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Associations between Anxiety and Depression Symptoms and Cognitive Testing and Neuroimaging in Type 2 Diabetes

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Structured Abstract

Aims—Anxiety, depression, accelerated cognitive decline, and increased risk of dementia are observed in individuals with type 2 diabetes. Anxiety and depression may contribute to lower performance on cognitive tests and differences in neuroimaging observed in individuals with type 2 diabetes.

Methods—These relationships were assessed in 655 European Americans with type 2 diabetes from 504 Diabetes Heart Study families. Participants completed cognitive testing, brain magnetic

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resonance imaging, the Brief Symptom Inventory Anxiety subscale, and the Center for Epidemiologic Studies Depression-10.

Results—In analyses adjusted for age, sex, educational attainment, and use of psychotropic medications, individuals with comorbid anxiety and depression symptoms had lower performance on all cognitive testing measures assessed ($p = 0.005$). Those with both anxiety and depression also had increased white matter lesion volume ($p=0.015$), decreased gray matter cerebral blood flow ($p=4.43 \times 10^{-6}$), decreased gray matter volume ($p=0.002$), increased white and gray matter mean diffusivity ($p = 0.001$), and decreased white matter fractional anisotropy ($p=7.79 \times 10^{-4}$). These associations were somewhat attenuated upon further adjustment for health status related covariates.

Conclusions—Comorbid anxiety and depression symptoms were associated with cognitive performance and brain structure in a European American cohort with type 2 diabetes.

Keywords

Type 2 diabetes; anxiety; depression; cognition; magnetic resonance imaging

Introduction

Type 2 diabetes is associated with accelerated age-related cognitive decline and elevated risk of Alzheimer's disease and vascular dementia (Lu, Lin et al. 2009; Reijmer, van den Berg et al. 2010). Studies have demonstrated differences in the brain in individuals with type 2 diabetes, including cerebral atrophy, declines in connectivity, and increased signs of small vessel disease, including infarcts and white matter hyperintensities (Biessels and Reijmer 2014). Individuals with type 2 diabetes also have increased incidence of depression (Mezuk, Eaton et al. 2008) and anxiety (Li, Barker et al. 2008), and individuals with depression and anxiety have been shown to have an increased incidence of type 2 diabetes as well (Mezuk, Eaton et al. 2008; Farvid, Qi et al. 2014). Symptoms of depression are also associated with increased incidence of dementia and accelerated declines in sensitive cognitive testing measures in adults with type 2 diabetes (Sullivan, Katon et al. 2013; Katon, Pedersen et al. 2015). However, few studies have assessed both anxiety and depression symptoms and their contribution to poorer performance on cognitive testing and differences in neuroimaging measures in individuals with type 2 diabetes.

These relationships were examined in the Diabetes Heart Study (DHS), a single-site, family-based study enriched for type 2 diabetes which assessed cognitive performance and brain magnetic resonance imaging (MRI) in the ancillary DHS-Mind study from 2008–2013. Symptoms of anxiety and depression were also assessed. We hypothesized that anxiety and depression symptoms would be associated with poorer performance on cognitive tests and with neuroimaging differences observed in type 2 diabetes. Several studies reveal that anxiety and depression are often comorbid diagnoses (Kessler, Gruber et al. 2008; Farvid, Qi et al. 2014), and we hypothesized that individuals with comorbid anxiety and depression symptoms would demonstrate poorer performance on cognitive testing and greater differences in neuroimaging than those with depression or anxiety symptoms alone.

Subjects, Materials, and Methods

Study Design and Sample

Participants in the DHS were recruited from outpatient internal medicine and endocrinology clinics and from the community from 1998 through 2005 in western North Carolina. Siblings affected by type 2 diabetes without advanced renal insufficiency (serum creatinine concentrations >2.0 mg/dl) were recruited, along with additional non-diabetic siblings. Ascertainment and recruitment have been described in detail (Bowden, Cox et al. 2010). Type 2 diabetes was defined as diabetes developing after the age of 35 years treated with changes in diet and exercise and/or oral agents in the absence of initial treatment solely with insulin and without historical evidence of diabetic ketoacidosis.

