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Brain structural changes in late-life generalized anxiety disorder

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Abstract

Late-life Generalized Anxiety Disorder (GAD) is relatively understudied and the underlying structural and functional neuroanatomy has received little attention. In this study, we compare the brain structural characteristics in white and gray matter in 31 non-anxious older adults and 28 late-life GAD participants.

Gray matter indices (cortical thickness and volume) were measured using FreeSurfer parcellation and segmentation, and mean diffusivity was obtained through Diffusion Tensor Imaging (DTI). We assessed both macroscopic white matter changes [using white matter hyperintensity (WMH) burden] and microscopic white matter integrity [using fractional anisotropy (FA)].

No differences in macro- or microscopic white matter integrity were found between GAD and non-anxious controls (HC). GAD participants had lower cortical thickness in the orbitofrontal cortex (OFC), inferior frontal gyrus, and pregenual anterior cingulate cortex (ACC). Higher worry severity was associated with gray matter changes in OFC, ACC and the putamen. The results did not survive the multiple comparison correction, but the effect sizes indicate a moderate effect.

The study suggests that late-life GAD is associated with gray matter changes in areas involved in emotion regulation, more so than with white matter changes. We conclude that anxiety-related chronic hypercortisolemia may have a dissociative effect on gray and white matter integrity.

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1. Introduction

Generalized Anxiety Disorder (GAD) is the most prevalent anxiety disorder in older adults (Beekman et al., 1998; Le Roux et al., 2005). With an estimated community prevalence of 7.3%, late-life GAD is more prevalent than late-life depression (Wittchen and Hoyer, 2001), (Beekman et al., 1998). Late-life GAD is associated with decreased quality of life (de Beurs et al., 1999), as well as increased risk of coronary heart disease (Tully et al., 2013) and stroke (Lambiase et al., 2014).

Community-based studies have indicated that generalized anxiety has a second peak of incidence in late-life (after age 50) (Beekman et al., 1998; Chou, 2009; Le Roux et al., 2005). The second peak of GAD incidence later in life may be related to the age-related reconfiguration of the structural and functional architecture of the brain (Andrews-Hanna et al., 2007). Late-life GAD is relatively understudied, and in particular, the underlying structural and functional neuroanatomy has received little attention (Andreescu et al., 2011; Mohlman et al., 2009).

Midlife studies of GAD show that decreased hippocampal volume and decreased fractional anisotropy (FA) in the uncinate fasciculus are associated with a lifetime diagnosis of GAD (Hettema et al., 2012). Other structural changes include decreased FA in the mid-cingulate white matter (Zhang et al., 2013) and decreased FA in the uncinate fasciculus (Tromp do et al., 2012). GAD status and severity correlated with larger ACC and dorso-medial prefrontal cortex volumes (Schienle et al., 2011), but with lower hippocampal volume (Terlevic et al., 2013).

The only published study that explored the structural neuroanatomy of late-life GAD described a positive correlation between orbitofrontal cortex volume (OFC) correlated and worry severity, a finding pointing toward the role of OFC in emotional decision-making under uncertain conditions (Mohlman et al., 2009).

In our previous studies we have demonstrated that late-life GAD has a different functional connectivity profile than midlife GAD (Andreescu et al., 2014). Taken together with the increased prevalence of GAD after age 50 and the cognitive changes associated with GAD in late-life (Butters, 2011), these data suggest that late-life GAD is most likely associated with specific brain changes such as neuronal degeneration and cerebrovascular disease. These structural changes most likely involve both the gray matter [through macrostructural changes such as decreased cortical thickness and volume, as well as through microstructural changes such as increased gray matter mean diffusivity (MD) (Pierpaoli et al., 1996)] and the white matter (through macrostructural lesions measured by the total white matter hyperintensity (WMH) burden and through microstructural damage in the white matter tracts, as measured by fractional anisotropy (FA)).

We hypothesize that, compared with older non-anxious comparison participants, late-life GAD participants have 1) more damage in the gray matter as measured by a) decreased thickness and volume and b) more microstructural damage (as measured by gray matter mean diffusivity) in regions implicated in emotion regulation, cognitive control and threat response; 2) greater white matter disease as demonstrated by a) whole brain macrostructural

white matter hyperintensities (as measured by WMH burden) and b) specific microstructural damage (as measured by FA) in the white matter tracts connecting these regions (e.g. cingulum bundle, uncinate fasciculus). Additionally, we use a dimensional approach to explore the correlations between structural changes in both gray and white matter and worry severity. In the GAD group, we also explore whether age of onset correlate with structural changes (early onset defined as onset before age 50 (Le Roux et al., 2005; Zhang et al., 2014, 2015).

