modulating effects of sex, degree of subclinical depression, alcohol consumption, general intellectual abilities, or years of education.

Conclusions: Increased HA is associated with decreased WM microstructure, implying that structural connectivity modulates anxiety-related aspects of personality. Decreased WM integrity reflects increased susceptibility to psychiatric disease and represents a promising biomarker that might ultimately facilitate targeted pharmacological and psychological interventions and treatment of disease.

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EMOTIONAL, COGNITIVE, AND behavioral response patterns underlying temperament and personality dimensions are established early and remain stable from childhood.[1-3] Anxiety-related personality traits are associated with and represent important predisposing factors for depression and anxiety-related disorders.[4-13] Emotional processing relies on the integrity and function of distributed neuronal brain circuits, including corticolimbic pathways.[14] Therefore, an intriguing hypothesis is that high scores on anxiety-related personality traits are caused by disruptions of such large-scale neuronal networks. The aim of the present study was to test the hypothesis that individuals with high scores on the harm avoidance (HA) subscale of the Temperament and Character Inventory by Cloninger et al[15] exhibit decreased quality of white matter (WM) microstructure as quantified by diffusion tensor imaging (DTI).

Recent advances in neuroimaging methods have made it possible to map the organization and strength of brain wiring in vivo. Diffusion tensor imaging is sensitive to the direction and degree of water displacement in biological tissues.[16,17] Diffusion in brain parenchyma is restricted

by cytoskeletal axonal elements such as the plasma membrane, microtubules, and myelin sheaths.[16,18,19] Because water diffuses more rapidly along than across the axon, DTI enables detailed depiction and quantification of the local organization of WM bundles wiring the cerebral neuronal circuitry.[20] Recent methodological advances have motivated a growing interest in disconnection models proposing that WM structural connectivity modulates symptoms in various psychiatric disorders.[21-25]

The multidimensional and cumulative nature of personality traits suggests that the integrity of WM pathways may be of particular importance. It was recently shown that pathways connecting the amygdala and ventromedial prefrontal cortex are related to variability in trait anxiety in healthy young adults.[26] Therefore, WM structural integrity may represent a promising biomarker in risk detection and ultimately facilitate targeted pharmacological and psychological interventions in prevention and treatment of psychiatric disease. However, existing evidence relating brain structure to personality and emotional processing is based on small samples, and large-scale studies with more power are needed.

The objective of this study was to test the relationships between WM integrity and HA in a large sample comprising 263 healthy adults. Functional neuroimaging investigations have demonstrated associations between amygdala reactivity to affective stimuli and mood and anxiety disorders, as well as normal variability in personality dimensions, including trait anxiety.[27] The amygdala is part of a corticolimbic neurocircuit and forms strong connections to other limbic structures, in particular the subgenual anterior cingulate cortex (sACC).[28] Functional coherence between the amygdala and medial prefrontal areas, including the sACC[29] and ventromedial prefrontal cortex,[30] has been shown to predict individual differences in trait anxiety. Based on the putative link between trait anxiety and the functional connectivity of corticolimbic circuits, including the sACC and amygdala, we hypothesized that the structural connectivity in WM pathways connecting critical hubs within this network would be negatively correlated with HA. Therefore, we hypothesized a negative relationship between HA and fractional anisotropy (FA) and a positive relationship between HA and mean diffusivity (MD) and radial diffusivity (RD) in these pathways.

Assuming that variability in HA is normally distributed and that biological psychopathologic susceptibility exists in healthy individuals, we restricted our analysis to a sample without psychiatric diagnoses to minimize the influence of accumulated secondary disease–related and environmental confounders. Because HA is a multidimensional trait comprising cognitive, emotional, and behavioral characteristics, it is likely that a wide array of cerebral circuits mediate the interindividual variability. To minimize type II errors, we did not restrict the analyses to a priori hypothesized regions and instead applied an unbiased whole-brain approach and strict nonparametric permutation–based corrections for multiple comparisons (type I errors).

METHODS

PARTICIPANTS

The sample was drawn from the ongoing longitudinal research project Cognition and Plasticity Through the Life-Span[31] coordinated by the Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo, Norway. Volunteers were recruited through newspaper advertisements and underwent a standardized health screening before enrollment to ensure that the study sample represented a healthy population. Participants were required to be right-handed Norwegian speakers older than 20 years, have vision and hearing that were normal or corrected to normal, and be free of neurological injuries or diseases known to affect nervous system functioning, including multiple sclerosis, previous symptoms of brain infarct or stroke, neurodegenerative disorders, and head injury with subsequent loss of consciousness or amnesia. Most important, individuals were excluded from participation if they (1) reported any previous or current psychiatric diagnoses or (2) had received any psychological or pharmacological treatment for psychiatric disease within the last 2 years. Because the screening procedure was not aimed at differential diagnostics or characterization of the incidence of different diagnoses in a population but rather at exclusion based on any prior or current psychiatric illness, we did not use a standardized psychiatric interview, such as the Mini-International Neuropsychiatric Interview[32] or Structured Clinical Interview for *DSM-IV* diagnostics.

