ALTERED CEREBRAL BLOOD FLOW PATTERNS ASSOCIATED WITH PATHOLOGIC WORRY IN THE ELDERLY

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Background: Generalized anxiety disorder (GAD) is the most prevalent anxiety disorder among the elderly and has high functional and cognitive morbidity. However, late-life GAD is relatively understudied and its functional neuroanatomy is uncharted. Several imaging studies have suggested abnormalities in the cognitive control systems of emotion regulation in anxiety disorders in young adults. The aim of this study was to examine the neural correlates of emotion regulation in late-life GAD.

Method: We compared 7 elderly GAD subjects and 10 elderly nonanxious comparison subjects using functional MRI. Regional cerebral blood flow (rCBF) was measured using pulsed arterial spin labeling perfusion MRI at rest and during an emotion regulation paradigm.

Results: Relative to the rest condition, elderly nonanxious comparison subjects had increased rCBF during worry induction (WI) in the right insula, bilateral amygdala, and associative temporocipital areas. Elderly GAD subjects had increased rCBF during WI in the associative temporocipital areas, but not in the insula or the amygdala. During worry suppression (WS), elderly nonanxious comparison subjects had increased rCBF in the prefrontal cortex (PFC) and dorsal ACC. Elderly GAD subjects had no changes in rCBF during WS in the PFC.

Conclusions: When attempting to regulate their emotional responses, elderly anxious subjects failed to activate prefrontal regions involved in the downregulation of negative emotions. These results, showing that elderly anxious subjects are not effectively engaging the PFC in suppressing worry, may be clinically relevant for developing personalized therapeutic strategies for the treatment of late-life GAD. Depression and Anxiety 28:202–209, 2011.

Key words: pathologic worry; generalized anxiety; elderly; functional MRI; arterial spin labeling

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INTRODUCTION

Generalized anxiety disorder (GAD) is centrally defined by chronic, uncontrollable worry that causes significant distress and impairment in functioning.\(^1,2\) With an estimated community prevalence of 7.3\%, late-life GAD is the most common anxiety disorder among the elderly.\(^3,4\) Late-life GAD is associated with decreased quality of life,\(^5,6\) cognitive impairment,\(^7,8\) increased health care utilization,\(^9,10\) and poorer recovery after disabling medical events.\(^5,9\) Elderly GAD subjects have a three-fold increase in risk of health-related activity limitation, compared to nonanxious elderly,\(^5\) which is on par with the disability associated with late-life major depressive disorder.\(^11\)

Despite its prevalence and clinical impact, GAD is the least studied, the least understood, and arguably the least treated mental disorder in the elderly.\(^6,10\) Due in part to our lack of understanding of GAD in the elderly, treatment response in late-life GAD is highly variable\(^11\) and established treatments for midlife GAD, such as CBT, have failed to prove advantageous in late-life GAD.\(^12,13\)

Emotion regulation facilitates adaptive behavior and decision-making in response to salient events. Poor emotion regulation strategies, such as abnormalities in the capacity to downregulate negative affect, are crucial in defining the vulnerability to anxiety disorders.\(^14\) Data from anxiety-prone adolescents and young adults suggest an excessive engagement of the lateral prefrontal cortex (PFC) during downregulation of negative emotions.\(^15,16\) In midlife GAD subjects, Etkin et al. recently reported abnormal amygdala-lateral PFC coupling.\(^17\) As the lateral PFC-amygdala connectivity was strongest in the least anxious subjects, the authors suggested a compensatory role for the lateral PFC in the cognitive regulation of emotion in GAD.\(^17\) Other data reported in young adults show that GAD is associated with deficits in emotion regulation through failure to engage the ACC,\(^18\) exaggerated amygdala reactivity to warning cues preceding aversive/neutral pictures,\(^19\) disrupted connectivity patterns of the amygdala subregions (basolateral and centromedial nuclear groups),\(^12\) treatment response correlated with greater pretreatment reactivity of the rACC and lesser pretreatment reactivity of the amygdala,\(^20\) or increased activation in the medial PFC and ACC during mood-induction sentences/faces.\(^21\) Furthermore, alterations have been described in other structures, such as insula\(^24\) and the bed nucleus of stria terminalis.\(^22,23\)

Overall though, the brain circuits altered in GAD and anticipatory anxiety are less well known at this time as the ones involved in fear and panic.