2. Method

2.1. Participants

Participants were recruited from an NIMH-funded trial (“Structural and functional neuroanatomy of late-life GAD”). Older adult GAD participants (age 60 and over) had a principal diagnosis of GAD for at least six months according to the Structured Clinical Interview for DSM-IV (SCID)(First M, 1995) and a score of 17 or higher on the Hamilton Anxiety Rating Scale (HARS)(Hamilton, 1959) at the time of their baseline MRI scan. Participants with other anxiety disorders were included if GAD was the principal diagnosis: 4/28 (14%) GAD participants were diagnosed with another anxiety disorder, including social phobia (n=1), panic disorder (n=2), and post-traumatic stress disorder (n=1). Participants with Mini Mental Examination Scale (MMSE)(Folstein MF, 1975) scores of 24 or lower, or with a clinical diagnosis of dementia were excluded, as were the participants with a current Major Depressive Disorder diagnosis at the time of MRI scan. Other exclusion criteria were lifetime psychosis or bipolar disorder, increased suicide risk, medical instability according to review of medical chart data, ongoing psychotherapy, and current antidepressant or anxiolytic use (Andreescu et al., 2011).

2.2. Assessments and treatment

Thirty-one non-anxious elderly and twenty-eight elderly GAD participated in this study. All participants were psychotropic-free at the time of scanning. Participants were evaluated clinically with the PSWQ (Meyer et al., 1990), the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), the Generalized Anxiety Disorder Severity Scale(Andreescu et al., 2008; Shear, 2006), the Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960), and the Response Style Questionnaire – Rumination Subscale (RSQ)(Nolen-Hoeksema et al., 1993). Global medical burden was assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992).

For the cognitive evaluation, we used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)(Randolph et al., 1998) and the Delis-Kaplan Executive Function System (D-KEFS)(Delis, 2001). The RBANS provides a Total Index Score and Subscale Index Scores measuring Attention (forward digit span and coding tasks), Immediate Memory (list and story recall), Visuospatial Constructional Skills (figure copy and line orientation tasks), Delayed Memory (delayed list, story, and figure recall/recognition), and Language (confrontation naming and category fluency). From the D-KEFS, we used the Color-Word interference and Sorting subtests.

2.3. Data acquisition

Imaging data were acquired using three MRI sequences. T1-weighted anatomical images were also acquired using a 3D-MPRAGE sequence (TR/TE = 500/11 ms, FOV = 240 × 240mm, flip angle=9°, slice thickness = 1 mm, matrix = 256×256). A T2-weighted fluid attenuation inversion recovery (FLAIR) sequence was employed for WMH measurements. Sequence parameters: slice thickness = 3 mm, number of slices = 48, FOV = 212 × 256 mm², voxel size = 1 × 1 × 3 mm³, repetition time (TR) = 9160 ms, echo time (TE) = 90 ms, inversion time (TI) = 2500 ms, flip angle = 150°. Diffusion tensor imaging (DTI) sequence: slice thickness = 3 mm, number of slices = 40, FOV = 256 × 256 mm², voxel size = 2 × 2 × 3 mm³, TR = 5300 ms, TE = 88 ms, TI = 250 ms, and flip angle = 90°, 12 diffusion directions, diffusion weighted values b = 1000 s/mm² with reference b = 0 s/mm², four repeats, and radial generalized auto-calibrating partially parallel acquisitions (GRAPPA) = 2.

2.4. Data analysis

2.4.1. White matter hyperintensities (WMH)—WMHs were quantified with an automated method developed and validated by Wu et al (Wu et al., 2006)(see figure 1). The localized WMHs were then quantified by multiplying the voxel size by the number of WMH voxels. Normalized WMH (nWMH) values were calculated by dividing the total WMH size (mm) by the total brain volume.