The health screening interview was repeated at the time of the first assessment. In addition, all eligible participants were assessed for symptoms of depression using the Beck Depression Inventory (BDI), and participants scoring above 16 (aggregate consistent with a mild depression) were excluded. Self-reported weekly alcohol consumption (in standard units) was recorded and was used to test and control for mediating effects of alcohol use on the relationships between HA and DTI.

Magnetic resonance (MR) images were examined by a neuroradiologist and had to be deemed free of significant anomalies. One individual was excluded based on radiological findings. Complete data sets were available for 263 participants (150 female) aged 20 to 85 years (mean [SD] age, 50 [17.3] years). All participants scored above 26 on the Mini-Mental State Examination[33] and below 17 on the BDI.[34] The mean (SD) full-scale IQ (FIQ) as measured using the Wechsler Abbreviated Scale of Intelligence[35] was 114.7 (8.8) (range, 92-145).

The study was approved by the Regional Ethical Committee of Southern Norway and was performed in accord with the Declaration of Helsinki. Written informed consent was obtained from all individuals before examinations.

Based on the rigorous health screening procedure used in the present study, we believe it is unlikely that underlying psychiatric diseases influenced the reported findings. However, because we cannot ascertain that no such effects were present, we also performed outlier rejection analysis to test the robustness of the results (described in the "Statistical Analysis" subsection).

TEMPERAMENT AND CHARACTER INVENTORY

The Temperament and Character Inventory consists of 240 items comprising 7 dimensions, including 4 temperament scales (novelty seeking, HA, reward dependence, and persistence) and 3 character scales (self-directedness, cooperativeness, and self-transcendence).[15] We focused on the scale from the Tridimensional Personality Questionnaire (TPQ) for HA, known to be a stable trait with high heritability.[36-38] Harm avoidance describes a tendency to respond intensely to aversive stimuli,

leading to avoidance behavior. Individuals with high HA are characterized as cautious, tense, fearful, worried, shy, and easily fatigable. Individuals with low HA are characterized as confident, optimistic, carefree, outgoing, uninhibited, and energetic.[36,37] High HA is associated with affective disorders,[5,8,11,12,39] indicating a link between affective symptoms and a stable anxiety-related trait.

MR IMAGING ACQUISITION

A 12-channel head coil on a 1.5-T imaging system (Siemens Avanto; Siemens Medical Solutions, Erlangen, Germany) at Oslo University Hospital Rikshospitalet was used. A single-shot, twice-refocused, spin-echo echo planar imaging pulse sequence with 30 diffusion-sensitized gradient directions and the following parameters was used: repetition time/echo time, 8200 milliseconds/82 milliseconds; b value, 700 s/mm^2; voxel size, $2.0 \times 2.0 \times 2.0$ mm; and 64 axial sections. The sequence was repeated twice with 10 b values of 0 and 30 diffusion-weighted volumes per run. This sequence minimizes eddy current–induced distortions.[40]

DTI ANALYSIS

Analyses were performed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library.[41,42] Each volume was affine registered to the first volume with a b value of 0 using FMRIB's linear image registration tool[43] to correct for motion between images and eddy currents. After removal of nonbrain tissue,[44] FA, eigenvector, and eigenvalue maps were computed. The MD was defined as the mean of the 3 eigenvalues and RD as the mean of the second and third eigenvalues. Fractional anisotropy volumes were skeletonized and transformed into common space.[45,46] All volumes were warped to the FMRIB58_FA template using local deformation procedures performed by FMRIB's nonlinear image registration tool.[47,48] Excellent native-to-standard warping across individuals in a partly overlapping life span sample was previously demonstrated.[31] A mean FA volume of all individuals was thinned to create a mean FA skeleton representing the centers of all tracts. We thresholded and binarized the mean skeleton at FA exceeding 0.2 to minimize partial voluming at the boundaries between tissue classes, yielding a skeleton of 127 694 voxels. Individual FA values were warped onto this mean skeleton by searching perpendicular from the skeleton for maximum FA, further minimizing partial voluming.[45] The resulting tract-invariant skeletons were fed into voxelwise permutation–based statistics. Similar warping and analyses were used on MD and RD data, yielding diffusivity skeletons sampled from voxels with FA exceeding 0.2.

