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Emotion reactivity and regulation in late-life generalized anxiety disorder: Functional connectivity at baseline and post-treatment

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Abstract

Objectives—Generalized Anxiety Disorder (GAD) is one of the most prevalent mental disorders in the elderly, but its functional neuroanatomy is not well understood. Given the role of emotion dysregulation in GAD, we sought to describe the neural bases of emotion regulation in late-life GAD by analyzing the functional connectivity (FC) in the Salience Network and the Executive Control Network during worry induction and worry reappraisal.

Design, setting and participants—Twenty-eight elderly GAD and thirty-one non-anxious comparison participants were included. Twelve elderly GAD completed a 12-week pharmacotherapy trial. We used an in-scanner worry script that alternates blocks of worry induction and reappraisal. We assessed network FC, employing the following seeds: anterior insula (AI), dorso-lateral prefrontal cortex (dlPFC), the bed nucleus of stria terminalis (BNST), the paraventricular nucleus (PVN).

Results—GAD participants exhibited greater FC during worry induction between the left AI and the right orbito-frontal cortex (OFC), and between the BNST and the subgenual cingulate. During worry reappraisal, the non-anxious participants had greater FC between the left dlPFC and the medial PFC, as well as between the left AI and the medial PFC, while elderly GAD had greater FC between the PVN and the amygdala. Following twelve weeks of pharmacotherapy, GAD participants had greater connectivity between the dlPFC and several prefrontal regions during worry reappraisal.

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Conclusion—FC during worry induction and reappraisal points toward abnormalities in both worry generation and worry reappraisal. Following successful pharmacologic treatment, we observed greater connectivity in the prefrontal nodes of the Executive Control Network during reappraisal of worry.

INTRODUCTION

Generalized Anxiety Disorder (GAD) is the most prevalent anxiety disorder in the elderly [1–3]. Late-life GAD is associated with decreased quality of life [4, 5], cognitive impairment (6, 7), and increased health care utilization (4). The onset of GAD in the elderly may reflect both the exposure to age-specific stressors and age-specific brain structural changes (e.g., neuronal degeneration and cerebro-vascular disease)(8).

Late-life GAD is relatively understudied, and the underlying structural and functional neuroanatomy has received little attention (9, 10). This is a particularly unfortunate gap in our knowledge given the mediocre treatment response in late-life GAD[8], [11, 12]. Compared with midlife GAD, late-life GAD has a poorer response to cognitive behavioral therapy (CBT) [13, 14]. To date, there is no published study addressing the neural changes following pharmacotherapy in late-life GAD. The identification of such changes could provide a target for developing targeted treatments for late-life GAD.

Given the role of emotion dysregulation in GAD (15, 16), we were interested in the functional connectivity (FC) in two networks involved in emotion generation and emotion regulation [17]: the Salience Network (SN) and the Executive Control Network (ECN). The SN, comprised of anterior insula, dorsal anterior cingulate (ACC), amygdala, ventral tegmental area and the ventromedial nucleus of the thalamus, is involved in monitoring the salience of interoceptive and external events [18, 19]. Abnormal SN connectivity has been implicated in anxiety disorders as the neural basis for pathologically enhanced salience detection(20–22), but no studies have focused on its FC during emotion regulation in GAD. The ECN, comprised of dorsolateral prefrontal cortex (dlPFC), ventrolateral PFC, dorsomedial PFC, dorsal ACC, lateral parietal cortex, orbital fronto-insula, dorsal caudate and anterior thalamus (23), is critical for complex cognitive tasks such as working memory, cognitive control and decision-making in the context of goal-directed behavior [18]. Recent studies showed that anxious subjects have abnormal dACC response suggesting poor conflict adaptation during an emotional Stoop test [24–26].

Prior research suggested two additional candidate regions that might play a key role in late-life GAD (27–29). The first is the bed nucleus of stria terminalis (BNST), which has been associated with sustained apprehension and considered a key brain region of interest for generalized anxiety [27, 30–32]. The second is the paraventricular nucleus (PVN), which is the apex of the HPA axis and has been frequently implicated in stress regulation and autonomic response [29, 33]. Recent research on the biology of late-life GAD has linked high cortisol with changes in cognitive domains such as immediate and delayed memory in elderly GAD [6, 34].

Our goal in the present study was to test for differences in FC during worry induction and worry reappraisal between (1) late-life GAD participants and non-anxious comparison participants, (2) late-life GAD participants before and after twelve weeks of antidepressant treatment. We hypothesized that pre-treatment, elderly GAD would have aberrant FC during worry induction and worry reappraisal. More specifically, based on the clinical literature regarding poor emotion regulation in GAD(15) and poor response to CBT in late-life GAD(35), we hypothesized that 1) compared with non-anxious older adults, elderly GAD would have greater connectivity during both worry induction and worry reappraisal in the anxiety-related networks (SN, BNST, PVN); 2) compared with non-anxious older adults, elderly GAD would have reduced FC in the ECN during reappraisal of worry. We further hypothesized that SSRI treatment would improve the FC in both SN and ECN.