However, the neural network abnormalities described in younger adults might not be entirely translatable into the elderly, given the anatomical and pathophysiological changes observed in the aging brain.\(^25\) One particular gap in our understanding of late-life GAD concerns the underlying structural and functional neuroanatomy of worry regulation. Uncontrollable worry \([=\) future-oriented anxious apprehension accompanied by a feeling of uncontrollability\] represents the cardinal feature of GAD, contributing to the clinical differentiation between GAD and depression.\(^26,27\) Thus, defining the neural basis of worry modulation in the elderly would facilitate further insights into the treatment-response particularities of late-life GAD.

In this study, we used arterial spin labeling (ASL) perfusion fMRI to study the neural basis of worry modulation of late-life GAD. ASL measures regional cerebral blood flow (rCBF) by magnetically labeling arterial blood water as an endogenous tracer.\(^28\) Because rCBF is a measure of changes at capillaries level, ASL offers a more accurate reflection of the neuronal activities than the gradient echo BOLD, which is biased toward venous blood flow. By labeling inflowing blood water proximal to the imaging location, the perfusion signal is subsequently obtained by subtracting the labeled image from the control image. Due to this pairwise subtraction of temporally adjacent images, ASL data demonstrate a reduction of the low-frequency signal drift that degrades fMRI based on BOLD contrast over time.\(^29\) This reduction renders ASL perfusion MRI a useful tool for the investigation of slow changes in neural activity (e.g. changes sustained over several minutes), such as the changes evoked by mood states such as worry.\(^29\) This choice is further supported by a recent fMRI study that described the persistent nature of worry in young adult GAD subjects undergoing a worry-induction paradigm.\(^30\)

We examined changes in rCBF patterns following worry modulation (induction and suppression) in elderly GAD subjects, compared to elderly nonanxious subjects. Given the variable response reported in late-life GAD to top-down psychotherapeutic approaches,\(^12\) we hypothesized that compared with nonanxious elderly, elderly GAD would have abnormal rCBF in the lateral PFC areas associated with top-down cognitive control of negative emotions.\(^31\)

METHODS

SUBJECTS

Seventeen participants, aged 60 and older, were recruited: 7 GAD subjects and 10 elderly comparison subjects. Participants were recruited using the registry from the Advanced Center for Intervention and Services Research in Late-Life Mood disorders from the University of Pittsburgh as well as subjects previously enrolled in a study of pharmacotherapy for late-life GAD.\(^11\)

The study was approved by the University of Pittsburgh Institutional Review Board.

INCLUSION AND EXCLUSION CRITERIA

Anxious subjects had a principal diagnosis of GAD for at least 6 months, according to the Structured Clinical Interview for DSM-IV\(^32\) and a score of 17 or higher on the Hamilton Anxiety Rating Scale (HARS).\(^31\) Patients with other anxiety disorders were
included if GAD was the principal diagnosis (based on severity and duration), as were patients with a past history of alcohol or substance abuse that was in full remission for at least 3 months. Although lifetime comorbid unipolar depression was allowed if GAD was the primary diagnosis (based on duration), none of the subjects included in this study had current Major Depressive Disorder at the time of scanning.

Exclusion criteria were lifetime psychosis or bipolar disorder, dementia, increased suicide risk (e.g. current ideation), medical instability according to review of medical chart data, ongoing psychotherapy, and current antidepressant or anxiolytic use. All subjects were psychotropic-free at the time of scanning.

MEASURES

Participants were further assessed using the self-report Penn State Worry Questionnaire[34] and the GAD Severity Scale (GADSS).[35] Cognitive status was evaluated with a comprehensive battery of neuropsychological measures widely used for older adults. The neuropsychological measures included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[40] The RBANS provides index scores measuring Attention (forwards digit span and coding task), Immediate Memory (list and story recall), Visuospatial Constructional Skills (figure copy and line orientation tasks), and Delayed Memory (delayed list, story, and figure recall). Because the RBANS does not assess executive functioning and other higher level abilities, such as working memory, we also administered the Delis–Kaplan Executive Function System,[36] Sorting Test, Inhibition Test, and Inhibition/Switching Tests to measure problem solving, conceptual ability, and mental flexibility.