Binary masks based on The Johns Hopkins University (Baltimore, Maryland) atlas[49-51] were created as previously described.[52] As tracts of interest, we chose 2 commissural tracts (forceps minor and forceps major) and the following 8 bilateral WM tracts: anterior thalamic radiation, dorsal cingulum bundle, parahippocampal cingulum bundle, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and corticospinal tract. We segmented the medial parts of the skeleton corpus callosum (CC) into an anterior part that included the genu, a posterior part that included the splenium, and an intermediate part that included the body of the CC.

STATISTICAL ANALYSIS

Parametric associations between HA and age, BDI scores, FIQ, years of education, and alcohol consumption were tested using Pearson product moment correlation. Main effects of sex were assessed using independent-samples t test. We evaluated for global effects of HA on DTI indexes using linear regression analyses with sex as a fixed factor, age and HA as covariates, and the mean skeleton FA, MD, and RD as dependent variables. To rule out that individuals at either extreme end on the HA subscale disproportionately influenced the associations between HA and DTI, we performed an additional outlier rejection analysis on the global DTI analysis using a deleted residuals strategy. We omitted cases with ±2 studentized residuals in the main analysis and tested whether the relationships between HA and DTI remained in the reduced sample.

We performed voxelwise analyses using nonparametric permutation–based inference[53] as implemented in Randomize in the FMRIB Software Library.[54] Linear effects of HA on FA, MD, and RD were tested using general linear models that allowed age and sex to covary. Sex × HA interactions were tested by applying appropriate contrasts. Five thousand permutations were performed for each contrast. Statistical P-maps were thresholded at $P < .05$, corrected for multiple comparisons across space. Tractwise variability was delineated by extracting the mean values from significant voxels and then estimating effect sizes and the proportion of voxels showing effects per tract of interest.

Because associations between HA and WM microstructure may be modulated by depression, substance abuse, and self-medication,[55,56] we controlled for subclinical depression and substance abuse by including BDI scores and weekly alcohol consumption, respectively, as covariates in the linear regression analyses. To control for modulating effects of general intellectual abilities and years of education, we included FIQ and years of education as additional covariates in the analyses on regions of interest. Effect sizes of HA on DTI controlling for age, sex, BDI scores, FIQ, years of education, and alcohol consumption, respectively, are reported. Unique effects of BDI scores, FIQ, years of eduction, and alcohol consumption, age, and sex are also reported. We also calculated the difference in percentage explained variance (Δ% variance) of HA on DTI indexes after including BDI scores, FIQ, years of education, and alcohol consumption in the models.

To rule out the possibility that age-related processes modulated the results obtained in the main analysis and to establish the stability of effects in a younger subsample, we reanalyzed data from 131 individuals (76 female) who were younger than the median age (53 years) of the main sample; the subsample had a mean (SD) age 35.6 (10.7) years and a mean (SD) HA score of 0.31 (0.15) compared with 0.30 (0.16) in the total sample. Age was still included as a covariate.

RESULTS

RELATIONSHIPS BETWEEN HA AND AGE, SEX, FIQ, YEARS OF EDUCATION, BDI SCORES, AND ALCOHOL CONSUMPTION

Table 1 gives the sample characteristics for age, HA scores, education, MMSE, FIQ, BDI, and alcohol consumption per decade of age and in total. The HA score distribution is comparable to that reported in a previous study.[15] Female participants had higher HA scores than male participants ($t = 2.9$, $P < .01$). There was a trend toward greater alcohol consumption among male participants ($P = .05$) but no differences in age, FIQ, or BDI scores between the sexes.

Table 1. Sample Characteristics by Age Group, Including HA, Years of Education, MMSE Scores, FIQ, BDI Scores, and Alcohol Consumption