DHS-Mind examinations included interviews for medical history and health behaviors, anthropometric measures, fasting blood draws, assessment of resting blood pressure, and assessment of anxiety and depression symptoms. All study protocols were approved by the Institutional Review Board at Wake Forest School of Medicine, and all study procedures were completed in accordance with the Declaration of Helsinki. Participants provided written informed consent prior to participation. The current analyses were limited to individuals with type 2 diabetes, including 337 original DHS participants and 318 new DHS-Mind participants. Original DHS participants were examined on average 6.6 ± 1.4 years after their first study visit. Recruitment criteria in new participants were the same as in the original DHS, barring the requirement that participants have a type 2 diabetes-affected sibling. Diabetes diagnosis was confirmed for all participants by review of medications and measurement of fasting glucose and glycated hemoglobin (HbA_{1C}) at the exam visit.

Cognitive Testing

The cognitive testing measures assessed in the DHS-Mind study have been described (Hugenschmidt, Hsu et al. 2013; Cox, Hugenschmidt et al. 2014). Briefly, they included the Modified Mini-Mental State Examination (3MSE), a global test of global cognitive function often used clinically, the Digit Symbol Substitution Task (DSST), a test where participants match numbers and symbols to assess processing speed and working memory, the Stroop Task, an assessment of executive function (reported as the response time difference between subtest 2 and subtest 3 with the number of errors from each subtest added to the time scores), the Rey Auditory-Verbal Learning Task (RAVLT), where participants are asked to recall word lists (reported as the total words recalled across five trials), and tests for Phonemic Fluency (reported as the total words generated for F, A, and S) and Semantic Fluency (reported as the total words generated for the categories kitchen and animals). Subjects were not excluded for 3MSE scores or other indices of cognitive function indicative of mild cognitive impairment or dementia. Colorblind individuals were excluded from the Stroop Task. For the 3MSE, DSST, RAVLT, and Phonemic and Semantic Fluency, higher scores indicate better cognitive performance, but for the Stroop Task lower scores indicate better performance.

Neuroimaging

MR image acquisition—MR imaging was performed on two 1.5T GE EXCITE HD scanners (n=373 for one 1.5T scanner, n= 202 for the other) with twin-speed gradients using a neurovascular head coil (GE Healthcare, Milwaukee, WI), with imaging in a small subset of participants (n= 7) performed using a 3.0T GE scanner. Neuroimaging protocols have already been described in detail (Raffield, Cox et al. 2015).

Briefly, for the volumetric measures, structural T1 images were segmented and native space gray matter volume (GMV), white matter volume (WMV), and intracranial volume (ICV) (gray matter + white matter + cerebrospinal fluid) were determined using the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>) automated segmentation procedure. Diffusion tensor imaging (DTI) scalar metrics, including fractional anisotropy (FA) and mean diffusivity (MD) in the gray and white matter, were computed using FSL (Jenkinson, Beckmann et al. 2012) and the Diffusion Tensor Imaging ToolKit (DTI-TK) (<http://www.nitrc.org/projects/dtitk>) as previously described (Raffield, Cox et al. 2015). Cerebral blood flow perfusion images were generated using a previously described fully automated data processing pipeline (Maldjian, Laurienti et al. 2008), allowing derivation of gray matter cerebral blood flow (GMCBF). White matter lesion segmentation was performed using the lesion segmentation toolbox (LST) for SPM8 at a threshold (k) of 0.25, which has been previously validated in DHS-Mind (Maldjian, Whitlow et al. 2013). The total white matter lesion volume (WMLV) measure used in these analyses was determined by summing the binary lesion maps and multiplying by the voxel volume.

In total, eight neuroimaging measures were analyzed in this study: GMV, WMV, WMLV, GMCBF, white matter mean diffusivity (WMMD), gray matter mean diffusivity (GMMD), white matter fractional anisotropy (WMFA), and gray matter fractional anisotropy (GMFA). All analyses of GMV, WMV, and WMLV included ICV as a covariate.