METHODS

Participants

Elderly GAD and elderly non-anxious participants were recruited from an ongoing NIMH-funded trial ("Structural and functional neuroanatomy of late-life GAD"). Additionally, the Brain and Behavior Foundation funded a 12-week treatment trial for a sub-sample of the elderly GAD. Elderly 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) (36) and a score of 17 or higher on the Hamilton Anxiety Rating Scale (HARS)(37) at the time of first scanning. 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). Exclusion criteria: Mini Mental Examination Scale (MMSE)(38) scores of 24 or lower, clinical diagnosis of dementia, Major Depressive Disorder at the time of scanning. Other exclusion criteria were lifetime psychosis or bipolar disorder, increased suicide risk (e.g. current ideation), ongoing psychotherapy, and current antidepressant or anxiolytic use(10).

Assessments and treatment

Thirty-one non-anxious elderly and twenty-eight elderly GAD have been included in this study. Twelve elderly GAD completed the 12-week open pharmacotherapy trial. All participants were psychotropic-free at the time of first scanning. Participants were also evaluated clinically with the Penn State Worry Questionnaire (PSWQ) (39), the Hamilton Depression Rating Scale (HDRS)(40) and the Cumulative Illness Rating Scale, Geriatric (CIRS-G)(41). Following the initial MRI scan, participants were treated with citalopram (titrated to 20 mg/d, as tolerated). All post-treatment participants had a HARS of 14 or lower, which is considered the cutoff point for treatment response [(43)].

Experimental design

The fMRI block design involved an initial five-minute resting state phase followed by five blocks of the worry task. During the resting state participants were asked to lie still in the scanner, eyes closed and not to think of anything in particular.

To examine the functional neurobiology of worry reactivity and regulation, we used a personalized worry script. The worry script consisted of three individualized worry generating statements alternating with instructions to reappraise worry. During participants' initial evaluation, we elicited specific worry themes. These themes were used to create sentences that instructed the participant to worry "as hard as s/he can, as s/he usually does it" about that specific theme. In order to standardize the paradigm, participants rehearsed the worry script prior to the experiment and they offered feedback regarding the accuracy of each worry induction and each worry reappraisal sentence. During the experiment, each worry induction/reappraisal statement remained on the screen for one minute. During the worry reappraisal the participant read on the screen a sentence instructing him/her to reappraise the worry theme as discussed prior to the in-scanner experiment.

Data acquisition

We used the pseudo continuous arterial spin labeling (pCASL) sequence (44–47) on the Sieman 3T MR scanner at the University of Pittsburgh Medical Center. Twenty-two slices (slice thickness 4mm, gap = 2 mm) were acquired sequentially from inferior to superior for each volume using a gradient-echo EPI sequence. Interleaved images with and without labeling were acquired with the following parameters: matrix size 64X64, FOV=320×320mm, flip angle=90°, TR/TE = 4000/28 msec. We obtained 80 volumes of ASL images for each participant during rest and 296 volumes of ASL images for each participant during the worry script. A T1-weighted anatomical image was 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) for registering functional images to standard MNI space.

Data analysis

The ASL images were processed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Center for Neuroimaging, London, UK. http://www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab version R2012b (Mathworks, Natick, MA). For each subject, the images were realigned, smoothed, and reconstructed for the perfusion and BOLD images by a kinetic model implemented in the algorithm by Wang et al. (ASLtbx, May 2012, http://cfn.upenn.edu/perfusion/software.htm). The estimated whole brain BOLD images were submitted for the seed based connectivity analysis using Conn FC toolbox (http://www.nitrc.org/projects/conn, version 13p) [48].

The voxel-wise connectivity of the whole brain to each seed of interest was estimated by regression, with time series from white matter, CSF and motion included as nuisance covariates. Prior to the regression, the quality of images was evaluated using the Artifact Detection and Correction Tool (ART) version 2.1. (http://www.nitrc.org/projects/art/). The outlier images were detected and scrubbed from subsequent analyses. Individual whole-brain seed-to-voxel connectivity maps were collected and tested for the difference between elderly GAD and non-anxious groups by two-sample t-tests. Pre- and post-treatment difference in FC for the elderly GAD participants was tested by paired t-test. We corrected for multiple comparisons by using Monte Carlo simulations implemented in AlphaSim

(version 2.0/2002; http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html)(49). A corrected $p \leq 0.05$ was deemed significant.

We used as seed the left anterior insula (AI) for the SN, the left dorso-lateral prefrontal cortex (dlPFC, BA 46) for the ECN, the BNST (bilateral), and the PVN. The BNST and the PVN were hand drawn using MRIcron (version 6/2013) on a built in MNI template (ch2better). These non-overlapping regions of interest (ROI) were based on the structures described in the Atlas of the Human Brain (50, 51). The BNST ROI was based on plates 18 (using Talairach reference systems, y=−2.7mm) through 24 (y=+2.7mm) and encompassed the central, medial, lateral, and ventral divisions(50) (see Figure 1). The PVN ROI was based on plates 20 (y=−1.3mm) through 28 (y=8.0mm) and included parvocellular, magnocelluar, dorsal, and posterior subnuclei (50) (see Figure 1). Additional details regarding these ROIs are provided in Table 1.

For the clinical and demographic data, the Mann-Whitney U test was used to test if there were any differences between the distribution of the following variables the non-anxious and elderly GAD groups: age, education, HDRS, PSWQ, HARS, and CIRS-G. The sex and race differences were assessed by the chi-square test.

