The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder

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Abstract

Despite the widespread prevalence of generalized anxiety disorder (GAD) in later life, almost nothing is known about the neural aspects of worry in adults over the age of 60. Given the ongoing rapid increase in the older adult population, the relatively poor response rates to current interventions for late life GAD, and the effects of age-related changes to the brain, additional research on worry neurobiology is needed. The study group comprised 15 older GAD patients and 15 matched controls who were compared on clinical measures and brain volumes. It was expected that prefrontal cortex (PFC) volumes [medial orbital cortex (mOFC), dorsolateral cortex (DLPFC)] would show positive relations to worry scores, and weaker relations to more general measures of anxiety and depression. Negative relations were expected between amygdala volumes and worry scores. As expected, mOFC volumes were positively related to worry scores; however, DLPFC and amygdala volumes were not. The mOFC is involved in emotional decision-making under uncertain conditions and has the ability to suppress the amygdala, both of which are hypothesized functions of worry. Results are partly consistent with GAD theory and suggest that worry may involve neural areas that are also involved in the successful control of anxiety.

Keywords

Aging; Worry; Geriatric anxiety; Prefrontal cortex; Anxiety neurobiology

1. Introduction

The world's older adult population is increasing at an estimated rate of 800,000 people per month (Kinsella and Velkoff, 2001), which will have a dramatic impact on global health issues. For instance, along with the growing older adult population comes a corresponding

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expectation of increased rates of psychiatric conditions such as anxiety and depression (Jeste et al., 1999; Blazer, 2003). However, research in anxiety disorders has not kept pace with the aging trend. Mental health specialists now face a burgeoning public health problem, given the relative lack of empirical knowledge to inform the conceptualization and treatment of late life anxiety.

Generalized anxiety disorder (GAD), a condition characterized by excessive, uncontrollable worry, is the most common anxiety disorder among adults over the age of 60, with estimated prevalence rates ranging widely from 0.71 to 7.3% (Flint,1994; Beekman et al.,1998; Flint, 1999). Current diagnostic criteria according to the *Diagnostic and Statistical Manual IV-TR* (DSM-IV-TR; American Psychiatric Association, 2000) require at least 6 months of frequent worry about several real-life problems, occurring more days than not, accompanied by at least three associated symptoms such as tension, fatigue, irritability, trouble concentrating, or insomnia. GAD is a prevalent but underrecognized public health problem, associated with significant functional impairment (Mogotsi et al., 2000), serious disability (Kessler et al., 1999), and increased risk for acquisition of additional psychiatric disorders and medical conditions (Brown et al., 1994; Kennedy and Schwab, 1997; Noyes, 2001; Barger and Sydeman, 2005). Response rates in most studies of late life GAD pharmacological and psychosocial treatment are surprisingly low (Mohlman, 2004; Mitte, 2005), highlighting the need for additional data on the causal and maintenance factors of the disorder.

1.1. Neurobiology and theoretical models of GAD

Although the neurobiology of GAD remains largely obscure (Mathew et al., in press; Sinha et al., 2004), neural patterns characterizing two broad types of anxiety have been proposed (Heller et al.,1997; Nitschke et al., 2000). Anxious apprehension, a construct that encompasses cardinal symptoms of GAD such as worry and concern about imminent and future events (Borkovec et al., 1983; Barlow, 1991), is posited to involve increased activity in the left hemisphere, particularly in frontal areas (Heller et al., 1997). By contrast, those emotional states characterized by exaggerated somatic symptoms, sympathetic arousal, and a focus on imminent fear cues (such as panic disorder) are believed to be characterized by right posterior activity (Nitschke et al., 1999).

Models of GAD have posited a more specific relation between the PFC and the amygdala. In addition to a distinct left hemisphere profile, GAD may be associated with frontal overcontrol (e.g., excessive worry) and limbic hypoactivity (e.g., blunted sympathetic arousal; Hoehn-Saric et al., 1989; Thayer and Lane, 2000), which is in contrast to the common anxiety disorder profile of limbic overactivity coupled with poor frontal control of negative affect (e.g., Kent and Rauch, 2004; Lorberbaum et al., 2004). According to Borkovec (1994), GAD patients and high worriers use worry instrumentally as a strategy to dampen or avoid strong feelings of emotional arousal, which they may perceive to be more aversive than worry itself. Although it is likely that there are both excitatory and inhibitory processes at work during worry (Gray et al., 2003), these models and the few neurobiological studies that do exist implicate increased activity in the prefrontal cortex (PFC) both at rest and during worry in adults with GAD, perhaps due to the ability of areas of PFC to suppress or inhibit activation of the limbic system (Hoehn-Saric et al., 2005).