Assessment for Anxiety and Depression

Anxiety was assessed using the Brief Symptom Inventory (BSI) Anxiety subscale, previously used to reliably assess anxiety symptoms in older individuals (Abu Ruz, Lennie et al. 2010; Khalil, Hall et al. 2011). Participants scoring >8 on this subtest were classified as having significant anxiety symptoms in these analyses. Depression was assessed using the Center for Epidemiologic Studies Depression (CES-D) 10 item measure, which has good sensitivity and specificity in adults with diabetes. Participants scoring >10 on the CES-D 10 item measure were classified as having significant depression symptoms. A total of 655 European Americans with type 2 diabetes (from 504 families) completed both measures and were included in analyses. Self-report of antianxiety (for example benzodiazepines) or antidepressant (for example SNRIs and SSRIs) medication use was adjusted for in analyses but was not considered for definition of anxiety/depression symptom groupings, as some medications could have been prescribed for either anxiety or depression symptoms or for other purposes, such as migraine headaches or insomnia (Buscemi, Vandermeer et al. 2007; Banzi, Cusi et al. 2015). As a supplementary analysis, CES-D and BSI Anxiety scores were analyzed as continuous measures.

Statistical Analysis

Continuous variables were transformed as necessary to approximate normality. Relationships between anxiety/depression symptom groupings (depression only, anxiety only, both anxiety and depression, or neither anxiety nor depression, the reference group) and cognitive testing and neuroimaging were examined using marginal models with generalized estimating equations. The models account for familial correlation using a sandwich estimator of the variance under exchangeable correlation. The overall 3 degrees of freedom (df) test was calculated using a type III test and used to assess whether there were any significant differences between the four anxiety and depression symptom groups. Nominal statistical significance was accepted at $p < 0.05$. Associations were adjusted for covariates including age, MRI scanner, sex, use of antidepressant medications, use of anxiolytic medications, BMI, educational attainment (less than high school, high school, greater than high school), HbA_{1C}, pulse pressure, prior history of cardiovascular disease (CVD) events, and ICV as indicated. An exploratory supplemental analysis of 93 participants unaffected by type 2 diabetes was also performed using similar methods. All analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

Results

Table 1 summarizes the demographic and clinical characteristics of study participants, stratified by anxiety and depression symptom groupings. The mean diabetes duration in the cohort was 15 ± 7.9 years. Most individuals were overweight or obese with a high prevalence of hypertension and prior CVD events, as expected for a type 2 diabetes affected cohort.

We first assessed the relationships between anxiety and depression symptoms and performance on cognitive testing in models adjusted for age, sex, use of antidepressant and anxiolytic medications, and educational attainment. Significant differences in cognitive scores between the anxiety and depression groups were observed for all tests except Phonemic Fluency ($p = 0.006$). Individuals with comorbid anxiety and depression displayed the lowest cognitive testing scores as compared with the reference group of individuals without anxiety or depression symptoms; these individuals had significantly poorer performance on all tests ($p = 0.005$). Individuals with depression alone demonstrated a trend towards poorer performance on all cognitive testing measures assessed except Phonemic Fluency ($p = 0.027$). Few significant associations, other than a nominal association with poorer performance on the RAVLT ($p = 0.011$), were observed for those with only anxiety symptoms (Table 2). Additional adjustment for health status, including HbA_{1C}, BMI, pulse pressure, and history of CVD, which might mediate the observed associations, attenuated, but did not eliminate, the observed relationships with comorbid anxiety and depression symptoms ($p = 0.046$ for worse performance on all cognitive tests). Adjustment for the health status covariates strengthened association between anxiety symptoms alone and performance on the RAVLT ($p = 0.009$) and revealed a nominal association with performance on the Stroop Task ($p = 0.030$). Associations with depression symptoms alone were attenuated with adjustment for health status ($p = 0.026$ for 3MSE, Stroop Task, RAVLT, and DSST) (Supplementary Table 1).

Associations between anxiety and depression symptoms and neuroimaging measures, including brain volumes, white matter lesion volume, fractional anisotropy and mean diffusivity measures, and cerebral blood flow, were subsequently assessed to determine whether the observed associations with cognitive performance were reflected on brain MRI. Nominally significant differences between the anxiety and depression groupings were observed for WMMD, GMMD, WMFA, GMCBF, WMLV, and GMV. Comorbid anxiety and depression symptoms were associated with lower WMFA and higher WMMD ($p = 7.79 \times 10^{-4}$) (Table 3). Anxiety and depression symptoms were also associated with lower GMCBF ($p = 4.43 \times 10^{-6}$) and higher WMLV ($p = 0.015$). These relationships were not observed in individuals with anxiety alone or depression alone. Higher GMMD and lower GMV was observed in those with depression alone and those with anxiety and depression symptoms ($p = 0.040$), with higher GMMD also observed in those with anxiety symptoms alone ($p = 0.002$) (Table 3). In models further adjusted for health status, associations were attenuated but remained significant for comorbid anxiety and depression symptoms with GMMD, WMMD, WMFA, GMCBF, WMLV, and GMV ($p = 0.041$) (Supplementary Table 2).