Age Group, y	No.	Age, Mean (SD), y	Female Sex, No. (%)	Mean (SD)					
				HA	Education	MMSE	FIQ	BDI	Alcohol
20-29	48	23.9 (2.5)	25 (52.1)	0.33 (0.14)	15.5 (1.9)[a]	NA	112.9 (7.0)	3.5 (3.2)	4.2 (4.1)
30-39	32	34.8 (2.8)	20 (62.5)	0.31 (0.17)	17.2 (2.4)	29.4 (0.7)	115.6 (8.2)	3.7 (3.7)	3.5 (3.7)
40-49	32	45.1 (3.1)	20 (62.5)	0.29 (0.61)	15.4 (2.1)	29.4 (0.6)	115.6 (7.4)	3.6 (4.2)	3.7 (2.6)
50-59	67	54.2 (2.7)	39 (58.2)	0.31 (0.15)	15.3 (2.2)	29.2 (0.8)	113.5 (7.2)	4.1 (3.2)	5.3 (3.8)
60-69	46	64.1 (2.8)	28 (60.9)	0.26 (0.16)	16.3 (3.4)	29.2 (0.7)	113.7 (10.8)	4.7 (3.9)	4.7 (4.8)
70-79	27	72.7 (2.4)	14 (51.9)	0.28 (0.17)	15.7 (3.1)	28.8 (1.2)	117.7 (11.0)	5.9 (4.3)	6.1 (5.9)
80-85	11	81.9 (1.7)	4 (36.4)	0.36 (0.15)	15.1 (2.5)	28.5 (0.8)	121.6 (11.7)	6.9 (4.4)	5.2 (3.7)
Total	**263**	50.0 (17.3)	**150** (57.0)	0.30 (0.16)	15.7 (2.6)	29.2 (0.8)[b]	114.7 (8.8)	4.4 (3.8)[c]	4.7 (4.2)[d]

Abbreviations: BDI, Beck Depression Inventory; FIQ, full-scale IQ; HA, harm avoidance; MMSE, Mini-Mental State Examination; NA, not available.
[a] Many individuals in the group aged 20 to 29 years were still attending college or university at the time of assessment. Completed years of education at the time of assessment is used in the present study.
[b] Scores on the MMSE were unavailable for participants younger than 30 years. In total, MMSE scores were available for 210 of 215 participants 30 years or older.
[c] Based on 260 participants.
[d] Based on 253 participants.

Table 2. Pearson Product Moment Correlations Among HA, Age, BDI Scores, FIQ, Years of Education, and Alcohol Consumption[a]

Variable	HA	Age	BDI	FIQ	Education
Age	−0.08				
BDI[b]	**0.43**	**0.20**			
FIQ	−0.01	0.12	0.02		
Education	−0.09	0.02	−0.10	**0.32**	
Alcohol consumption[c]	−0.09	*0.13*	0.07	*0.14*	0.04

Abbreviations: BDI, Beck Depression Inventory; FIQ, full-scale IQ; HA, harm avoidance.
[a] Boldface indicates $P<.01$; italic, $P<.05$.
[b] Based on 260 participants.
[c] Based on 253 participants.

Table 2 gives Pearson product moment correlations between variables. The HA scores were positively correlated with BDI scores ($r=0.43$, $P<.001$), indicating an association between subclinical depression and increased HA. We found no correlation between HA scores and age ($r=-0.08$), FIQ ($r=-0.01$), years of education ($r=-0.09$), or alcohol consumption ($r=-0.09$) ($P>.05$ for all). We found positive correlations between the following: age and BDI scores ($r=0.20$, $P<.01$), age and alcohol consumption ($r=0.13$, $P<.05$), FIQ and alcohol consumption ($r=0.14$, $P<.05$), and FIQ and years of education ($r=0.32$, $P<.01$).

RELATIONSHIP BETWEEN HA AND GLOBAL DTI

All analyses were performed using age and sex as covariates. We found a negative association between HA and the mean skeleton FA ($F_{259,1}=10.78$, $P<.001$), where HA accounted for 4.0% of the variance in FA. A negative association indicated lower FA with higher HA. Furthermore, we found a significant positive association between HA and global MD ($F_{259,1}=5.60$, $P<.05$), where HA accounted for 2.1% of the variance in global MD. Finally, we found a positive association between HA and RD ($F_{259,1}=7.97$, $P<.01$), where HA accounted for 3.0% of the variance in RD.

To rule out that statistically outlying individuals disproportionately influenced the associations, we omitted all cases with ±2 studentized deleted residuals from the main analysis and repeated the analysis on the reduced sample. The outlier rejection analysis revealed a significant effect of HA on FA ($F_{248,1}=13.84$, $P<.001$), MD ($F_{248,1}=4.89$, $P<.05$), and RD ($F_{247,1}=8.50$, $P<.01$), indicating associations robust to outlier rejection. In the robust analysis, FA, MD, and RD accounted for 5.3%, 1.9%, and 3.3% of the variance, respectively. Because the outlier rejection analysis indicated associations that were robust for statistical outliers, we performed the regional analysis on the full sample (described in the next subsection).

RELATIONSHIP BETWEEN HA AND REGIONAL DTI

Figure 1 shows the spatial distribution of voxels with linear effects of HA on DTI indexes ($P<.05$, corrected). Yellow (upper panel) and red (lower panel) indicate voxels showing negative (FA) and positive (MD and RD) associations with HA, corrected for multiple comparisons. We found widespread effects of HA on FA, MD, and RD. Forty-two percent of all skeleton voxels showed significant negative associations between HA and FA, and 15.4% and 36.3% showed positive associations with MD and RD, respectively. No significant sex × HA interactions on the DTI measures were found, indicating that the relationships between HA and WM integrity were not modulated by sex.