EXPERIMENTAL DESIGN

The fMRI block design involved an initial 5 min resting state (RS) phase followed by five blocks of the worry modulation task. During the RS, patients were asked to lie still in the scanner with eyes closed and not to think of anything in particular.

To examine the functional neurobiology of worry modulation, we used a personalized worry script. The worry script consists of five individualized worry statements alternating with instructions to suppress worry. During subjects’ initial evaluation, we elicited five specific worry themes. These themes were used to create sentences that instructed the subject to worry “as hard as s/he can, as s/he usually does it” about that specific theme (e.g. “worry about your back pain”). In order to standardize the paradigm, subjects rehearsed the worry modulation task before the experiment and they offered feedback regarding the accuracy of each worry sentence. During the experiment, each worry induction (WI) statement remained on the screen for 1 min. The periods of WI alternated with five periods of worry suppression (WS). During the WS, the subject read on the screen a sentence instructing him to stop worrying and to think about a beautiful sunset at the beach.” After each worry modulation block (WI or WS), subjects were asked to self-report the severity of anxiety [1 = no anxiety, 4 = severe anxiety].

DATA ACQUISITION AND ANALYSIS

We used the FAIREST pulsed ASL sequence.[29,38–40] The water saturation pulse was applied at 800 msec after the global (corresponding to the control) or slice selective inversion (corresponding to the label). The delay after the saturation pulse was chosen was 1,200 msec. Twenty-two slices were acquired sequentially from inferior to superior using a gradient-echo EPI sequence. Imaging parameters: matrix size 64X64, TR/TE = 4,000/28 msec, slice thickness 4 mm, gap = 2 mm.

The field of view (FOV) was set at 24 cm to insure full coverage of the head. We obtained 80 acquisitions followed by a standard T1 map sequence. T1-weighted anatomical images were acquired parallel to the plane connecting the anterior and posterior commissures (TR/TE = 500/11 msec, FOV = 24 x 24 cm, slice thickness = 3.8 mm, matrix = 256 x 256).

Functional MRI data were preprocessed using the SPM5 software package (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MathWorks Inc., Natick, MA). After motion correction, the functional images from each subject were normalized into the standard Montreal Neurological Institute template space (Co-lin27).[41] A Gaussian smoothing filter (10 mm full width at half maximum) was then used on the normalized functional images to reduce spatial noise.

The ASL data were analyzed with the SPM toolkit provided by Wang et al. (http://cfn.upenn.edu/perfusion/software.htm). This method generates quantitative cerebral perfusion maps estimates by subtracting the tagged and untagged EPI images. These quantitative maps, one for each task block, were then used for the first- and second-level analysis.

In the first-level analysis, the following conditions were modeled for each subject: RS, WI, and WS.

In the second-level analysis, in order to locate the regions with increased rCBF during WI, we subtracted the RS perfusion map from the WI perfusion map (WI-RS). Similarly, in order to locate the regions with increased rCBF during worry suppression, we subtracted the WS perfusion map from the WS perfusion map (WS-RS). Next, we used a group-level one-sample two-tailed t-test to identify within-group differences: nonanxious comparison subjects WI-RS, nonanxious comparison subjects WS-RS, GAD subjects WI-RS, and GAD subjects WS-RS.

Between groups differences were identified using a two-sample two-tailed t-test (nonanxious comparison group versus GAD group).

For both within-group and between-groups analyses, the resulting t-maps were then thresholded at a corrected P<.05 using False Discovery Rate (FDR).