In contrast to these results in individuals with type 2 diabetes, few significant associations with cognitive performance or neuroimaging measures were observed in a small cohort of unaffected individuals ($n = 93$), with no significant results from type III tests (Supplementary Tables 3 and 4). Results in unaffected individuals are difficult to interpret due to the very small sample size, however. When analyzing CES-D and BSI Anxiety scores as continuous measures, with the exception of both the CES-D and BSI Anxiety scores and Phonemic Fluency and the BSI Anxiety scores and the DSST, associations were observed with lower performance on all cognitive tests ($p = 0.040$), though these associations were somewhat attenuated upon further adjustment for health status covariates (Supplementary Table 5). However, for the neuroimaging measures, the only associations observed were for the CES-D scores with GMV, WMLV, and GMMD ($p = 0.011$) (Supplementary Table 6).

Discussion

Individuals with type 2 diabetes have an accelerated rate of mild age-related cognitive decline and increased incidence of dementia. There is increasing interest in factors, for example poorer glycemic control, dyslipidemia, and hypertension (Bryan, Bilello et al. 2014; Williamson, Launer et al. 2014), which may contribute to cognitive and brain anatomic differences in type 2 diabetes. Diabetic individuals have higher rates of depression and anxiety, which may also contribute to cognitive decline. The present analyses in adults with type 2 diabetes replicated the previously reported association of depression symptoms with poorer performance on tests of cognitive function (Sullivan, Katon et al. 2013) but identified stronger associations with cognitive testing performance in individuals with comorbid anxiety and depression symptoms as opposed to depression symptoms alone. Poorer performance on cognitive tests was also reflected by associations with a number of neuroimaging measures, including associations with gray matter volume, white matter lesion volume, fractional anisotropy, mean diffusivity, and cerebral blood flow. These results highlight the importance of assessing both anxiety and depression symptoms as potential risk factors for cognitive decline in individuals with type 2 diabetes.

Consistent associations between anxiety and depression symptoms and poorer performance on all cognitive tests were observed, including tests assessing global cognitive function, processing speed, and executive function; associations with depression symptoms alone were also observed for most cognitive measures. Previous studies in type 2 diabetes detected poorer performance on cognitive testing and higher incidence of dementia in those with depression symptoms (Sullivan, Katon et al. 2013; Katon, Pedersen et al. 2015). The impact of anxiety and comorbid anxiety and depression symptoms on cognitive performance is less clear in type 2 diabetes; however, anxiety symptoms in older adults are associated with poorer cognitive performance (Pietrzak, Maruff et al. 2012). The present results suggest that it is important to assess both anxiety and depression symptoms in individuals with type 2 diabetes. We consistently found that comorbid anxiety and depression symptoms were more strongly associated with lower cognitive performance than either anxiety or depression symptoms alone. A prior analysis of cognitive testing measures in the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes Study found that self-reported depression symptoms were associated with accelerated cognitive decline in individuals with type 2 diabetes and that this did not appear to be mediated by poor glycemic control, blood pressure, or lipids (Sullivan, Katon et al. 2013). Similarly, we found that even after adjustment for health status, depression and anxiety symptoms were associated with lower performance on cognitive testing and differences in neuroimaging.

Associations of depression and anxiety with poorer cognitive performance may be confounded by differences in motivation and other factors (Austin, Mitchell et al. 2001). As such, we note that the current associations observed with cognitive testing measures were further reflected in concurrently performed neuroimaging studies. Few existing neuroimaging studies of depression and anxiety symptoms focused on type 2 diabetes; however, many of the associations in the present report mirror those in general populations. Increased white matter lesion volume, reflective of increased small vessel disease in the brain (Biessels and Reijmer 2014), was seen in those with comorbid anxiety and depression. Depression has previously been associated with elevated white matter lesion volume independent of other risk factors (e.g., diabetes and CVD) (Taylor, MacFall et al. 2005). The associations observed with higher MD and lower FA, generally reflective of decreases in fiber integrity and brain connectivity, suggests cerebral microstructural differences exist in type 2 diabetes with anxiety and depression. A previous analysis of older adults with atherosclerosis found reduced WMFA in those with increased anxiety (Bijanki, Stillman et al. 2013), and differences in white matter microstructure, as reflected in FA and MD measures, have also been reported in late-life depression (Shimony, Sheline et al. 2009). Reductions in GMV have been observed in late life depression (Sexton, Mackay et al. 2013) as well as anxiety (Moon, Kim et al. 2014). We saw lower GMV in this type 2 diabetes affected cohort in participants with depression alone and comorbid anxiety and depression. Lower GMCBF was also present in individuals with anxiety and depression symptoms; positron emission tomography studies reported associations between depression and reduced cerebral blood flow (Dotson, Beason-Held et al. 2009). While neuroimaging associations were somewhat attenuated upon adjustment for health status, residual associations indicate that anxiety and depression symptoms may be important contributors to variation in cerebral anatomy in individuals with type 2 diabetes independent from established risk factors.