2.4.2 DTI processing—Diffusion tensor images were preprocessed using the FMRIB's Diffusion toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>), which accounts for the correction of eddy current distortion, diffusion tensor fitting, and the calculation of voxel-wise diffusion statistics maps, namely, mean diffusion (MD) and fractional anisotropy (FA) maps. To avoid confounding with WMH, the DTI statistical maps were masked to exclude the WMH voxels before submitted to the Tract-Based Spatial Statistics analysis (TBSS). Individual DTI statistical maps were eroded and normalized to the standard MNI 152 space using FMRIB58_FA template. Mean FA maps were calculated, thinned and thresholded for FA>0.2 to create the “skeleton” mask of the white matter tracks. Individual DTI skeleton maps were created by projecting the DTI statistical maps onto the skeleton masks with the local maximum values across the skeleton tracts. This method compensates the residual misalignments in spatial voxel-wise registration (Jenkinson et al., 2012; Smith et al., 2006). The DTI skeleton maps were segmented into tracks of interest with JHU DTI-based white-matter atlases. Mean DTI measures (FA and MD) were calculated for each tract and region of interest for analysis.

2.4.3. Free surfer parcellation and segmentation—The morphometric properties of brain structure were evaluated using the FreeSurfer 5.3.0 software package (<http://surfer.nmr.mgh.harvard.edu>), in which the surface-based pipeline (Dale et al., 1999; Desikan et al., 2006) was utilized to assess cortical thickness, surface area, and volume, and the volume-based pipeline (Fischl et al., 2002) was used to segment subcortical white matter and deep gray matter volumetric structures, such as hippocampus and amygdala. Detailed methods were described in the FreeSurfer publication (Desikan et al., 2006; Fischl et al., 2002). Briefly, subjects' MPRAGE images were preprocessed to remove non-brain tissue, affine-register to the Talairach atlas, correct intensity bias, and normalize intensity. The

surface-based analysis, which identifies gray/white matter boundaries and reconstructs representations of white and pial surfaces, consists of cortical white matter segmentation, surface tessellation and deformation. Cortical thickness was measured as the distance between the white and pial surfaces at each vertex on the tessellated surface. The resulting smooth cortical surfaces were further segregated into 34 regions of interest (ROIs) in each hemisphere based on the probabilistic information estimated from the Desikan-Killiany cortical atlas in Freesurfer (Desikan et al., 2006). The volume-based pipeline segmented subcortical structure by combining the information about voxel intensity relative to the tissue probability map with the spatial relationship of the voxel to the location of neighboring structures of a manually labeled atlas (Fischl et al., 2002). Intracranial volume (ICV) (estimated from the atlas-scaling factor) was used to adjust for individual differences in head size. Both cortical and subcortical measures have been validated for their accuracy and reliability in several studies (Han et al., 2006; Jovicich et al., 2009; Morey et al., 2009).

To assess for differences in structural indices between GAD and HC, a two-sample t-test was performed. Simple effects sizes (Cohen's d) are presented, as well as effect sizes adjusted by age (using the age adjusted means instead). Also, the Wilcoxon's rank sum test was used to test for differences between the distributions of the early GAD onset (<50 years old) compared to late GAD onset (>50 years old). A p value of 0.05 was deemed significant. Additionally, to assess the association between worry severity and age with structural indices, Pearson correlation coefficients were computed for the entire sample using all the available structural indices. False Discovery Rate (FDR) was used to control for multiple comparisons.

3. Results

Clinical and demographic data and comparisons are presented in Table 1. Compared with HC, GAD participants were younger and performed worse on executive function tests (DKEFS trail making and color word interference), a result that replicates previous findings (Butters, 2011).

3.1. Group differences

3.1.1. White Matter Hyperintensities Burden—No difference was found between GAD and HC, neither in the global WMH burden nor for the WMH burden in major tracts ($p=0.83$, Cohen's $d=0.05$ for the global WMH burden).

3.1.2. Functional Anisotropy—No difference was found between GAD and HC, neither for global nor for the major white matter tracts ($p=0.44$, Cohen's $d=0.27$ for global FA).

3.1.3. Mean Diffusivity—Differences in MD were observed in two regions – the left pallidum (GAD>HC, $t(17)=2.19$, $p=0.04$, Cohen's $d=1.06$) and the frontal middle orbital gyrus (GAD<HC, $t(35)=-2.26$, $p=0.03$). When adjusted for age, the differences between GAD and HC remain significant ($F(1,34) = 4.92$, $p=0.033$) for left pallidum and ($F(1,34) = 4.832$, $p=0.035$) for left frontal middle orbital gyrus. However, when we adjusted the p -values using the FDR correction none of these associations remained significant.