RESULTS

Clinical and demographic data are presented in Table 2. A summary of the regions (including the peak MNI coordinates and clusters sizes) that showed significant FC effects is presented in Table 3. Unless specified, all the findings presented below survived multiple comparison correction.

A. Group differences in functional connectivity between non-anxious and anxious participants

A.1. Differences during worry induction (Figure 2)

Differences in the SN connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC between the left AI and the right orbito-frontal cortex (OFC). No areas where the GAD showed lower FC during worry induction survived multiple comparison correction.

Differences in the ECN connectivity: Compared with non-anxious participants, GAD participants exhibited the following differences: greater FC between the left dlPFC and cerebellar vermis, the left fusiform gyrus, and the left superior frontal gyrus (BA 10) and lower FC between the left dlPFC and the left and right insular cortex (BA13).

Differences in the BNST connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC between the BNST and subgenual cingulate (BA 24) and lower FC between the BNST seed and the left thalamus.

Differences in the PVN connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC during worry induction between the PVN and the middle

frontal gyrus (BA 6). The results in the opposite direction (non-anxious>GAD) did not survive multiple comparisons correction.

In summary, during worry induction elderly anxious participants had greater connectivity between the left insula seed and the OFC, between the left dlPFC and the fusiform gyrus and the prefrontal cortex (BA10), between BNST seed and the subgenual cingulate, and between the PVN seed and the middle frontal gyrus (BA6).

A.2. Differences during worry reappraisal (Figure 3)

Differences in the SN connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC between the left AI and the left temporal pole (BA 38), left hippocampus, and right superior frontal gyrus (BA 6), and lower FC between the left AI and several frontal regions: left medial frontal (BA 6), dorsal ACC (BA 24), and middle frontal gyrus.

Differences in the ECN connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC between the left dlPFC and the left fusiform gyrus, and lower FC between the left dlPFC and the right PFC (BA 9, BA 10).

Differences in the BNST connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC between the BNST and left medial frontal gyrus.

Differences in the PVN connectivity: Compared with non-anxious participants, GAD participants exhibited greater FC during worry reappraisal between the PVN and the right amygdala. The results for the opposite direction (non-anxious > GAD) did not survive multiple comparisons correction.

In summary, during worry reappraisal, elderly anxious participants had greater connectivity between the left insula seed and the temporal cortex (temporal pole and hippocampus) and BA6, between the dlPFC seed and the fusiform gyrus, between the BNST and the medial frontal gyrus, and between the PVN and the right amygdala. Non-anxious participants had greater connectivity during worry reappraisal between the insula seed and multiple prefrontal regions and between the dlPFC seed and the right prefrontal cortex.

B. Within-subject differences in FC for elderly GAD participants before and after 12 weeks of pharmacotherapy

B.1. Differences during worry induction (Figure 4)

Differences in the SN connectivity: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited lower FC between the left AI and the following regions: left precentral gyrus (BA 6), left medial frontal gyrus (BA 6), and left subgenual cingulate (BA 25).

Differences in the ECN connectivity: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited lower FC between the left dlPFC and the left inferior frontal gyrus (BA 45) and right OFC (BA 47).

Differences in the connectivity of the BNST: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the BNST and the left frontal middle and superior gyri as well as the left lingual gyrus and lower FC between the BNST and the left insula and right supramarginal gyrus (BA 2).

Differences in the connectivity of the PVN: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the PVN and the left medial frontal gyrus (BA 9) and the left lingual gyrus (BA 18) and lower FC between the PVN and the left OFC (BA 11), the supramarginal gyrus (BA 40), left insula (BA 13), and middle frontal gyrus (BA 8).

In summary, during worry induction, elderly GAD had lower connectivity in the salience network and the executive control network after 12 weeks of treatment, while they had greater connectivity between the BNST and PVN seeds and several frontal regions.

B.2. Differences during worry reappraisal (Figure 5)

Differences in the SN connectivity: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the left AI and the cerebellar vermis, as well as the supplemental motor area and the superior frontal cortex (the last did not survive multiple comparison correction) and lower FC between the left AI and the left anterior cingulate (BA 32), left middle temporal gyrus, and the left temporal pole (BA 38).

Differences in the ECN connectivity: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the left dlPFC and the right supramarginal gyrus (BA 40), right superior frontal gyrus (BA 11), right inferior frontal gyrus (BA 47), middle cingulate gyrus, and right cuneus and lower FC between the left dlPFC and the left fusiform gyrus, left rectus (BA 11), and left parahippocampal gyrus (uncus).

Differences in the connectivity of the BNST: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the BNST and the right lingual gyrus (BA 19) and right frontal superior gyrus (BA 10) (did not survive multiple comparison correction) and lower FC between the BNST and the left frontal superior gyrus (BA 6).

Differences in the connectivity of the PVN: Compared with themselves pre-treatment, the post-treatment GAD participants exhibited greater FC between the PVN and prefrontal cortex (right superior frontal gyrus) (this finding did not survive multiple comparison correction) and lower FC between the PVN and the right transverse temporal gyrus (BA 41), left putamen, and middle cingulum (BA 31) (did not survive multiple comparison correction).

In summary, during worry reappraisal, elderly GAD had greater connectivity between the dlPFC and several prefrontal areas after 12 weeks of treatment.