Many factors may mediate links between type 2 diabetes, anxiety, depression, and cognition and neuroimaging phenotypes. Anxiety and depression are thought to be important risk factors for vascular disease (Scherrer, Chrusciel et al. 2010; Brunner, Shipley et al. 2014), which could be an important mediator of the observed differences in cognition and brain anatomy given the well-established link between vascular disease and risk of cognitive impairment (Warsch and Wright 2010; Hugenschmidt, Hsu et al. 2013). However, some reports indicate that depression is an independent risk factor for cognitive impairment adjusting for vascular disease (Barnes, Alexopoulos et al. 2006), and we observed associations between anxiety and depression with cognitive performance and neuroimaging in models adjusted for prior CVD. The potential mediating effects of vascular disease on the observed relationships between anxiety and depression symptoms and cognition and neuroimaging measures was also explored in a subset of the DHS-Mind cohort (n=322) who were affected by type 2 diabetes and had both anxiety and depression data and measures of coronary artery calcified plaque, a measure of subclinical CVD and a powerful predictor of CVD events (Kramer, Zinman et al. 2013). Addition of coronary artery calcification to regression models did not substantively change associations of anxiety and depression with poorer performance on cognitive tests and increased age-related differences in neuroimaging measures in this analysis, suggesting associations of anxiety and depression observed here are not primarily mediated by vascular disease burden. Other factors may also play a role in the links between depression and anxiety and cognition and neuroimaging measures in individuals with type 2 diabetes. Symptoms of depression are associated with poorer diabetes self-care, including lack of adherence to medications, diet, and exercise (Gonzalez, Safren et al. 2008). Depression, anxiety, diabetes, and dementia are all associated with systemic inflammation (Pitsavos, Panagiotakos et al. 2006; Leonard 2007; Stuart and Baune 2012).

Studies have also linked perturbations in insulin signaling to both cognitive impairment and increases in anxiety and depression (Kleinridders, Ferris et al. 2014). Strengths of this study include concurrent assessment of multiple cognitive and neuroimaging phenotypes, the large sample of type 2 diabetes affected participants, type 2 diabetes diagnoses confirmed by assessment of fasting glucose and HbA_{1C} and review of medications, and assessment of both anxiety and depression symptoms, as opposed to only depression. Limitations include the lack of strict correction for multiple comparisons; however, given the consistency of the associations between anxiety and depression, poorer cognitive performance, and increased age-related differences in the brain, we felt that nominal associations were of interest. Self-reported anxiety and depression data are not equivalent to a clinical diagnosis, and we lacked data on dose and duration of antidepressant and antianxiety treatment or participation in psychotherapy, so we were unable to adjust for those factors. Differences in diet and exercise patterns between depressed and non-depressed participants not reflected in measures of glycemic control, BMI, and CVD could also be a source of confounding. MRI data were not available for all participants due to a variety of exclusions (pacemakers, claustrophobia, etc.), and some of these exclusions may be associated with anxiety and depression symptoms. Lack of a large cohort of controls unaffected by type 2 diabetes is also a limitation; exploratory analyses of cognitive testing and neuroimaging measures were undertaken in a small cohort of DHS siblings unaffected by type 2 diabetes (n=93).