Figure 2 shows effects from the FA analysis highlighting critical hubs in the corticolimbic neurocircuitry. Significant bilateral effects are seen in amygdala-prefrontal pathways, in the sACC, and in the orbitofrontal WM.

Table 3 gives tractwise effect sizes (percentage explained variance) and proportion of voxels showing effects of HA on FA, MD, and RD. Total variance of FA explained by HA varied from 1.7% in anterior parts of the

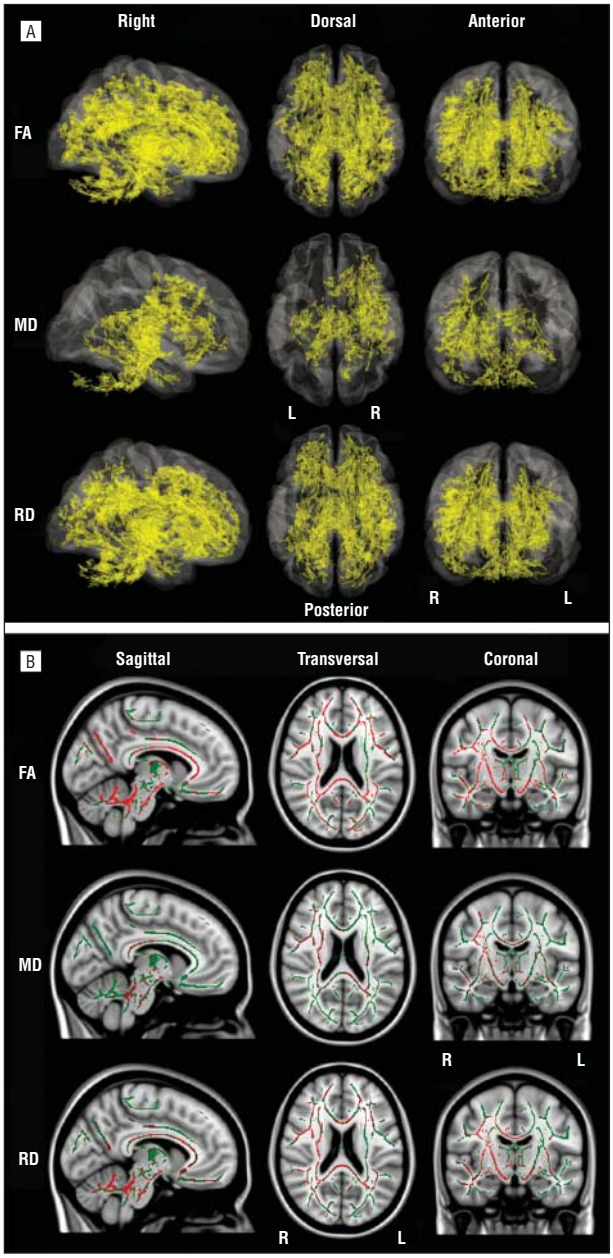

Figure 1. Harm avoidance and white matter microstructure. The spatial distribution of voxels shows significant relationships between harm avoidance and fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD). Linear effects of harm avoidance were tested voxelwise using general linear models while covarying for age and sex. In the upper panel, significant effects ($P<.05$, fully corrected for multiple comparisons across space) are shown as 3-dimensional renderings in right, dorsal, and anterior views. Yellow indicates voxels showing negative (FA) and positive (MD and RD) associations with harm avoidance. The lower panel shows the same effects superimposed on sagittal, transversal, and coronal sections of a template brain. Red indicates negative (FA) and positive (MD and RD) associations with harm avoidance. Widespread effects of harm avoidance on FA, MD, and RD were found. Green indicates the nonsignificant remains of the skeleton. R indicates right; and L, left.