3.1.4. Cortical thickness—Compared with HC, GAD had lower cortical thickness in the following regions: left medial OFC ($t(54)=-2.03$, $p=0.046$, Cohen's $d=0.54$) and right medial OFC ($t(54)=-2.27$, $p=0.03$, Cohen's $d=0.60$), and left rostral ACC ($t(54)=-2.89$, $p=0.005$, Cohen's $d=0.76$). When adjusted for age, the differences between GAD and HC remained significant for left rostral ACC ($F(1,53)=5.99$, $p=0.018$) but not for the other regions. The p-values did not survive the FDR correction.

3.1.5. Gray Matter Volume—Compared with HC, GAD had lower gray matter volume in the following regions: right inferior frontal gyrus pars triangularis ($t(54)=-2.24$, $p=0.030$, Cohen's $d=0.59$) and opercularis ($t(54)=-2.02$, $p=0.040$, Cohen's $d=0.54$). The results remained significant when adjusting for age [right inferior frontal gyrus pars triangularis ($F(1,53)=6.926$, $p=0.011$) and for pars opercularis ($F(1,53)=5.35$, $p=0.03$)]. The p-values did not survive the FDR correction.

3.1.6. Age of onset—The sample had 11 early-onset GAD participants and 16 late-onset GAD participants. However, the DTI sequence was acquired only on a sub-sample which contained 6 early-onset GAD participants and 12 late-onset GAD participants. Late-onset GAD had higher MD in the right and left fusiform gyrus [Wilcoxon rank sum=73, $p=0.024$]. Early-onset GAD had higher volume in the left rostral ACC [Wilcoxon rank sum=219, $p=0.0038$, while late-onset GAD had higher thickness in the right medial OFC [Wilcoxon rank sum=108, $p=0.033$]. The results did not survive FDR correction.

3.2. Correlation analysis

3.2.1—Higher worry severity was associated with decreased MD in the left OFC ($r=-0.37$, $p=0.02$) and left ACC ($r=-0.35$, $p=0.03$), and with increased MD in the right putamen ($r=0.335$, $p=0.042$). After controlling for age, the correlations changes were minimal: left OFC, $r=-0.38$ ($p=0.02$), left ACC $r=-0.36$ ($p=0.03$), and right putamen $r=0.35$ ($p=0.04$).

Higher worry severity was associated with decreased thickness in left caudal ACC ($r=-0.27$, $p=0.04$) and left rostral ACC ($r=-0.36$, $p=0.007$). When controlling for age, the associations between cortical thickness and PSWQ have changed as follows: left caudal ACC $r=-0.22$ ($p=0.11$), and left rostral ACC $r=-0.30$ ($p=0.023$).

3.2.2—Age of participants was significantly correlated with global WMH burden ($r=0.32$, $p=0.02$) and with WMH burden in the left cingulum bundle ($r=0.34$, $p=0.01$) and left ILF (inferior longitudinal fasciculus) ($r=0.27$, $p=0.05$). Age was significantly correlated with lower FA in the right uncinate fasciculus ($r=-0.37$, $p=0.02$), with lower mean diffusivity in left amygdala ($r=-0.39$, $p=0.02$), left caudate ($r=-0.33$, $p=0.04$), left inferior OFC and left lateral OFC ($r=-0.41$, $p=0.01$ and $r=-0.39$, $p=0.02$).

4. Discussion

Our results indicate that late-life GAD is associated with gray matter changes in areas involved in emotion regulation (e.g., inferior frontal gyrus, rostral ACC, striatum, OFC) (Etkin, 2015; Ochsner and Gross, 2005). Although the results did not survive multiple comparison correction, the effect sizes suggest a large effect regarding decreased cortical

thickness in the OFC, rostral ACC and inferior frontal gyrus in late-life GAD. Some of our results confirm previous reports regarding the role of OFC in late-life GAD (Mohlman et al., 2009). The results also indicate a moderate effect of worry severity, although these results also did not survive FDR correction. The moderate effect of worry severity supports a dimensional approach to investigations focused on the structural neurobiology of late-life worry. Thus, GAD status but also worry per se seem to have an impact on the structural integrity of specific brain regions, but our study was underpowered to detect these changes in the context of multiple comparison corrections.

While the results were consistent with regard to white matter when analyzing both macro- and microstructural changes, the results in the grey matter are more discrepant. Thus, the decreased cortical thickness noticed in GAD participants in the OFC, pACC and inferior frontal is replicated only in the OFC when we examined the mean diffusivity changes. These discrepancies between findings in different modalities may be related to the small sample size, but also to true differences in the underlying structural features (e.g., cortical thickness or mean diffusivity) measured by the different modalities.