DISCUSSION

Compared with non-anxious participants, elderly GAD show multiple differences in the FC in networks involved in both emotion generation and emotion regulation. Following successful pharmacologic treatment of late-life GAD, we observed several significant changes in the same networks (see Table 4, Fig 6).

The differences reported in the SN during worry induction indicate a stronger connectivity between the insula and the OFC for the GAD participants. As OFC is involved in anticipating the negative affective value of future events [52], our results may indicate that GAD participants attribute negative affective value to worry statement to a larger degree than the non-anxious participants. This observation about FC has a clinically correlate in the dysphoric nature of worry thoughts and it further supports the model of emotion dysregulation in GAD [16]. This model suggests that GAD participants have deficits in emotion generation including a tendency for strong emotional responses mediated by motivational salience to perceive threats (16, 53).

During worry reappraisal, non-anxious participants increased, as expected, the connectivity between the anterior insula and various prefrontal regions [54]. In contrast, the GAD participants show only limited insula connectivity with the prefrontal cortex during reappraisal. As the SN assigns salience to emotional or homeostatic stimuli and accesses the ECN for future weighting of behavioral choices (18), the differences noticed between non-anxious and GAD participants indicate aberrant SN connectivity during both worry generation and reappraisal – excessive attribution of negative affect to worry statements followed by failure to engage the prefrontal cortex during reappraisal (Table 4).

The ECN results reveal a different feature of GAD functional networks pathology. Thus, the greater connectivity between dlPFC and insula noticed during induction of worry in non-anxious participants probably reflects the fine-tuning between salience detection and cognitive demand. The same non-anxious participants switch to a robust ‘in-network’ connectivity during reappraisal, tapping into prefrontal regions frequently engaged in emotion reappraisal [55, 56]. In contrast to the flexibility displayed by non-anxious participants when switching from induction to reappraisal of worry, GAD participants display a rather rigid connectivity of the dlPFC. Thus, during both induction and reappraisal, GAD participants maintain greater connectivity between the dlPFC and the fusiform gyrus and fail to increase the connectivity between the dlPFC and other prefrontal regions. This lack of flexibility in the ECN, especially with regard to the lack of ‘in-network’ prefrontal connectivity may be linked to the poor CBT response noticed in late-life GAD [13]. These results are further supported by the pre-post treatment analysis. Post-treatment GAD participants have greater connectivity between dlPFC and several frontal regions as well as the supramarginal gyrus [57]. These results suggest that pharmacotherapy may ameliorate a connectivity deficit during reappraisal in the ECN and consequently promote efficacy of reappraisal and other cognitive restructuring strategies. Although these results need further confirmation on larger samples, we may speculate that sequential treatment strategies (pharmacotherapy followed by CBT) would prove more efficacious in late-life GAD in order to consolidate response and prevent future relapses [58].

The BNST has been implicated in mediating environmental threat monitoring (59, 60). Our results regarding the greater connectivity between BNST and the subgenual cingulate (GAD>non-anxious), as well as between BNST and insular cortex (pre-treatment>post-treatment GAD) outline a possible hyperactive network involving limbic and paralimbic structures implicated in stress response (60) and excessive attribution of threat [53]. This excessive salience/sustained apprehension/excessive stress response network received additional support when examining the PVN connectivity.

The most striking result from our analysis is the PVN FC differences noted during worry reappraisal. GAD participants have greater connectivity than non-anxious participants between PVN and the right amygdala during worry reappraisal, a result that suggests an increased autonomic response during reappraisal in GAD. Given PVN's role in stress response (33), we may speculate that GAD participants perceive cognitive strategies of worry regulation as stress-inducing and anxiety-provoking. Our results suggest that normative cognitive reappraising strategies may be at odds with the engrained strategies used during worry [15] to the point of triggering somatic anxiety in participants who otherwise are notorious for low cardiovascular flexibility [15, 61, 62].

Our study has several strengths: it analyzes a relatively large sample of elderly GAD participants and it uses an age and cognition matched control group. An additional strength of the GAD sample is that participants were psychotropic free at baseline, as well as "purely" anxious (with no other comorbid psychiatric illnesses at the time of scan, including no Major Depressive Disorder). We used a tailored worry induction and reappraisal task, which allowed us to track the neural response correlated with both generation of worry and reappraisal. We have also explored the FC of seeds that are particularly relevant for the neural basis of GAD (BNSD, PVN, Anterior Insula). Some limitations are worth noting also. The pre/post treatment analysis had a reduced sample, limiting the power to observe differences between the two groups. We did not measure autonomic response following induction and reappraisal of worry and thus we cannot correlate the results that suggest increased stress response with autonomic changes. The worry script used to test emotion regulation lacks test-retest reliability data at this time. Although the GAD participants did not satisfy the criteria for major depression, they have significantly higher HDRS scores than the non-anxious participants. However, the mild range of depressive symptoms associated with high PSWQ and HARS scores are prototypical for the clinical presentation of GAD.

Other future directions would involve expanding the study to midlife and young subjects with generalized anxiety, including autonomic measures of stress response, and comparing the post-treatment effects for pharmacologic and psychotherapeutic interventions in generalized anxiety.