(Supplementary Tables 3 and 4); however, few firm conclusions could be drawn given the small sample size. Comparison of associations with anxiety and depression symptoms in type 2 diabetes versus unaffected individuals is an important goal for future studies. We also do not have data on complications of diabetes such as neuropathy and hypoglycemic events that may modify the association of anxiety and depression symptoms with cognitive testing and neuroimaging measures (Chiu, Ho et al. 2015). Our cross-sectional analysis is also not able to resolve the direction of causality or potential longitudinal changes for the impact of anxiety and depression on cognitive decline and type 2 diabetes.

In summary, in a cohort of individuals with type 2 diabetes, anxiety and depression symptoms were evaluated for associations with cognitive performance and brain imaging. Consistent associations of comorbid anxiety and depression, as well as depression symptoms alone, were detected with poorer cognitive performance; however, associations were strongest for comorbid anxiety and depression, which were also associated with increased white matter lesion volume, decreased gray matter volume and cerebral blood flow, and higher mean diffusivity and lower fractional anisotropy. These results highlight the importance of assessing anxiety and depression symptoms as potential contributors to cognitive decline in adults with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic characteristics of Diabetes Heart Study participants with type 2 diabetes stratified by anxiety and depression scores.

	Neither Depression nor Anxiety (n=461)		Depression Only (n=104)		Anxiety Only (n=33)		Anxiety and Depression (n=57)		N
	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	
Age (years)	66.8 ± 9.7	67 (38 – 93)	62.5 ± 9.8	62 (41 – 84)	66.4 ± 8.0	65 (48 – 83)	61.4 ± 10.2	62 (38 – 81)	655
Gender (% female)	47.51		60.58		63.64		52.63		655
BMI (kg/m ²)	32.5 ± 6.7	31 (15 – 59)	34.8 ± 6.3	34 (22 – 52)	33.1 ± 6.1	32 (23 – 48)	35.3 ± 6.5	34 (25 – 55)	654
Smoking (current or past)	54.34		51.96		45.45		66.67		652
Hypertension	88.5		88.46		90.91		82.46		655
Pulse Pressure	58.7 ± 16.5	57 (18 – 124)	55.5 ± 14.5	56 (25 – 93)	60.5 ± 13.7	60 (35 – 92)	54.9 ± 16.2	54 (17 – 92)	655
Self-reported history of prior CVD	33.56		38		43.75		57.69		628
Diabetes Duration (years)	15.1 ± 8.1	13 (0.4 – 45)	14.7 ± 6.6	14 (2 – 33)	17.6 ± 8.0	17 (4 – 45)	13.3 ± 7.3	13 (2 – 35)	623
Glucose (mg/dL)	145.0 ± 50.5	135 (40 – 389)	161.2 ± 71.3	145 (56 – 408)	149.5 ± 54.3	131 (60 – 319)	158.5 ± 66.7	138 (57 – 345)	650
Hemoglobin A _{1c} (%)	7.4 ± 1.4	7 (2 – 13)	7.9 ± 1.7	8 (5 – 15)	7.6 ± 1.4	7 (6 – 12)	8.0 ± 1.6	8 (6 – 13)	650
Hemoglobin A _{1c} (mmol/mol)	57 ± 15	54 (–3 – 122)	63 ± 19	60 (33 – 138)	60 ± 16	55 (39 – 103)	64 ± 17	58 (41 – 115)	650
Anti-diabetic Medication *	84.4		83.7		75.8		77.2		654
Cholesterol-lowering Medication	51.6		52.9		54.8		53.9		629
Anti-hypertensive Medication	68.1		68.3		75.8		56.1		655
Level of educational attainment: Less than high school	8.9		18.5		15.2		21.1		653
Level of educational attainment: High school	44.4		51.5		45.5		47.4		653
Level of educational attainment: Greater than high school	46.7		30.1		39.4		31.6		653
Antidepressant medication	10.0		12.5		24.2		12.3		655
Antianxiety medication	3.9		5.8		9.1		7.0		655
Either antidepressant or antianxiety medication	12.6		14.4		27.3		14.0		655
Digit Symbol Substitution Task	52 ± 16	52 (14, 106)	49 ± 15	49 (13, 106)	52 ± 15	52 (22, 81)	46 ± 16	45 (16, 89)	652
Stroop Task	33 ± 18	28 (7, 151)	35 ± 22	29 (5, 147)	35 ± 17	32 (9, 81)	38 ± 17	34 (13, 87)	651
Rey Auditory-Verbal Learning Task	41 ± 10	42 (11, 65)	40 ± 10	39 (16, 64)	40 ± 11	37 (22, 60)	39 ± 10	39 (20, 61)	655
Modified Mini-Mental State Examination	92 ± 7	93 (62, 100)	91 ± 7	92 (69, 100)	90 ± 7	91 (74, 100)	90 ± 7	91 (71, 100)	655