Our results do not support the hypothesis regarding the association of white matter changes with late-life GAD. Given the well-known association between age and white matter hyperintensity burden (Gunning-Dixon et al., 2008), we conducted an age-WMH correlation analysis to verify the accuracy of our negative results. As expected, age was associated with higher WMH burden, both globally and in specific white matter tracts. A recent study from our group reported on the role of WMH in moderating emotion regulation in late-life GAD (Karim et al., 2016). Thus, although the changes in white matter integrity are limited, these changes may interfere with the neural basis of emotion regulation in late-life.

The dissociation between gray and white matter structural changes may be related to the differential impact of high cortisol on gray/white matter. Several studies have reported that late-life GAD is associated with elevated basal and peak salivary cortisol (Mantella et al., 2008) and that pharmacotherapy significantly reduces both peak and total cortisol (Lenze et al., 2011). Recent studies have indicated that higher cortisol levels are associated with significantly smaller gray than white matter differences in non-demented older adults (Geerlings et al., 2015)(Cox et al., 2015b). This dissociating effect is supported by basic research findings showing that stress and glucocorticoids decrease neurogenesis while increasing oligodendrogenesis (Chetty et al., 2014), a finding that suggests that chronic stress and high cortisol may affect gray and white matter differently.

Our study has several strengths: 1) we used a well characterized late-life GAD sample, 2) we used various methods (micro and macroscopic white matter lesions, cortical volume and thickness) to capture structural changes. Among our limitations, the most relevant one is the reduced sample size and consequently the effect of multiple comparison correction. We are also aware that the small size may render unstable effect sizes. Also, we could not explore adequately the effect of age of onset and thus we cannot make inferences whether the observed gray matter thinning in the prefrontal cortex is the effect of chronic anxiety (early-onset GAD) or the effect of aging underlying late-onset GAD, as the very limited sample size rendered difficult-to-interpret results. Although the lack of depression comorbidity

allowed us to make more targeted inferences regarding GAD, this sample characteristic diminishes the generalizability of the results (as the MDD-GAD comorbidity may reach 80%)(Goisman et al., 1995).

In conclusion, our results indicate some distinct structural differences associated with late-life GAD, especially in the gray matter areas associated with emotion regulation. Studies with larger samples and using higher resolution techniques will be needed to capture the rather subtle structural changes associated with late-life GAD.

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Highlights

- Elderly GAD participants had lower cortical thickness in the orbitofrontal cortex (OFC), inferior frontal gyrus, and pregenual anterior cingulate cortex (ACC) than elderly non-anxious participants.
- Higher worry severity was associated with gray matter changes in OFC, ACC and the putamen.
- Late-life GAD is associated with gray matter changes in areas involved in emotion regulation, more so than with white matter changes.
- Anxiety-related chronic hypercortisolemia may have a dissociative effect on gray and white matter integrity.

Fig. 1.
FLAIR image

Fig. 2.
Cortical parcellation: 2A. Overall parcellation map. 2B. Surface parcellation for one subject.
2C. Thickness map.

Fig. 3. Group differences in cortical thickness for 3A) left rostral ACC, 3B) right and 3C) left medial OFC and in gray matter volume 3D) right pars triangularis and 3E) right pars opercularis

Table 1

Clinical and demographic characteristics of the sample.