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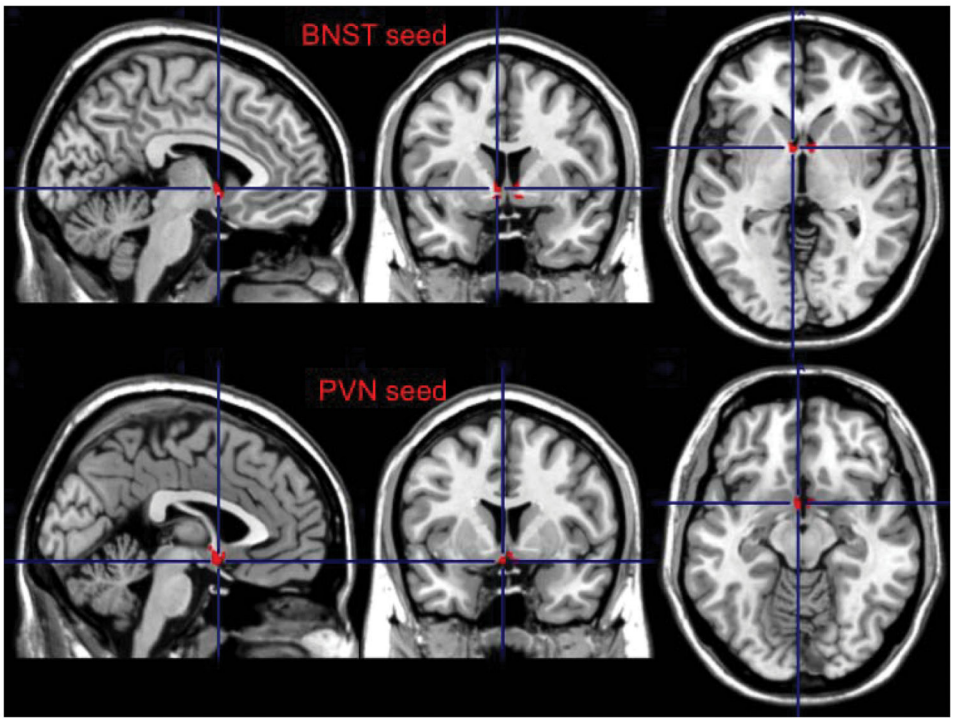

Figure 1.
The Bed Nucleus of Stria Terminalis (BNST) and Paraventricular Nucleus (PVN) seeds

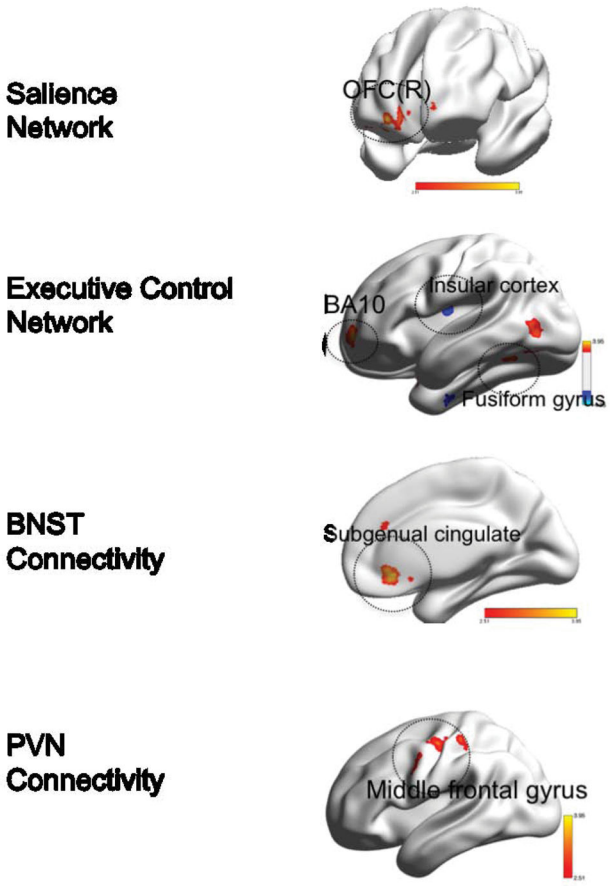

Figure 2. Group differences in functional connectivity during worry induction between elderly GAD participants and elderly non-anxious participants

Red: GAD>non-anxious comparison, blue: non-anxious comparison>GAD. BNST= bed nucleus of stria terminalis. PVN= paraventricular nucleus. OFC(R)=orbito-frontal gyrus, right. BA= Brodmann Area. Visualized using BrainNet Viewer, version 1.42 (64).Salience Network: OFC(R) (t=3.83; df=54). Executive Control Network: BA10 (t=3.71; df=54); Insular cortex (t=4.00; df=54); Fusiform gyrus (t-3.44; df=54). BNST Connectivity: Subgenual cingulate (t=3.95; df=54). PVN Connectivity: Middle frontal gyrus (t=4.25; df=54).