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	Neither Depression nor Anxiety (n=461)		Depression Only (n=104)		Anxiety Only (n=33)		Anxiety and Depression (n=57)		N
	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	Mean ± SD or %	Median (range)	
Semantic Fluency	32 ± 8	31 (11, 69)	30 ± 9	30(11,58)	31 ± 11	29 (12, 55)	27 ± 7	27 (11, 49)	654
Phonemic Fluency	31 ± 11	30 (3, 66)	30 ± 11	30 (5, 59)	29 ± 13	31 (7, 55)	26 ± 12	25 (9, 63)	654
Gray Matter Fractional Anisotropy	0.188 ± 0.023	0.193 (0.136, 0.264)	0.193 ± 0.026	0.197 (0.138, 0.28)	0.195 ± 0.026	0.193 (0.148, 0.251)	0.185 ± 0.022	0.188 (0.148, 0.227)	528
White Matter Fractional Anisotropy	0.341 ± 0.026	0.342 (0.261, 0.4)	0.343 ± 0.027	0.346 (0.281, 0.419)	0.337 ± 0.023	0.333 (0.298, 0.377)	0.331 ± 0.022	0.326 (0.291, 0.389)	528
Gray Matter Mean Diffusivity	1.08 ± 0.089	1.08 (0.806, 1.32)	1.065 ± 0.085	1.056 (0.895, 1.361)	1.041 ± 0.069	1.039 (0.888, 1.164)	1.087 ± 0.091	1.074 (0.919, 1.328)	528
White Matter Mean Diffusivity	0.789 ± 0.042	0.786 (0.694, 0.949)	0.785 ± 0.045	0.774 (0.709, 0.926)	0.797 ± 0.038	0.797 (0.71, 0.894)	0.798 ± 0.041	0.79 (0.708, 0.904)	528
Gray Matter Cerebral Blood Flow	33.41 ± 10.97	32.61 (1.19,74.76)	33.12 ± 11.06	32.13 (11.94, 65.97)	32.55 ± 10.98	32.11 (6.47, 50.78)	27.5 ± 10.68	28.35 (4.89, 59.32)	529
Total White Matter Lesion Volume	4.29 ± 8.31	1.63 (0,103.28)	4.3 ± 9.11	1.38 (0, 65.57)	5.51 ± 7.94	1.89 (0, 31.98)	6.62 ± 11.75	1.56 (0, 59.57)	567
Gray Matter Volume	526.5 ± 54.4	524.6 (373.2,709.1)	517.7 ± 53.5	517.3 (392.2, 666.2)	527.2 ± 59	531.3 (406.5, 635.4)	528.3 ± 49.9	537.1 (401.2, 626.2)	582
White Matter Volume	576.4 ± 71.2	574.1 (402.1,815.1)	558.4 ± 71.3	548.5 (430.2, 732.2)	557.7 ± 64.2	555.8 (461, 711.7)	575.7 ± 64.2	559.1 (460.6, 714.9)	582
Total Intracranial Volume	1368.6 ± 134.5	1363.6 (1027.9,1752)	1330.9 ± 140.4	1322.4 (1027.6, 1627.4)	1337.9 ± 149.1	1340.7 (1064.4, 1697.9)	1377.4 ± 130.5	1377.4 (1081.3, 1670.8)	582

* either oral hypoglycemic medications or insulin

Table 2

Associations between cognitive testing variables and depression symptoms only, anxiety symptoms only, and anxiety and depression symptoms (β value and 95% confidence interval (CI)).