Neuroimaging findings are mostly consistent with the notion that worry and related states of anxious apprehension recruit areas of the PFC (primarily DLPFC, mOFC), which may then suppress or inhibit activity in limbic regions including the amygdala (c.f. Sinha et al., 2004).

1.2. Additional considerations for older adults

All existing data on neurobiological correlates of worry have been collected from younger adults. However, factors related to aging are associated with changes in PFC structure, and could affect the neurobiological profile of worry. For instance, West's (1996) frontal lobe hypothesis posits accelerated volume loss brought about by cell shrinkage (Hachinski et al., 1987), decreased dopamine (DA) concentration, and a reduction in the number of DA receptors in the frontal cortex (Goldman-Rakic and Brown, 1981) with advancing age. Some evidence exists for inordinate degradation of the PFC relative to other brain areas (Raz et al., 1998; Tisserand et al., 2002) and of the DLPFC relative to other frontal areas (MacPherson et al., 2002). Consistent with the age-related decline of PFC-governed cognitive operations (e.g., executive skills; Hasher and Zacks, 1988), these effects could lead to decreased PFC involvement in worry and states of anxious apprehension in older adults.

Indeed, GAD symptoms are typically less severe in older patients as compared with young patients. Self-report and clinician-rated measures of worry consistently reveal lower mean scores in older (e.g., Beck et al., 1996; Stanley et al., 1996a,b, 2003; Wetherell et al., 2003a,b; Mohlman and Gorman, 2005) than younger GAD samples (e.g., Molina and Borkovec, 1994; Behar et al., 2003; Fresco et al., 2002). Older adults may experience additional age-related physiological changes such as blunted reactivity to stress (Whitbourne, 1985; Kogan et al.,1999), decreased neurochemical reactivity (DeBeurs et al., 1999), long-term habituation effects, increased coping abilities, or less anxiety about future goals (Borkovec, 1988), all of which could produce less severe and frequent emotion states (Lawton et al., 1993; Kogan et al., 1999). Not surprisingly, it can be difficult to distinguish late life GAD from subclinical anxiety states, which are believed to be common among the elderly (Wetherell et al., 2003a,b), and many healthy older adults intermittently experience symptoms of GAD (Stanley and Novy, 2000). This is consistent with recent findings on the taxonomy and structure of worry implicating the appropriateness of a dimensional approach (Ruscio and Borkovec, 2001). Therefore, we expect differences between older GAD and control samples to be of generally lesser magnitude than those found in studies conducted with younger samples, even on measures of worry, the hallmark symptom of GAD.

1.3. The present study

The aim of this study was to test hypotheses derived from the avoidance model of GAD (Borkovec, 1994) regarding the relation of worry to PFC and amygdala volumes in patients and age- and sex-matched controls, a sample that was meant to represent the full range of scores on a measure of worry. Such data could be useful in identifying regions of interest (ROIs) and neurobiological targets for possible treatment optimization in older worriers, as well as providing support for popular and useful models of GAD and anxious apprehension.

Brain structure and function may be related due to use-dependent neuroplasticity as well as in cases where degraded structure constrains function. Thus, we used structural MRI to test

the hypothesis that regional brain volumes would be related to symptom measures. Because worry involves the same neural areas and cognitive processes in nonclinical samples as in GAD patients (e.g., Hoehn-Saric et al., 2004, 2005), we did not expect substantial differences between the GAD and control groups on brain volumetric ROIs. Rather, consistent with a dimensional perspective, it was expected that scores on a continuous measure of worry would show a positive association with DLPFC and mOFC volumes, with stronger associations being found with left hemisphere ROIs due to the verbal component of worry. We also expected to find negative correlations between worry scores and amygdala volumes. Worry scores were expected to be significant predictors of PFC ROIs in linear regression models including variables related to PFC volume (age, hypertension [htn], whole brain volume [WBV]), and to outperform more general measures of anxiety and depression in these models, given the specific function of worry set forth in contemporary models (e.g., Borkovec, 1994).