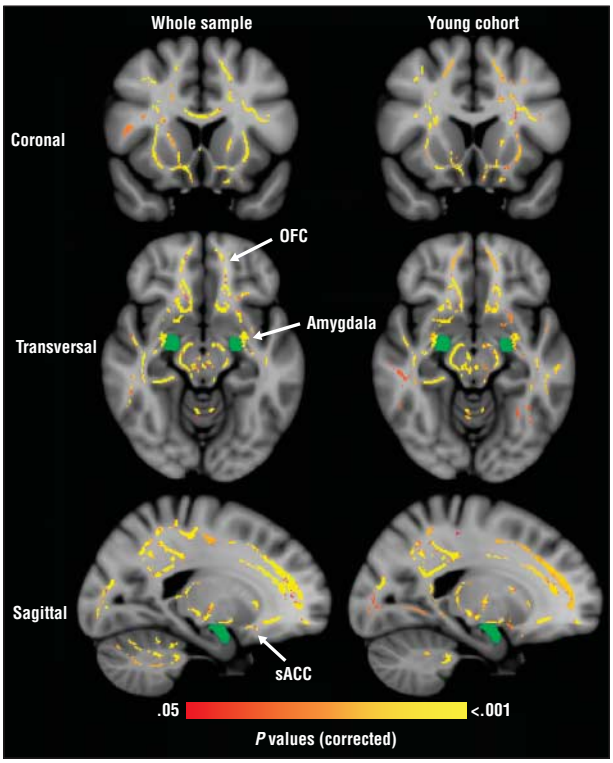

Figure 2. Corticolimbic white matter microstructure predicts harm avoidance. Shown is the spatial distribution of significant correlations between harm avoidance and fractional anisotropy in the total sample (left) and in the younger subsample (right). Shown are Montreal Neurological Institute coronal (y-coordinate, 141), transversal (z-coordinate, 60), and sagittal (x-coordinate, 109) sections of a Montreal Neurological Institute 1-mm template brain with significant voxels ($P<.05$, corrected) from the tract-based spatial statistics analysis superimposed in yellow-red. The amygdala from the Harvard-Oxford Subcortical Atlas provided by the Oxford Centre for Functional MRI of the Brain Software Library is indicated in green for anatomical reference. The spatial distribution of effects is highly similar across groups, and both reveal significant effects in pathways linking the amygdala and the subgenual anterior cingulate cortex (sACC), forming a corticolimbic pathway that is critical for emotional processing and reappraisal. OFC indicates orbitofrontal cortex.

CC to 9.8% in the left anterior thalamic radiation. Explained variance for the diffusivity values ranged from 1.8% in the posterior parts of the CC to 9.8% in the left corticospinal tract for MD and from 1.7% in the right parahippocampal cingulum bundle to 8.5% in the left corticospinal tract for RD.

REPLICATION OF EFFECTS IN A YOUNGER SUBSAMPLE

Tract-based spatial statistics revealed widespread significant ($P<.05$, corrected) associations between FA, MD, and RD across the brain closely resembling findings from the main analysis, which indicates stability of effects in a younger cohort. Figure 2 shows the spatial distribution of FA effects from the main analysis (left) and from the younger sample (right).

RELATIONSHIP BETWEEN HA AND DTI, COVARYING FOR SUBCLINICAL DEPRESSION, ALCOHOL CONSUMPTION, GENERAL INTELLECTUAL ABILITIES, AND YEARS OF EDUCATION

Results from tractwise linear regressions estimating the unique statistical contribution of HA, BDI scores, alcohol consumption, FIQ, years of education, sex, and age on FA, MD, and RD are given in eTables 1, 2, and 3 (available at http://archpsyc.ama-assn.org/). Because the aim of these analyses was to explore modulating effects of the vari-

Table 3. Tractwise Distribution of Effect Sizes and Proportion of Voxels Showing Significant Effects of HA on FA, MD, and RD[a]

	FA			MD			RD		
Variable	*F* Score	% Var	% Vox	*F* Score	% Var	% Vox	*F* Score	% Var	% Vox
Anterior thalamic radiation									
L	**28.2**	9.8	49.5	**26.1**	9.2	11.3	**23.2**	8.3	40.5
R	**19.5**	7.0	49.8	**22.6**	8.1	22.4	**18.7**	6.8	43.4
Corpus callosum									
Anterior	*4.3*	1.7	58.6	*4.9*	1.9	25.1	*5.2*	2.0	47.8
Body	**9.9**	3.7	89.8	**10.6**	3.9	66.3	**11.6**	4.3	88.0
Posterior	**6.7**	2.5	64.2	*4.8*	1.8	27.7	*5.3*	2.0	57.4
Dorsal cingulum bundle									
L	*5.9*	2.2	26.6	. . .	. . .	0.0	**9.5**	3.6	31.3
R	**8.2**	3.1	35.5	. . .	. . .	0.0	**9.5**	3.5	31.0
Parahippocampal cingulum bundle									
L	**15.4**	5.6	2.0	**9.8**	3.6	14.3	**7.3**	2.8	1.2
R	**11.0**	4.1	75.6	2.3	0.9	0.1	*4.5*	1.7	1.0
Corticospinal tract									
L	**21.4**	7.7	44.0	**28.1**	9.8	30.5	**23.9**	8.5	33.5
R	**17.7**	6.4	52.6	**16.3**	6.0	38.8	**16.5**	6.0	49.4
Forceps									
Major	**19.1**	6.9	41.8	**17.5**	6.3	9.6	**15.8**	5.8	31.1
Minor	**14.3**	5.3	59.8	**8.1**	3.1	6.3	**11.8**	4.4	48.4
Inferior fronto-occipital fasciculus									
L	**24.0**	8.5	48.6	**12.5**	4.6	6.7	**16.9**	6.1	37.2
R	**21.0**	7.5	52.3	**15.1**	5.5	28.2	**15.0**	5.5	49.5
Inferior longitudinal fasciculus									
L	**20.3**	7.3	21.9	**12.6**	4.7	5.7	**14.1**	5.2	11.7
R	**19.7**	7.1	42.5	**12.0**	4.4	25.2	**13.7**	5.0	45.2
Superior longitudinal fasciculus									
L	**20.7**	7.4	26.3	*6.7*	2.5	1.6	**14.2**	5.2	21.2
R	**24.4**	8.6	45.2	**12.8**	4.7	25.1	**15.0**	5.5	50.1
Uncinate fasciculus									
L	**19.4**	7.0	55.2	*5.7*	2.2	0.1	**13.5**	5.0	48.4
R	**15.9**	5.8	57.5	**10.2**	3.8	20.4	**11.2**	4.2	53.6