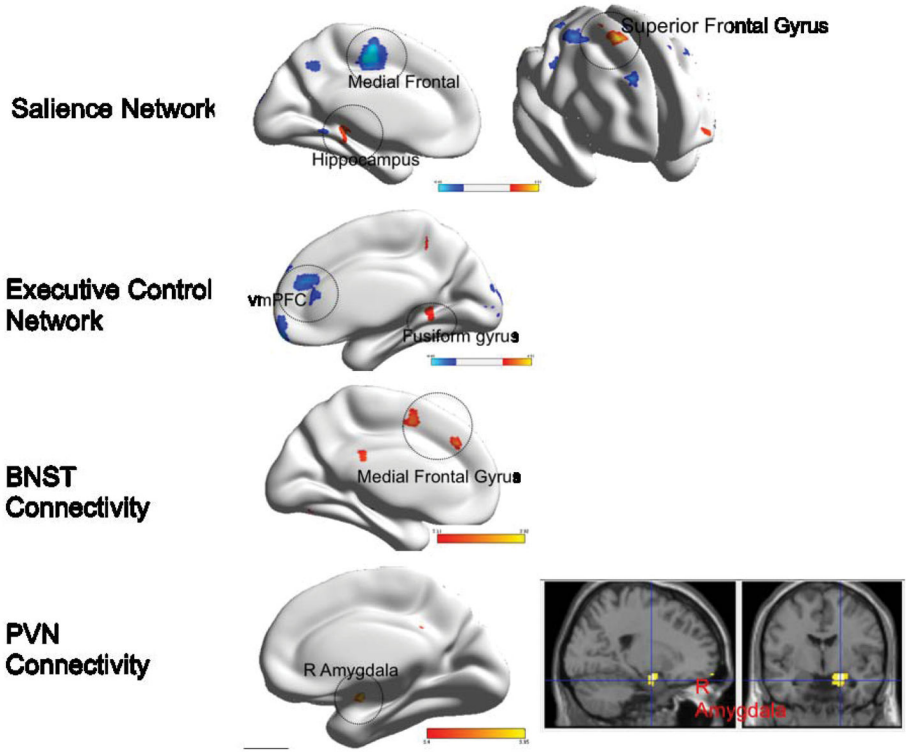

Figure 3. Group differences in functional connectivity during worry reappraisal between elderly GAD participants and non-anxious comparison participants

Red: GAD>non-anxious comparison, blue: non-anxious comparison>GAD. BNST= bed nucleus of stria terminalis. PVN= paraventricular nucleus. vmPFC= ventromedial prefrontal cortex. BA= Brodmann Area. Visualized using BrainNet Viewer, version 1.42(64). Salience Network: Medial Frontal (t=4.26; df=54); Hippocampus (t=4.28; df=54); Superior frontal gyrus (t=4.44; df=54). Executive Control Network: vmPFC (t=4.41; df=54); Fusiform gyrus (t=4.59; df=54). BNST Connectivity: Medial frontal gyrus (t=4.08; df=54). PVN Connectivity: Amygdala(R) (t=4.88; df=54).

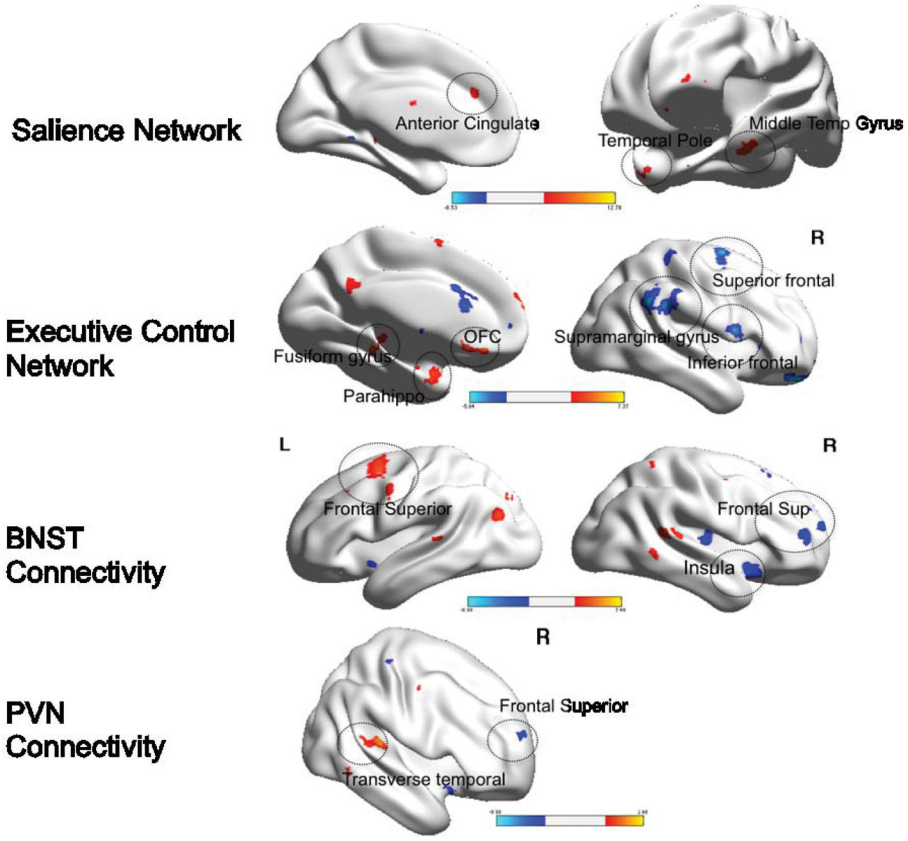

Figure 4. Within group differences in functional connectivity during worry induction between pre- and post-treatment elderly GAD participants