2. Methods

2.1. Participants

Participants were 30 adults aged 60 and over (mean=67.87, S.D. =5.39, range=60–77), 50% female, mostly Caucasian (90%), recruited from an urban community through media ads and community outreach, and assessed in an outpatient hospital clinic setting. Fifteen met criteria for a primary diagnosis of GAD according to the *Structured Clinical Interview Diagnostic for DSM-IV* (SCID; First et al., 1995), and 15 did not meet criteria for any current psychiatric disorder.

2.2. Measures

The SCID (First et al., 1995) was administered by trained Master's-or Ph.D.-level assessors who completed 6 months of training on administering the interview. Seventy-five percent of patient SCIDs (n=10) were observed by a supervisor to ensure reliability (J.M.). Additionally, a random sample of audiotaped SCID interviews (n=12) was then independently rated by a blind assessor to estimate interrater reliability. The kappa coefficient for the diagnosis of GAD was 0.92; however, all participants passed a preliminary phone screen that included a checklist of GAD symptoms, so this estimate might be somewhat inflated.

Rates of comorbidity were moderate; 57% of those in the GAD group also met criteria for at least one additional disorder, most often dysthymia (20%), specific phobia (20%), social phobia (20%), or panic disorder (14%). Because of the known differences in the neurobiology of GAD versus late life major depression (i.e., reduced PFC volumes in depression; Krishnan et al., 1992; Kumar et al., 2000; Taylor et al., 2004), we excluded any participant who reported major depressive episodes at the time of the interview (n=1). The mean age of GAD onset among patients was 43.50 (S.D. = 24.75; range =7–76), with 50% (n=7) reporting emergence of GAD at or prior to age 50.

The sample was generally in good health, as determined through self-reported medical history and a review of medical records. Most were retired, had at least a high school

diploma, and were married or divorced. Participants were required to be right-handed, have no metal implanted in the body, have intact basic cognitive skills (Mini-Mental State Examination score >25; Folstein et al., 1975), read and write in English, have no history of suicidality in the previous year, have never experienced psychotic symptoms, have no history of stroke or heart disease, and be free of anxiolytic and antidepressant medications at the time of and at least 1 year before the interview.

Participants completed the Penn State Worry Questionnaire (PSWQ; Meyer et al., 1990), Beck Depression Inventory (BDI; Beck and Steer, 1990), and trait scale of the Spielberger State-Trait Anxiety Inventory-Form Y (STAI; Spielberger et al.,1983). All measures have been shown to have sound psychometric properties in older adult samples (e.g., Himmelfarb and Murrell, 1983; Beck et al., 1995; Stanley et al., 1996a, b). Internal consistency coefficients were 0.87, 0.79, and 0.90 for the PSWQ, STAI, and BDI, respectively.

2.3. Procedure

After completing the consent process, SCID, questionnaires, and cognitive tests, each participant underwent a 15-min MRI scan. Because participants were screened for the presence of claustrophobic symptoms, all were able to complete the scan successfully. Structural images were acquired on a Philips Medical full body MRI scanner, a 1.5 T Intera with Gyroscan version 8.1.3 software. The MR brain images were acquired using a quadrature radiofrequency receive-only head coil and inversion recovery prepped T1-weighted radiofrequency pulse sequence covering the brain in transaxial view with a total of 100 1.5-mm slice thickness images. The preparation time and weighting were optimized to give the best distinction for image post-processing reconstruction and brain structure segmentation. The MRI data were exported in DICOM format to a PC for subsequent post-processing analysis using MEASURE software (Barta et al., 1997).

Non-brain tissue was removed and frontal lobe tissue was isolated, using previously described protocols. The prefrontal cortex was divided into lateral and medial subregions of the dorsal and orbital prefrontal cortices using the measurement protocol described by Gur et al. (2000). The frontal lobes were rendered in order to delineate (1) the inferior border of the anterior commissure, (2) the anterior border of the genu of the corpus callosum and (3) the medial posterior border of the transverse orbital sulcus. The amygdala was delineated using the scheme described in Kates et al. (1997). Parcellation was performed by two raters trained to a gold standard (W.K.), and intraclass correlation coefficients ranged from 0.89 to 0.99.