	GAD N=28	Controls N=31	Group Comparison (X, T (df), p value)
Age [mean (SD)]	66.91 (5.98)	70.38 (7.88)	T (57)= -2.0, p=0.05
Gender (F)	19	17	X(1)=1.05, p=0.31
Race (W/AA)	27/1	27/4	p =0.36 [#]
Education [years, mean (SD)]	15.82 (2.7), n=23	16.42 (3.9), n=26	T (47)= -0.61, p=0.54
HARS [mean (SD)]	20.46 (3.9)	3.12 (1.8)	T (37.17)=21.53, p<0.0001 *
HDRS [mean (SD)]	12.95 (3.02), n=21	1.28 (1.31), n=21	T (27.24)=16.22, p<0.0001 *
MMSE [mean (SD)]	28.96 (0.94), n=27	29.32 (0.94), n=31	T (56)= -1.45, p=0.15
PSWQ [mean (SD)]	57.32 (11.77)	33.65 (8.76)	T (57)=8.82, p<0.0001
Duration of illness [years, mean(SD)]	24.4 (24.46)	NA	NA
DKEFS trails making Con4vsCon5 [mean (SD)]	8.35 (2.35), n=20	10.24 (2.68), n=21	T (39)= -2.39, p=0.02
DKEFS Color Word interference			
Cond3Final [mean (SD)]	10.6 (1.73), n=20	12.55 (2.6), n=22	T (40)= -2.83, p=0.007
Cond4Final [mean (SD)]	9.9 (1.86), n=20	11.31 (3.44), n=22	T (40)= -1.64, p=0.10 *
DKEFS Sorting Test			
ConfCorrSortTotalScal [mean (SD)]	13.11 (2.47), n=19	13.18 (3.10), n=22	T (39)= -0.09, p=0.93
CombDescCompScal [mean (SD)]	11.37 (2.70), n=19	11.90 (3.59), n=22	T (39)= -0.54, p=0.59
RBANS Visuospatial Index [mean (SD)]	95.95 (9.81), n=20	102.5 (17.8), n=21	T (39)= -1.45, p=0.15
RBANS Language Index [mean (SD)]	102.2 (16.73), n=20	104.5 (9.75), n=22	T (40)= -0.53, p=0.60 *
RBANS Attention Index [mean (SD)]	104.6 (14), n=20	111.2 (16.53), n=22	T (40)= -1.39, p=0.17
RBANS Immediate Memory Index [mean (SD)]	104.6 (12.33), n=20	110.7 (11.22), n=22	T (40)= -1.69, p=0.10
RBANS Delayed Memory Index [mean (SD)]	101 (15.40), n=20	106.2 (14.91), n=22	T (40)= -1.12, p=0.27
RBANS Total Score [mean (SD)]	105.3 (24.90), n=20	110 (12.10), n=22	T (40)= -0.79, p=0.43
CIRS-G	5.6 (2.64) n=20	(2.11) (n=20)	T(38)=1.26, p=0.22

X=Chi-square ([#] Fisher's Exact as appropriate), T=T statistic (degrees of freedom).

* Satterthwaite approximation was used to compute the variance and adjusted degrees of freedom due to inequality of variances between the two groups.

Table 2

Structural differences between GAD participants and healthy comparison participants

Structural measures	Region	GAD participants (mean/SD) n	Healthy comparison participants (mean/SD) n	Statistical test/Effect size
Whole brain WMH burden		0.00202 (0.004) n=24	0.00180 (0.002) n=29	T(51)=0.21, p=0.83 (ES=0.07) (ES [#] =0.26)
Fractional Anisotropy		0.373 (0.015) n=18	0.377 (0.015) n=19	T(35)= -0.79, p=0.44 (ES=0.27) (ES [#] =0.27)
DTI-MD	Pallidum GM	0.33 (0.64) n=18	0.00005 (0.00002) n=19	T(17)=2.19 *, p=0.042 (ES=0.73) (ES [#] =0.73)
	Frontal mid orbital	0.63 (0.57) n=18	2.57 (3.61) n=19	T(18.97)= -2.32 *, p=0.030 (ES=0.74) (ES [#] =0.74)
Gray Matter Volume	Right IFG (pars triangularis)	3523.4 (542.6) n=27	3861.8 (584.9) n=29	T(54)= -2.24, p=0.03, (ES=0.59) (ES [#] =0.72)
	Right IFC (pars opercularis)	3282.4 (525) n=27	3631.4 (743.1) n=29	t (54)= -2.02 *, p=0.047, (ES=0.54) (ES [#] =0.64)
Cortical thickness	Left Pregenuel ACC	2.71 (0.21) n=27	2.89 (0.23) n=29	t(54)= -2.89, p=0.005, (ES=0.76) (ES [#] =0.66)
	Right Medial OFC	2.262 (0.12) n=27	2.36 (0.18) n=29	t(54)= -2.27, p=0.027, (ES=0.61) (ES [#] =0.52)
	Left Medial OFC	2.37 (0.16) n=27	2.46 (0.17) n=29	T(54)= -2.03, p=0.047, (ES=0.54) (ES [#] =0.48)

Legend: WMH=white matter hyperintensity, DTI-MD= Diffusion Tensor Imaging - Mean Diffusivity, GM=gray matter; IFG= inferior frontal gyrus; ACC=anterior cingulate cortex; OFC= orbito-frontal cortex.

* Satterthwhite approximation for variance adjustment. ES=effect size (Cohen's d). **ES[#]=adjusted by age effect size.**