Abbreviations: FA, fractional anisotropy; HA, harm avoidance; L, left; MD, mean diffusivity; R, right; RD, radial diffusivity; % Var, percentage explained variance; % Vox, proportion of voxels.

[a]Boldface indicates $P<.01$; italic, $P<.05$, uncorrected. Effect sizes were estimated using multiple linear regression analyses that included age and sex as covariates.

ables on the relationships between HA and DTI, we only included tracts showing significant main effects of HA on DTI. For FA, the effect sizes were generally unaffected by including the additional covariates, and all tracts showed significant relationships between HA and FA. The Δ% variance ranged from –2.7 (forceps major) to 0.7 (anterior CC). The unique statistical contributions of BDI scores, alcohol consumption, FIQ, and years of education on FA were marginal in all tracts, and no effects reached statistical significance ($P<.01$, uncorrected). For MD, the amount of variance explained by HA shifted in some areas, with Δ% variance ranging from –5.1 (left corticospinal tract) to 0.6 (left superior longitudinal fasciculus). We found no significant relationships between MD and BDI scores, alcohol consumption, FIQ, or years of education. Tractwise effects of HA on RD were modestly altered, with Δ% variance ranging from –3.7 (left corticospinal tract) to 0.0 (left parahippocampal cingulum bundle). Including BDI scores, alcohol consumption, FIQ, and years of education as additional covariates removed the relationships between HA and RD in the right parahippocampal cingulum bundle only. There were no significant relationships between RD and BDI scores, alcohol consumption, FIQ, or years of education.

We found no evidence of relationships between DTI and BDI scores, alcohol consumption, FIQ, or years of education. Overall, covarying for subclinical depression ratings, alcohol consumption, general intellectual abilities, and years of education did not influence the relationship between HA and DTI indexes of WM microstructure.

COMMENT

We have demonstrated that increased HA is associated with decreased WM microstructure. In line with our hypothesis, increased HA was associated with decreased FA and increased MD and RD in widely distributed WM tracts, including corticolimbic pathways known to be particularly involved in emotional processing and reappraisal (ie, the sACC and pathways linking the sACC and the amygdala bilaterally).

The effects were independent of age and sex and could not be explained by subclinical depression, alcohol consumption, general intellectual abilities, or years of education. Furthermore, we have shown that the associations cannot be explained by the advanced mean age of

the total sample and are thus not influenced by age-related decline. This is also supported by the Mini-Mental State Examination scores, which were well within the normal range, and by the IQ scores, which were above average in all age groups, indicating a high-functioning sample. These findings suggest that the associations between WM microstructure and anxiety-related personality traits are established early in life, which fits with the notion that temperament and personality factors are shaped early and remain stable across the life span. Also, outlier rejection analysis indicated that the associations cannot be explained by individuals at either extreme end of the HA dimension, supporting the conjecture that reported effects are indeed reflecting normal variability in an anxiety-related trait and not pathologic states.