3. Results

3.1. Data analysis plan

Data were checked for deviations from normality and outliers using appropriate diagnostic tests. When adjusted for whole brain volume (WBV, which is known to differ between males and females, and show positive relations to PFC volumes; Goldstein et al., 2001), data from one male in the GAD group on left mOFC (2.89 cm^3) met criteria for an outlying value as compared with the GAD group mean (12.63 cm^3, S.D.=2.69) and thus was removed for the analysis of this ROI, leaving 14 participants in the GAD group. Due to scheduling problems,

one male in the control group completed the SCID interview and MRI but not the questionnaire packet; therefore, the control group was adjusted to n=14 whenever pertinent. We tested for between-group differences based on GAD status, then investigated the relation of worry as a continuous variable to ROIs.

3.2. Participant characteristics

Participants were compared on age, number of medical problems, daily medications, and alcoholic beverages consumed per month with analyses of variance (ANOVA) with alpha set at 0.013 to control for four comparisons. There were no significant differences on any variables. Certain health problems (e.g., hypertension, diabetes, coronary heart disease) are associated with reduced PFC volumes (Kumar et al., 2007; Salerno et al., 1992; Strassburger et al., 1997). Participants with a history of heart disease or stroke were excluded from the current study; however, those with diabetes and hypertension were allowed; thus, these two conditions were examined in the sample. According to Fisher's exact test, rates of diabetes were equally distributed, reported by a total of four participants; two in the GAD group and two in the control group. Rates of hypertension (htn), which is common in older adults with anxiety disorders (Kim et al., 2000), particularly those who report frequent worry (Kubzansky et al., 1997), were also tested using a chi-square test. The GAD group had a higher proportion (57%) of hypertensive individuals than the control group (20%), χ^2 (1, N=28)=2.77, P<0.10, a difference that was marginally significant, indicating the use of htn as a covariate in subsequent analyses. Additional chi-square and Fisher's exact tests were used to compare the GAD and control groups on sex, marital, educational, ethnic, and occupational status. There were no other differences between the patient and control groups.

3.3. Psychiatric measures, brain volumes

Bonferroni-adjusted univariate ANOVAs with alpha set to 0.017 were conducted on PSWQ, STAI, and BDI scores. The GAD group scored significantly higher than controls on the PSWQ, F(1,26)=17.64, P<0.001, η^2=0.40, STAI, F(1,26)=41.97, P<0.001, η^2=0.62, and BDI, F(1,26)=5.91, P<.01, η^2=0.30. These results did not appreciably change when htn was included as a covariate. Consistent with prior findings, the mean PSWQ score from the GAD group was lower than published means from younger GAD samples (Antony et al., 2001), but similar to those published from other older samples (e.g., Beck et al., 1996; Stanley et al., 2003). Scores on the MMSE did not differ between patients and controls. Descriptive data are shown in Table 1.

Three brain ROIs (DLPFC, mOFC, amygdala) were examined across groups with ANOVAs. Because age, htn, and WBV were significantly or marginally related to PFC ROIs, analyses of covariance were also run (ANCOVAs), with alpha adjusted to 0.017 for three comparisons. The ANOVAs failed to reach significance (all Ps>0.25), indicating that there were no differences in ROIs between the GAD and control groups regardless of inclusion of the covariates. Brain volumes are displayed in Table 1.

Comorbidity in GAD is the rule rather than the exception; however, it is possible that findings could have been influenced by co-occurring psychiatric disorders characterized by limbic overactivity and PFC hypoactivity, which would have obscured between-group

effects. To test this possibility in the current small sample, we compared the GAD group according to those with (n=8) and without (n=7) comorbid conditions, and found no differences on any self-report measure or brain ROI (all Ps>0.29). Although we allowed comorbidity, we excluded cases of recent major depression, which is one of the most frequently occurring conditions with GAD (Bruce et al., 2001; Noyes, 2001; Gorwood, 2004). However, inclusion of these patients would have potentially obscured the effects of GAD per se, due to the chances of reduction in PFC volume in depressed older adults (Krishnan et al., 1992; Kumar et al., 2000; Taylor et al., 2004).