	Overall 3 df test	Depression Only (n=104)		Anxiety Only (n=33)		Anxiety and Depression (n=57)	
		β value (95% CI)	p-value	β value (95% CI)	p-value	β value (95% CI)	p-value
Phonemic Fluency	0.066	-0.504 (-2.84, 1.83)	0.672	-1.36 (-5.13, 2.40)	0.478	-4.28 (-7.26, -1.31)	0.005
Semantic Fluency	9.12×10^{-5}	-1.98 (-3.73, -0.231)	0.027	-1.09 (-4.27, 2.08)	0.500	-4.84 (-6.72, -2.96)	4.66×10^{-7}
Modified Mini-Mental State Examination	0.006	-1.53 (-2.82, -0.246)	0.020	-1.56 (-3.59, 0.458)	0.129	-2.47 (-4.17, -0.767)	0.005
Stroop Task	2.96×10^{-4}	0.137 (0.032, 0.242)	0.011	0.092 (-0.061, 0.245)	0.238	0.230 (0.124, 0.335)	1.87×10^{-5}
Rey Auditory-Verbal Learning Task	1.61×10^{-5}	-3.53 (-5.56, -1.50)	6.50×10^{-4}	-3.35 (-5.93, -0.772)	0.011	-4.31 (-6.50, -2.11)	1.18×10^{-4}
Digit Symbol Substitution Task	3.90×10^{-5}	-4.83 (-7.60, -2.06)	6.26×10^{-4}	-1.13 (-5.42, 3.16)	0.605	-8.08 (-11.73, -4.43)	1.42×10^{-5}

Models adjusted for age, gender, antidepressant medication use, antianxiety medication use, and educational attainment (less than high school, high school, greater than high school). Significant anxiety symptoms are defined as a Brief Symptom Inventory Anxiety subscale score > 8; significant depression symptoms are defined as a 10 item Center for Epidemiologic Studies Depression scale score > 10.

Reference group: n = 461 individuals with neither depression nor anxiety.

Analysis was performed using marginal models with generalized estimating equations. Results for both an overall 3 degrees of freedom (df) type III test and for each anxiety/depression grouping as compared with the reference group are displayed.

Table 3

Associations between neuroimaging variables and depression symptoms only, anxiety symptoms only, and anxiety and depression symptoms (β value and 95% confidence interval (CI)).

	Overall 3 df test	Depression Only (n=104)		Anxiety Only (n=33)		Anxiety and Depression (n=57)	
		β value (95% CI)	p-value	β value (95% CI)	p-value	β value (95% CI)	p-value
White Matter Mean Diffusivity	0.009	0.005 (-0.003, 0.014)	0.231	0.008 (-0.004, 0.021)	0.173	0.017 (0.007, 0.026)	5.20×10^{-4}
Gray Matter Mean Diffusivity	5.60×10^{-5}	0.016 (0.001, 0.031)	0.040	-0.03 (-0.049, -0.011)	0.002	0.032 (0.015, 0.049)	2.07×10^{-4}
White Matter Fractional Anisotropy	0.009	-0.003 (-0.008, 0.002)	0.303	-0.005 (-0.012, 0.002)	0.133	-0.01 (-0.016, -0.004)	7.79×10^{-4}
Gray Matter Fractional Anisotropy	0.416	0.0002 (-0.004, 0.004)	0.902	0.004 (-0.002, 0.011)	0.216	-0.003 (-0.007, 0.002)	0.289
Gray Matter Cerebral Blood Flow	0.001	-2.10 (-4.59, 0.39)	0.098	-2.52 (-6.29, 1.25)	0.190	-6.66 (-9.51, -3.81)	4.43×10^{-6}
Total White Matter Lesion Volume	0.031	0.18 (-0.01, 0.38)	0.063	0.19 (-0.1, 0.48)	0.210	0.36 (0.07, 0.66)	0.015
Gray Matter Volume	0.001	-6.49 (-12.15, -0.84)	0.025	6.61 (-0.89, 14.12)	0.084	-10.69 (-17.54, -3.84)	0.002
White Matter Volume	0.698	0.03 (-5.71, 5.77)	0.993	-3.6 (-11.36, 4.16)	0.363	-3.38 (-10.89, 4.14)	0.379

Models adjusted for age, scanner, gender, antidepressant medication use, antianxiety medication use, and educational attainment (less than high school, high school, greater than high school). Analyses of white matter lesion volume, gray matter volume, and white matter volume additionally adjusted for total intracranial volume. Significant anxiety symptoms are defined as a Brief Symptom Inventory Anxiety subscale score > 8; significant depression symptoms are defined as a 10 item Center for Epidemiologic Studies Depression scale score > 10.

Reference group: n = 461 individuals with neither depression nor anxiety.

Analysis was performed using marginal models with generalized estimating equations. Results for both an overall 3 degrees of freedom (df) type III test and for each anxiety/depression grouping as compared with the reference group are displayed.