RESULTS

Demographic and clinical data are presented in Table 1. Late-life GAD subjects were significantly younger than elderly nonanxious comparison subjects; therefore, between-group differences were confirmed while controlling for age. Other Anxiety Disorders diagnosed in the late-life GAD group were Social Phobia (3/7), Specific Phobia (2/7), and Obsessive–Compulsive Disorder (1/7). There were no significant differences between the two groups with respect to the multiple cognitive domains analyzed. There were no differences in self-reported worry between elderly GAD and nonanxious subjects after WI (mean worry severity 2.92 elderly GAD versus 2.87 nonanxious subjects; P = .89) or after WS (mean worry severity 1.73 elderly GAD versus 1.46 nonanxious subjects; P = .44).

EFFECTS OF WORRY INDUCTION ON rCBF (SEE TABLE 2)

Nonanxious comparison subjects: worry induction—resting state (Fig. 1A). Compared with RS, elderly controls showed increased rCBF during WI in the superior temporal gyrus [Brodmann area
TABLE 1. Demographic and clinical characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Late-life GAD subjects (N = 7)</th>
<th>Elderly comparison subjects (N = 10)</th>
<th>t-Test, DF, P (two-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>63.3 [3.9]</td>
<td>76.3 [4.0]</td>
<td>6.5, 15, P &lt;.001</td>
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<tr>
<td>Gender (female)</td>
<td>5/7</td>
<td>6/10</td>
<td></td>
</tr>
<tr>
<td>Race (white)</td>
<td>6/7</td>
<td>8/10</td>
<td></td>
</tr>
<tr>
<td>HRSA (mean, SD)</td>
<td>18.7 [2.8]</td>
<td>3.2 [1.3]</td>
<td>15.1, 15, P &lt;.001</td>
</tr>
<tr>
<td>PSWQ (mean, SD)</td>
<td>57.2 [11.5]</td>
<td>33 [8.2]</td>
<td>5.06, 15, P &lt;.001</td>
</tr>
<tr>
<td>GADSS (mean, SD)</td>
<td>9.5 [1.6]</td>
<td>2.3 [1.1]</td>
<td>7.3, 15, P &lt;.001</td>
</tr>
<tr>
<td>DKEFS inhibition (mean, SD)</td>
<td>11.8 [2.2]</td>
<td>12.1 [2.18]</td>
<td>0.2, 15, P =.8</td>
</tr>
<tr>
<td>DKEFS sorting (mean, SD)</td>
<td>12.8 [3.8]</td>
<td>11.5 [3.13]</td>
<td>0.8, 15, P =.4</td>
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<tr>
<td>DKEFS inhibition/switching (mean, SD)</td>
<td>11.4 [2.9]</td>
<td>11.5 [1.77]</td>
<td>0.06, 15, P =.9</td>
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<td>RBANS immediate memory index score (mean, SD)</td>
<td>98.4 [8.6]</td>
<td>105.7 [11.5]</td>
<td>1.04, 15, P =.2</td>
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<td>RBANS visuospatial construction index score (mean, SD)</td>
<td>82.7 [12.9]</td>
<td>91.0 [20.03]</td>
<td>0.9, 15, P =.3</td>
</tr>
<tr>
<td>RBANS attention index score (mean, SD)</td>
<td>99.2 [14.5]</td>
<td>109.8 [10.4]</td>
<td>1.7, 15, P =.1</td>
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<tr>
<td>RBANS delayed memory index Score (mean, SD)</td>
<td>101.1 [10]</td>
<td>96.4 [10.6]</td>
<td>0.9, 15, P =.4</td>
</tr>
</tbody>
</table>

HRSA, Hamilton Rating Scale for Anxiety; PSWQ, Penn State Worry Questionnaire; GADSS, Generalized Anxiety Disorder Severity Scale; DKEFS, Delis Kaplan executive function system; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Figure 1. Regional cerebral blood flow (rCBF) differences during worry induction ((A) nonanxious elderly subjects; (B) elderly GAD; (C) between-group comparison: elderly GAD versus elderly nonanxious subjects).