Red: pre>post-treatment. Blue: post>pre-treatment. BNST= bed nucleus of stria terminalis. PVN= paraventricular nucleus. L=left, R=Right. OFC=orbito-frontal cortex. PFC=prefrontal cortex. Visualized using BrainNet Viewer, version 1.42(64). Salience Network: Medial PFC (t=6.0; df=11); Subgenual cingulate (t=5.43; df=11); Postcentral gyrus (t=5.1; df=11). Executive Control Network: Inferior frontal gyrus (t=7.3; df=11); OFC (t=6.7; df=11). BNST Connectivity: Frontal superior gyrus (t=5.6; df=11); Frontal middle (t=6.6; df=11); Insula (t=7.8; df=11). PVN Connectivity: Frontal superior (t=5.3; df=11); Insula (t=5.79, df=11); Postcentral/supramarginal gyrus (t=6.6; df=11); Frontal middle (t=5.4, df=11); OFC (t=6.4; df=11).

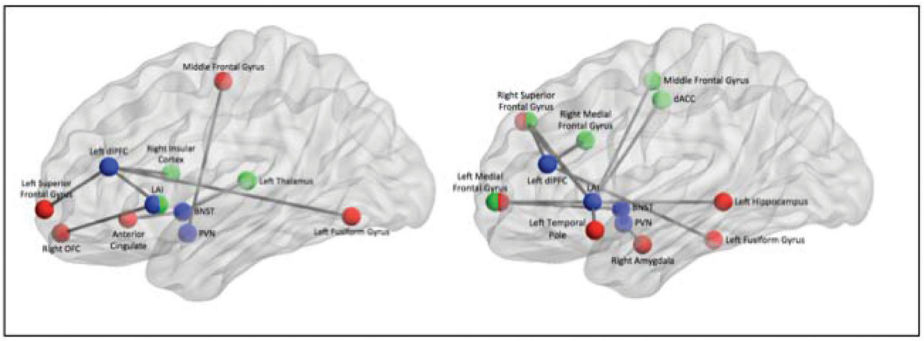

Figure 5. Within group differences in functional connectivity during worry reappraisal between pre- and post-treatment elderly GAD participants

Red: pre>post-treatment. Blue: post>pre-treatment. BNST= bed nucleus of stria terminalis. PVN= paraventricular nucleus. L=left, R=Right. OFC=orbito-frontal cortex. Parahippo=parahippocampal cortex; PFC=prefrontal cortex. Visualized using BrainNet Viewer, version 1.42(64). Salience Network: Anterior cingulate (t=12.7; df=11); Temporal pole (t=7.4; df=11); Middle Temporal Gyrus (t=9.1; df=11). Executive Control Network: Fusiform gyrus (t=11.6; df=11); Parahippocampus (t=8.4; df=11); OFC (t=9.1; df=11); Superior frontal (t=7.2; df=11); Supramarginal gyrus (t=13.2, df=11); Inferior frontal (t=6.9; df=11). BNST Connectivity: Frontal superior (L) (t=7.4, df=11); Insula (t=8.9; df=11); Frontal superior (R) (t=5.4; df=11). PVN Connectivity: Transverse temporal (t=6.5; df=11); frontal superior (5.7; df=11).