3.4. Correlation and regression analyses

Partial correlations controlling for age, htn, and WBV were run between psychiatric measures and brain volumes in the full sample, as shown in Table 2. Significant relations were found between PSWQ and right and left mOFC. These relations were then tested within the control and GAD groups. As shown in Tables 3 (GAD group) and 4 (control group), after alpha was adjusted to 0.005 to account for 10 correlations and after controlling for age, htn, and WBV, scores on the PSWQ were positively related to left mOFC, partial r=0.872, P<0.005 in the GAD group, but not in controls. No other correlations between ROIs and clinical measures reached significance.

Hierarchical linear regression models were tested to further investigate the relationship between scores on PSWQ, other psychiatric measures, and PFC and amygdala volumes. PFC ROIs (DLPFC, mOFC) were modeled with age, htn, and WBV entered on the first step, GAD status (coded '0' for the absence and '1' for the presence of GAD) on the second step, PSWQ scores on the third step, and the interaction term (PSWQ×GAD status) on the fourth step. Due to the relatively small sample and consequent threats to model reliability, ROIs were kept unified rather than lateralized in an attempt to minimize the number of predictors tested in each model.

The model of DLPFC (F(5,24)=4.259, P<0.008) was significant, adjusted r^2=0.40, however WBV was the only significant predictor, t(28)=4.03, P=0.001. The model of mOFC was significant (F(5,23)=6.643, P=0.001), adjusted r^2=0.54. WBV (t(27)=5.09, P=0.001), htn (t(27)=−2.51, P=0.05), and PSWQ (t(27)=3.60, P=0.002) were significant predictors. The model of amygdala (F(5,24)=1.906, P<0.40) was not significant. Entering the psychiatric measures on the first step of each model did not change the set of predictors identified for each ROI as described above.

Alternative models of DLPFC and mOFC including the BDI and STAI rather than the PSWQ were also tested. Regardless of order of entry of the set of variables (BDI or STAI, htn, WBV, GAD status), neither measure emerged a significant predictor of any ROI, with full model r^2's ranging from 0.26 to 0.41. When the model of mOFC was run with WBV and htn entered on the first step, BDI or STAI on the second, GAD status on the third, and PSWQ on the fourth, PSWQ was the only psychiatric measure to emerge as a significant predictor. Additional details of regression models appear in Table 5 and Fig. 1.

4. Discussion

Adding to limited research on the neurobiology of worry among older adults, this investigation provides support for the hypothesized link between PFC volume and worry, but not between amygdala volume and worry. As predicted on the basis of contemporary theory (Borkovec, 1994), the mOFC, a PFC region of interest, was significantly and positively related to worry scores in the GAD group, but not to more general measures of anxiety, depression, or illness chronicity (as measured by age of GAD onset). Consistent with earlier studies of anxious apprehension showing left hemisphere asymmetry at rest (e.g., Heller et al., 1997) and during worry (Carter et al., 1986; Hofmann et al., 2005), we also found a stronger relation of left than right mOFC to worry scores in the GAD group.

Amygdala volume was not associated with any PFC regions or worry, standing in contrast to the assertion by Hoehn-Saric et al. (2005) that the neural substrate of worry is likely to include the mOFC-amygdalar connection. The circuit connecting DLPFC to amygdala is indirect, and both regions may exert influence on each other via mutual projections to the orbital PFC and via thalamic and striatal circuits (Hariri et al., 2003). Alternatively, age-related changes in symptom presentation, including decreased severity of worry in older versus younger adults (Babcock et al., 2000; Skarborn and Nicki, 2000), could potentially obscure associations between regions that might have been present earlier in life. Unlike areas of the PFC, which are known to show structural changes with age (West, 1996), the amygdala is largely preserved, even in older individuals (Good et al., 2001; Grieve et al., 2005).