To our knowledge, this is the first large-scale study demonstrating associations between variability in HA and DTI-derived indexes of WM integrity. Results of previous neuroimaging studies[57-65] suggested a crucial role for neurocircuitry, including the amygdala, hippocampus, cingulate, and insula, in the pathogenesis of mood and anxiety disorders. Although some evidence suggests that similar structural variability is related to anxiety-related personality traits,[26,29,66-70] the nature of brain-temperament relationships in healthy individuals is poorly understood. Because emotional processing and reappraisal are assumed to be core cognitive modulators of anxiety-related personality traits, we expected a distribution of effects encompassing regions known to be important for emotional processing, including the corticolimbic system. Diffusion tensor imaging tractography has confirmed that the sACC forms part of a corticolimbic circuit that includes the amygdala.[28] Our analysis revealed significant correlations between HA and DTI in areas of the corticolimbic circuit acting as hubs in an amygdala-prefrontal network, including the sACC, amygdala-prefrontal projections, and the orbitofrontal cortex.

Microstructural properties in pathways linking the hubs in this network likely modulate the efficiency of neuronal synchronization, and decreased structural integrity might effectively shift or disrupt large-scale integration of the circuits involved in regulation of emotions and reappraisal of social and affective stimuli.[27,71] Therefore, decreased axonal integrity could lead to a relative decoupling of the critical nodes and subsequent functional disintegration of the network. Our findings thus provide a putative structural mechanism explaining that individuals with high-anxiety traits reappraise situations as more threatening and are more sensitive to social cues than are individuals with low-anxiety traits.[27] Consequently, individuals with high-anxiety traits may be at increased risk for developing psychiatric disease.

Previous DTI and functional MR imaging studies have shown associations between trait anxiety and connectivity of the amygdala and other corticolimbic regions, including the sACC and ventromedial prefrontal circuitry.[26,27,29,72] Furthermore, generalized social anxiety disorder is associated with reduced FA in the uncinate, a fiber tract connecting frontal regions to the amygdala and other limbic regions.[65] Therefore, it is likely that affective psychopathologic conditions are associated with reduced structural connectivity of the limbic pathways. Our results strengthen this hypothesis but extend the existing literature by demonstrating that the association between HA and WM integrity is not restricted to the limbic system. Structural properties of networks involved in emotional processing and reappraisal showed significant associations with HA, but effects were also seen in areas not primarily involved in emotional processing. The strongest effect sizes were observed in the anterior thalamic radiations, connecting thalamic nuclei and the frontal lobes, and in large association fibers (inferior fronto-occipital and right superior longitudinal fasciculus), wiring frontal, occipital, parietal, and temporal lobes.[50,73]

Previous structural MR imaging studies demonstrated associations between anxiety-related traits and reduced whole-brain volume,[67] reduced gray matter volume in the orbitofrontal regions[68] and occipital and parietal regions,[66] smaller hippocampus and reduced volume of the left anterior prefrontal cortex,[69] and larger right anterior cingulate surface area.[70] These findings pertain to the regional specificity of brain-temperament relationships and emphasize the importance of obtaining WM integrity measures throughout the brain. Further studies that include both healthy and clinical groups are needed to establish convergence in brain-temperament relationships across subclinical variability and clinical symptoms. Follow-up studies are warranted to establish whether individuals with high HA tend to develop psychiatric symptoms and whether WM integrity increases the predictive values with respect to psychopathologic conditions.

In accord with previous studies,[5,66,70,74] female participants had higher HA scores than male participants. Although a thorough investigation of possible sex interactions on emotional processing is beyond the scope of the present study, sex did not influence the relationship between HA and DTI indexes, which suggests that common neuronal circuits are responsible for individual differences in HA across the sexes.

The present analysis demonstrated effects of HA on FA, MD, and RD. Although interpretations should be made with caution without available histological data, this analysis suggests alterations in axonal density and membranes, as well as in the architecture of the insulating myelin sheaths, as candidate mechanisms underlying HA differences.[75-77] A fundamental question is to what degree the effects are established during early neurodevelopment or by later environmental factors, including toxic influences of stress-induced cortisol or substance abuse. The associations between WM integrity and HA were not explained by subclinical depression or alcohol consumption. This finding partly suggests that neurodevelopmental processes are of particular importance, which is in line with the notion that differences in temperament and personality are established early in life. However, it is likely that inventory measures, such as the HA subscale, reflect multidimensional hierarchies of emotional, behavioral, and cognitive variables and that the various environmental influences are interacting with genotypic and temperamental variance. Further studies investigating specific genotypes might help disentangle the mechanisms responsible for the relationships among anxiety-related personality traits, affective symptoms, and WM microstructure.

Our results demonstrate that HA is associated with WM microstructure in anatomically widespread brain areas, including corticolimbic pathways known to be strongly involved in emotional processing and reappraisal. These findings indicate that WM microstructural properties represent a fundamental key to understanding individual differences in anxiety-related temperament and personality and the associated increased risk of psychiatric disease.

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