EFFECTS OF WORRY SUPPRESSION ON rCBF (SEE TABLE 2)

Nonanxious comparison subjects: worry suppression—resting state (Fig. 2A). Compared with RS, elderly controls showed increased rCBF during WS in the left dlPFC (BA 46), left vlPFC (BA 10), and right dmPFC (BA 8) [t = 9.7, df = 9, P <.001 (FDR corrected)]

Elderly GAD subjects worry suppression—resting state (Fig. 2B). Compared with RS, elderly GAD subjects showed increased rCBF during WS in posterior temporo–parieto–occipital associative areas (left > right) (BA 21, BA 37) [t = 15.5, df = 6, P <.001 (FDR corrected)] and left dorsal ACC (BA 24) [t = 4.8, df = 6, P <.05 (FDR corrected)] while having no suprathreshold rCBF in the prefrontal areas.
Between groups comparison worry suppression—resting state (Fig. 2C). Compared with nonanxious elderly, GAD subjects had increased rCBF in the left fusiform gyrus \([t = 3.7, df = 15, P = .001\) uncorrected, \(x = -34.5, y = -56.7, z = -11.6\)]. Compared with GAD subjects, nonanxious elderly had increased rCBF in the left lateral prefrontal area \([t = 1.75, df = 15, P = .05\) uncorrected, \(x = -48.1, y = 30.3, z = 4.7\)]. We repeated the analysis adding age as the covariate and the results were similar (results available upon request).

None of the between-groups comparison analyses survived FDR multiple comparison corrections.

### CONCLUSION

Our results indicate that during WI, elderly GAD subjects have increased rCBF in the posterior associative temporooccipital areas, most likely due to the role of these areas in the required mental visual imagery of the worry modulation task. Nonanxious elderly also engage the associative temporooccipital areas but, in addition, they have increased rCBF in the insula and the amygdala. These two latter areas have been cited frequently in the literature in connection with emotion processing. It is unclear why elderly GAD subjects engage less the insula/amygdala during WI. One explanation may be that these subjects have a baseline hyperactive limbic system, and thus the differences in rCBF between RS and WI would be minimal. To test this, we analyzed the between-groups rCBF differences during RS; we found no differences between elderly GAD and nonanxious subjects with regard to either amygdala or prefrontal areas, even when we relaxed the significance criteria to \(P < .01\), uncorrected (results available upon request). A more fitting interpretation places the “silent amygdala” in the...
context of the Borkovec model of GAD. The model considers worry a cognitive process designed to avoid the anxiogenic images that induce somatic activation through increased noradrenergic discharge. Thus, as worry represents an avoidance process of anxious experiences, activation of amygdala during WI is unlikely in pathological worriers. Recent data support a possible malfunction of the amygdalar complex, reporting disrupted amygdalar subregions connectivity in midlife GAD. Our preliminary data extend the support of the model of a “silent” amygdala in GAD into late-life.

The between-group comparison showed that elderly GAD had increased rostral ACC rCBF during WI. The rostral ACC has been frequently involved in the neurobiology of emotional regulation as a key region in assessing the salience of emotional information and the regulation of emotional response. It is possible that the observed increased rCBF in rostral ACC during WI represents a first attempt of elderly GAD to automatically regulate overwhelming negative emotions. We can speculate that WI triggers unconscious appraisal of threat and spontaneous response of areas, such as the ACC, involved in automatic emotion regulation, whereas WS (a prototypical top-down, conscious instruction) increases rCBF to areas involved in instructed emotion regulation.

During WS, elderly nonanxious subjects engaged predominantly the lateral prefrontal areas and the dorsal ACC, areas involved in cognitive control of negative emotions. Elderly GAD subjects did not present any increased lateral prefrontal rCBF during WS.

Our results diverge from findings in young adults and adolescents, which described an excessive engagement of the lateral PFC during downregulation of negative emotions in anxiety-prone participants. There are several factors that might contribute to these divergent results in older age.