Interestingly, no relation was found between the diagnosis of GAD and any of the variables of interest in regression analyses, indicating that it was worry specifically, rather than the more general GAD syndrome, that drove the current results. When participants were dichotomously categorized on the basis of the full GAD symptom profile (insomnia, feeling restless or 'keyed up,' difficulty concentrating, mind going blank, muscle tension, irritability, and fatigue in addition to frequent and uncontrollable worry), the prediction of mOFC volume did not improve. The present findings are then consistent with the increasingly popular notion that worry in GAD is likely to be more quantitatively than qualitatively different from normal worry (Ruscio, 2002; Borkovec et al., 2004; Ruscio et al., 2005), and indicate a continued focus on the specific process of worry as a phenomenon of clinical interest.

The mOFC is part of the orbitofrontal cortex (OFC), an area that is known to play a role in inhibiting or terminating inappropriate, and initiating appropriate, responses according to changing context (Beer et al., 2006; Evans et al., 2004). Elliot et al. (2000) posit that the role of the OFC is to inform choices made under uncertain or unpredictable circumstances. Indeed, in the clinical setting the subjective experience of worry is often described as a 'holding pattern.' It interferes with task initiation and subsequently leads to procrastination and mounting anxiety, which is perhaps an example of an adaptive behavioral modification system gone awry. The OFC also contributes to perseverative and obsessional thoughts and behaviors. Lesions to the OFC in rats lead to impaired reversal learning (i.e., impairment in learning to return to a strategy that was previously unrewarded) despite intact set switching

abilities; McAlonan and Brown, 2003; Schoenbaum et al., 2003), suggesting that high worriers might be particularly prone to engage in repetitive nonreinforced thoughts and behaviors when attempting to solve problems. In other words, they might be likely to return to a strategy that was previously ineffective or unsuccessful, when contingencies have remained the same. This maladaptive pattern (which would not be expected in low worriers) in some ways parallels the unproductive nature of pathological worry and related behaviors, such as repeated checking or reassurance-seeking under unchanging conditions.

The finding of a link between mOFC and worry suggests support for a limited resource model; interventions for worry and GAD should include worry reduction techniques imparted early in treatment (e.g., stimulus control, relaxation, acceptance and mindfulness), which would ostensibly increase the availability of frontal resources such as the mOFC, followed by training in alternative decision making and emotion regulation strategies (e.g., ruling out nonreinforced behaviors, conducting cost–benefit analyses, resolution of perceived uncertainty or unpredictability, accepting unknown aspects of situations). These are adaptive skills that could supplant worry as a strategy for managing anxiety and other negative emotions, but are also likely to involve (and perhaps compete for) activity in areas such as the mOFC.

The study had a range of limitations. The small sample might have limited statistical power to detect all but large effects. All GAD patients were participating in a clinical trial of cognitive behavior therapy and might have had a different clinical profile than those who do not seek treatment. Additionally, the high demand on participants (MRI, neuropsychological testing) might have biased our sample toward those older adults who are high functioning and mobile. It is unclear what role age-related neural atrophy could have played in the older sample. Although there is support for the notion that orbitofrontal regions contribute to anxiety even in pediatric samples (Vasa et al., 2004), the inclusion of a younger GAD group would have eased interpretation regarding age-specific effects. The correlational design of this study precludes interpretation of directionality. It is possible that interindividual differences in regional PFC volumes in older adults could impact the availability of prefrontal resources for symptomatic behaviors such as worry. Thus, individuals with larger PFC volumes may be more vulnerable to developing chronic worry habits; conversely, habitual behaviors such as worry may gradually alter brain structure as a result of use-dependent neuroplasticity. Or, an unidentified third variable could contribute to or cause both worry and PFC volume changes, such as a temperamental disposition for cognitive overcontrol. Additionally, the lack of functional brain measures limits inference about brain activity, a more sensitive measure. Clearly, more research on anxiety, worry, and brain integrity in the OFC in participants of all ages is needed.

This is the first study to examine brain volumes and worry in older adults with and without GAD. Findings were somewhat consistent with those from studies of younger analog and patient samples, and suggest a potentially unique neurobiology of worry that diverges from other types of anxiety states (i.e., those characterized by high somatic arousal and PFC hypoactivity; Kent and Rauch, 2004; Lorberbaum et al., 2004). GAD is considered the most refractory anxiety disorder, poses risk for the acquisition of additional psychiatric and medical conditions, and is prevalent among older adults. Additional studies are needed to

increase knowledge of late life anxiety and worry, with the overarching goal of reducing the mental health care burden for upcoming cohorts of older adults.

