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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.

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

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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 et al., 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 et al., 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 et al., 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 et al., 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 et al., 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-KFES, 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 × 240 mm, 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 mm^2, voxel size = 1 × 1 × 3 mm^3, 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 mm^2, voxel size = 2 × 2 × 3 mm^3, TR = 5300 ms, TE = 88 ms, TI = 250 ms, and flip angle = 90°, 12 diffusion directions, diffusion weighted values b = 1000 s/mm^2 with reference b = 0 s/mm^2, 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 Fig. 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 tenser

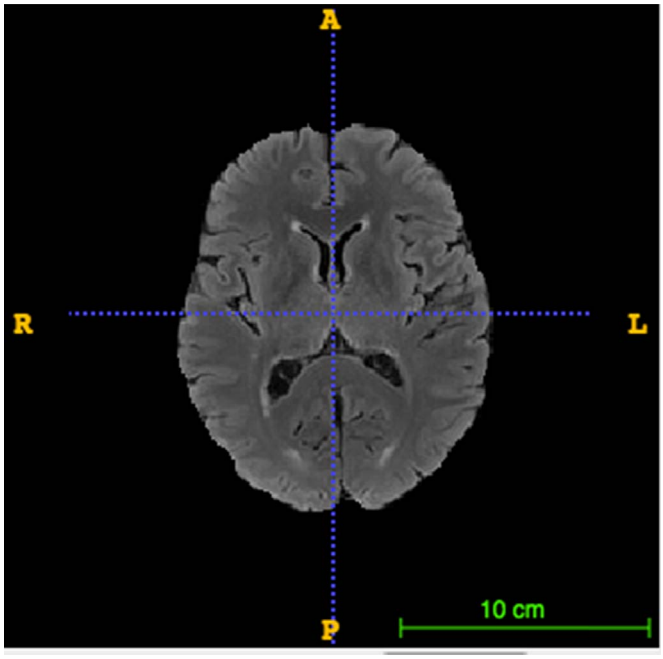

Fig. 1. FLAIR image.