First, our project included only elderly with GAD. The disruption of the control network in the elderly due to white matter tracts age-induced damage [e.g. demyelinations, gliosis or axonal degeneration, induced by inflammation or ischemic changes] might contribute to the different results. Our results suggest a rather distinct dysfunctional point in the emotion regulation process in elderly GAD: the prefrontal cognitive control regions fail to engage during attempts to suppress worry. We may speculate that this feature is a central part of the neurobiological signature underlying the persistent and uncontrollable quality of worry experienced by these subjects. Although therapies, such as CBT, are efficacious in midlife GAD, several clinical trials and meta-analyses failed to prove an advantage of CBT over supportive therapy/waiting list in late-life GAD. The failure of elderly GAD to engage the prefrontal areas would offer a neurobiological basis for the decreased efficacy of top-down regulation psychotherapies (e.g. CBT) in elderly with GAD. This distinctive feature may be relevant for novel treatment development (i.e. treatments that correct this deficit), before initiating psychotherapeutic strategies for the treatment of late-life GAD.

Second, the variability of tasks used to probe the emotion regulation may explain some of the differences in results. Thus, in a study exploring emotion regulation in social anxiety disorder (SAD), subjects with SAD engaged cognitive control regions (DLPFC, dACC) to a larger degree than controls when exposed to physical threat stimuli but to lesser degree during regulation of responses to social threat stimuli (the latter being most relevant for SAD psychopathology). We used a task that specifically targeted the suppression of personally relevant worry themes, which may explain the relative decrease in cerebral blood flow in the lateral PFC.

Third, differences in the subject samples across studies influence the aspect of emotion regulation that is highlighted in the anxious subjects. The inclusion criteria of various studies exploring the neurobiology of anxiety encompass a vast array of symptoms from panic or simple phobia to social anxiety or pathological worry. Thus, the subjects’ heterogeneity across studies might also contribute to different results.

Although, relative to the nonanxious comparison subjects, the elderly GAD had significantly higher anxiety scores on all three scales (HARS, PSWQ, GADSS), they did not report significantly higher anxiety during either WI or WS. The trend of higher self-reported anxiety in elderly GAD versus controls (1.73 versus 1.46) during WS was not significant; but given the small sample we cannot make inferences regarding any correlation between persistent perceived anxiety and failure to engage the lateral PFC.

Our study has several strengths. We used an imaging technique (ASL perfusion fMRI) that reduces the low-frequency signal drift that usually degrades BOLD fMRI contrast over time, allowing us to investigate slower changes in neural activity, such as those evoked by WI and suppression. Also, we applied an emotion regulation paradigm designed to specifically probe the core of GAD clinical presentation, namely the persistent and incontrollable quality of worry. As GAD may be particularly detrimental to cognition in older adults, subjects received a comprehensive cognitive evaluation that did not find any significant differences between the two groups. We had a control group and the GAD subjects were scanned medication free, thus eliminating interferences related to treatment response.

LIMITATIONS AND FUTURE DIRECTIONS

The small sample size makes the results unstable and increases the risk for false negatives when using high significance thresholds including multiple comparison corrections. Although the within-group results survived stringent multiple comparison correction, due to
the modest sample size and the variance components in brain perfusion, we obtained a weaker signal during the between-group comparison.\[64\] The comparison group was significantly older than the GAD group; however, our results did not change when we controlled the age difference. Moreover, there were no significant differences in cognitive performance between the two groups. One other limitation was the lack of behavioral data (heart rate, blood pressure, respiration rate, skin conductance) to correlate autonomic response with the phases of emotional regulation. However, behavioral data are more difficult to interpret in elderly samples, given the age-related changes in autonomic response and the modifications to heart rate and blood pressure induced by medications, such as -blockers, which are widely used by the elderly. Our self-reported anxiety index, measured after WI and WS, would have been more informative if compared with a baseline self-reported anxiety index. Although the GAD subjects were free of psychotropics at the time of scanning, we do not know the duration of the medication-free prescanning interval. Further analysis exploring the correlation between worry severity (as measured by HARS, PSWQ, and GADSS) and rCBF changes during worry modulation would require a larger sample.

In conclusion, our results provide evidence of the altered top-down regulation of worry modulation in elderly with GAD. Our results point toward several dysfunctional nodes in the extended network of emotion regulation that include sACC, amygdala and the hippocampus, insula, lateral and orbital PFC.\[31,51\] The recruitment sequence of each of these nodes, the feedforward/feedback interplay in the network during various stages of emotion regulation as well as the role of white matter structural lesions in altering the network’s architecture are subject for future research.

REFERENCES