Acknowledgments

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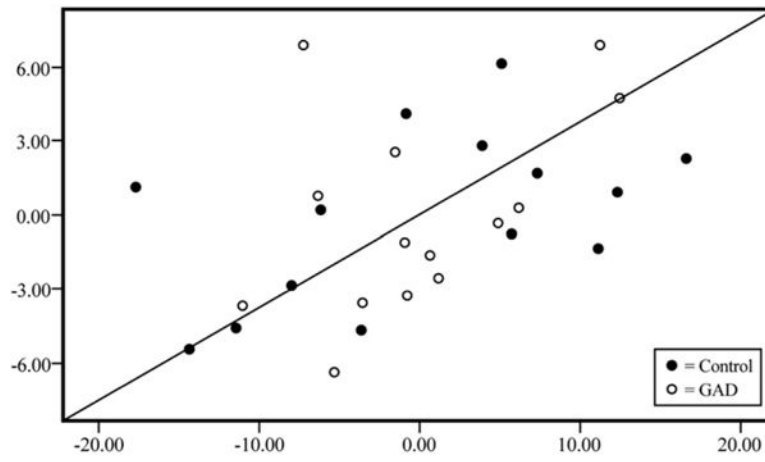
Fig. 1.
Standardized partial regression plot of medial orbital cortex volumes (*y*-axis) and PSWQ scores (*x*-axis) in control and GAD groups, controlling for age, htn, and WBV.

Table 1

Participant characteristics, scores on self-report measures, brain volumes.

		Control (*n*=15)	GAD (*n*=15)
Age		67.50 (4.94)	67.39 (5.42)
Female		60%	40%
Hypertension		20%	57% [†]
Alcoholic drinks/month		13.67 (19.17)	9.88 (16.22)
MMSE[a]		28.93 (1.19)	27.69 (1.89)
PSWQ[a]		39.31 (11.55)	59.38 (7.47) [*]
STAI-trait[a]		29.07 (6.34)	54.61 (14.28) [*]
BDI[a]		5.92 (4.18)	14.47 (10.72) [*]
WBV		1176.12 (85.65)	1164.33 (102.93)
Amygdala		3.30 (0.62)	3.52 (0.74)
	Right	1.76 (0.44)	1.88 (0.48)
	Left	1.54 (0.31)	1.64 (0.41)
DLPFC		41.03 (4.23)	41.06 (7.82)
	Right	21.20 (2.09)	21.09 (4.34)
	Left	19.63 (3.45)	20.04 (3.94)
mOFC[b]		22.26 (4.58)	23.34 (5.50)
	Right	11.07 (2.30)	11.64 (2.85)
	Left	11.25 (2.40)	12.03 (2.54)

Note.

[*] $P<.017$;

[†] $P<.10$.

[a] =control *n*=14;

[b] =GAD *n*=14.

MMSE=Mini-Mental State Exam; PSWQ=Penn State Worry Questionnaire; STAI-trait=trait scale of State Trait Anxiety Inventory; BDI=Beck Depression Inventory. WBV=whole brain volume; DLPFC=dorsolateral cortex; mOFC=medial orbital cortex. All brain volumes were measured in cubic centimeters, no cerebrospinal fluid.

Table 2

Partial correlations with age, htn, and wbv controlled below the diagonal (n=28).

	Lamyg	Ramyg	Ldlpfc	Rdlpfc	LmOFC	RmOFC	PSWQ	BDI	STAI
Lamyg	–	0.405	0.014	–0.304	–0.074	0.202	0.093	–0.146	–0.087
Ramyg		–	0.071	0.098	0.069	0.186	0.186	0.037	0.016
Ldlpfc			–	0.071	–0.327	–0.200	–0.056	0.044	–0.050
Rdlpfc				–	0.186	–0.040	0.135	0.235	0.052
LmOFC[a]					–	–0.872**	0.582**	0.428	0.488
RmOFC[a]						–	0.546**	0.488	0.403
PSWQ							–	0.547**	0.551**
BDI								–	0.598**

Note.

*
P<0.005;

**
P<0.001.

[a]
=n=28 due to one outlying value on mOFC volumes; amyg = amygdala; dlpfc = dorsolateral cortex; mOFC = medial orbital cortex; wbv=whole brain volume; PSWQ=Penn State Worry Questionnaire; BDI=Beck Depression Inventory; STAI=Trait Scale, State Trait Anxiety Inventory. All brain volumes were measured in cubic centimeters, without cerebrospinal fluid.

Table 3

Within group partial correlations between brain ROIs (left, right) and clinical measures, controlling for wbv, age, and htn; GAD group.

	Lamyg	Ramyg	Ldlpfc	Rdlpfc	LmOFC	RmOFC	PSWQ	BDI	STAI	Onset
Lamyg	–	0.388	0.199	−0.476	−0.099	0.234	−0.471	−0.371	−0.261	−0.179
Ramyg		–	0.120	−0.143	0.119	0.271	−0.040	−0.073	−0.159	0.309
Ldlpfc			–	0.592	−0.264	−0.204	−0.190	0.084	−0.007	0.371
Rdlpfc				–	0.206	0.058	0.467	0.409	0.122	0.348
LmOFC					–	0.879 **	0.872 **	0.459	0.513	−0.022
RmOFC						–	0.661	0.195	0.373	0.168
PSWQ							–	0.579	0.538	0.199
BDI								–	0.427	0.090
STAI									–	0.159

Note.

**
P<0.001.

amyg=amygdala; dlpfc=dorsolateral cortex; mOFC=medial orbital cortex; wbv=whole brain volume; PSWQ=Penn State Worry Questionnaire; BDI=Beck Depression Inventory; STAI=Trait Scale, State Trait Anxiety Inventory; Onset=age of GAD onset. All brain volumes were measured in cubic centimeters, without cerebrospinal fluid.

Table 4

Within group partial correlations between brain ROIs (left, right) and clinical measures, controlling for wbv, age, and htn; control group.

	Lamyg	Ramyg	Ldlpfc	Rdlpfc	LmOFC	RmOFC	PSWQ	BDI	STAI
Lamyg	–	0.431	0.176	0.073	-0.295	-0.092	0.248	-0.109	-0.187
Ramyg		–	0.319	0.400	-0.396	-0.295	0.174	-0.011	-0.302
Ldlpfc			–	0.462	-0.241	-0.008	0.532	-0.001	0.224
Rdlpfc				–	-0.072	-0.214	-0.184	0.021	-0.016
LmOFC					–	0.839[**]	0.269	0.463	0.592
RmOFC						–	0.488	0.337	0.681
PSWQ							–	0.461	0.497
BDI								–	0.550

Note.

[**] $P < 0.001$.

amyg=amygdala; dlpfc=dorsolateral cortex; mOFC=medial orbital cortex; wbv=whole brain volume; PSWQ=Penn State Worry Questionnaire; BDI=Beck Depression Inventory; STAI=Trait Scale, State Trait Anxiety Inventory; All brain volumes were measured in cubic centimeters, without cerebrospinal fluid.

Table 5

Summary of linear regression models predicting brain volumes (n=28).

Predictor		B	SE B	β	adj. r^2	F	adj. r^2
DLPFC							
Step 1	WBV *	0.035	0.007	0.709	0.490	11.529 ***	
	age	−0.097	0.218	−0.087			
	htn	1.359	2.158	0.109			
Step 2	GAD	0.998	2.451	0.085	0.002		0.085
Step 3	PSWQ	−0.032	0.108	−0.065	0.004		0.090
Step 4	GAD×PSWQ	−0.106	0.247	−0.491	0.005		0.183
mOFC							
Step 1	WBV *	0.033	0.008	0.628	0.293	6.328 **	
	age	0.197	0.155	0.221			
	htn	−2.296	1.647	−0.245			
Step 2	GAD	−0.899	1.871	−0.097	0.043		0.954
Step 3	PSWQ *	0.205	0.082	0.546	0.145		12.932 ***
Step 4	GAD×PSWQ	0.094	0.156	0.607	0.007		0.362

Note.

*
P<0.05;

**
P<0.01;

***
P<0.005;

WBV=whole brain volume; htn=hypertension; DLPFC=dorsolateral cortex; mOFC=medial orbital cortex. Volumes measured in cubic centimeters, no cerebrospinal fluid.