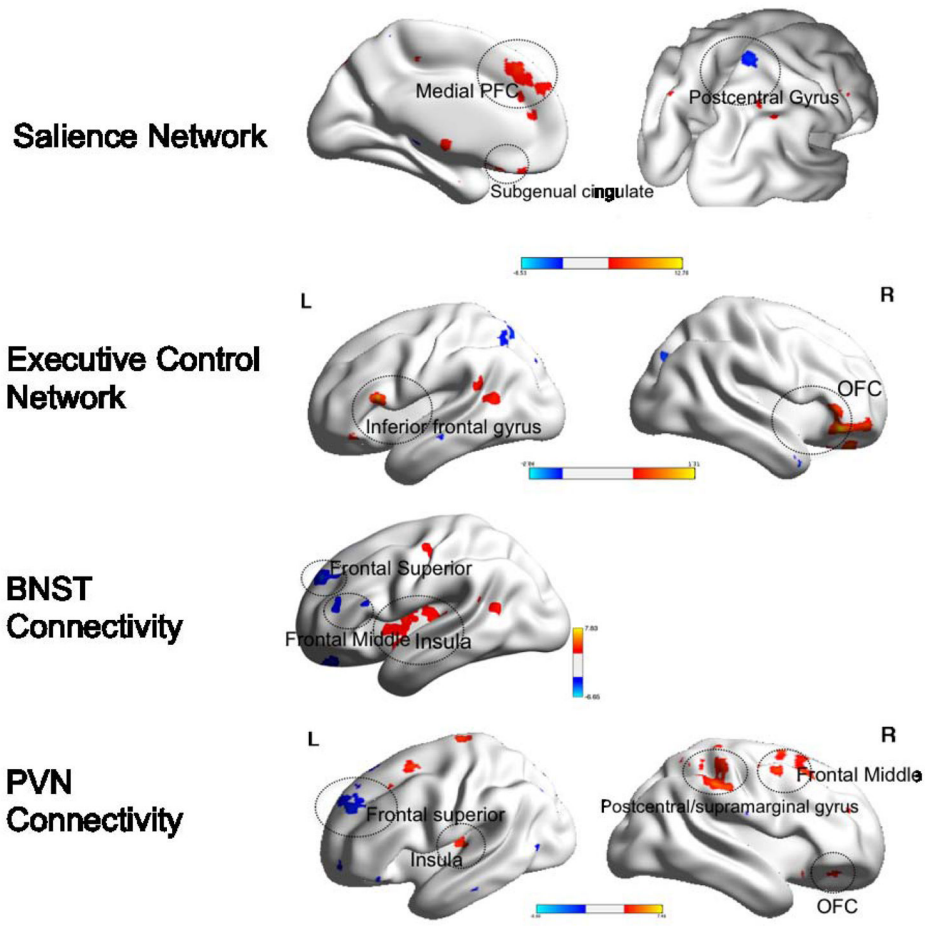

Fig 6. Summarized findings showing differences in functional connectivity between non-anxious participants and elderly GAD during worry induction (left) and during worry reappraisal (right)

In blue – the four seeds (LAI=left anterior insula, dlPFC=dorso-lateral prefrontal cortex, BNST=bed nucleus of stria terminalis, PVN=paraventricular nucleus. In red-regions of interest that had greater connectivity with the seed for GAD than for non-anxious participants. In green: regions of interest that had greater connectivity with the seed for non-anxious participants than for GAD.

Table 1

Coordinates of the BNST and PVN Regions of Interest

ROIs	Center of Mass	X-extent (mm)	Y-extent (mm)	Z-extent (mm)	Volume (mm^3)
Left BNST	−6.6, 5.15, −3.19	−19.5, −2	3, 8	−10.5, 7.5	223.5
Right BNST	7.55, 5.1, −2.79	3, 23.5	3, 8	−9, 8	234
PVN	0.72, 4.49, −9.36	−5.5, 7.5	0, 8	−15.5, 2	225.25

ROI= region of interest. BNST=Bed Nucleus of Stria Terminalis. PVN=Paraventricular Nucleus.

Table 2

Clinical and demographic characteristic of the sample

Variable	Non-anxious elderly comparison participants N=31	Elderly GAD (pre-treatment) N=28	Test Statistic (p-value)
Age	69 (12.50)	64 (6.75)	U=546, p=0.089
Sex	17F (55%)	19F (68%)	X^2(df=1)=0.574, p=0.449
Race	27 W (87%)	27W (96%)	p=0.356 *
PSWQ	32 (10)	58.50 (21.25)	U=42.5, p<0.001
RBANS	108 (20)	103.5 (16.5)	U=553.5, p=0.070
HARS	3 (2)	19 (3.25)	U=0, p<0.001
HDRS	1 (2) n=21 **	13 (4) n=21 **	U=0, p<0.001
CIRS.G	4.5 (2.5) n=20 **	6 (4.25) n=20 **	U=148, p=0.160

All data are median and IQR range. U= Mann-Whitney U test; F= female. W= white; PSWQ=Penn State Worry Questionnaire; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; HDRS=Hamilton Depression Rating Scale HARS= Hamilton Anxiety Rating Scale. CIRS.G=Cumulative Illness Rating Scale, Geriatrics.

* Fisher's exact test;

** missing data

Table 3

Summary of functional connectivity data

Condition	Seed	Controls vs. GAD (x/y/z; k_E)		Pre- vs. post-treatment GAD (x/y/z; k_E)	
		Controls > GAD	GAD > Controls	Pre > Post	Post > Pre
Worry Induction	Left anterior insula		Right OFC: (10/56/−12; k_E =388; t=3.83; df=54)	Left precentral gyrus [BA6]: (−54/2/42; k_E=163; t=6.3, df=11) Left medial frontal gyrus [BA6]: (−2/34/42; k_E=95; t=6.0; df=11) Left subgenual cingulate [BA25]: (−7/22/−14; k_E=149; t=5.43; df=11)	Right postcentral gyrus [BA5]: (18/−46/72; k_E=76; t=5.1; df=11)
	Left BA46 (dlPFC)	Left insula: (−34/−8/12; k_E=730; t=3.99; df=54) Right insular cortex [BA13]: (40/−7/13; k_E=288; t=4.00; df=54)	Left superior frontal gyrus [BA10]: (−22/63/−2; k_E=174; t=3.71; df=54) Cerebellar vermis: (6/−52/−2; k_E 261; t=4.14; df=54) Left fusiform gyrus: (−35/−66/−14; k_E=263; t=3.44; df=54)	Left inferior frontal gyrus [BA45]: (−54/20/12; k_E=55; t=7.3; df=11) Right OFC [BA47]: (46/34/−12; k_E=275; t=6.7; df=11)	
	BNST	Left thalamus: (−18/−22/10; k_E=190; t=4.35; df=54)	Anterior cingulate (subgenual) [BA24]: (4/28/−6; k_E=172; t=3.95; df=54)	Left insula [BA13]: (−38/−20/10; k_E=146; t=7.8; df=11) Right supramarginal gyrus [BA2]: (48/−33/42; k_E =456; t=7.1; df=11)	Left frontal medial gyrus: (−11/37/38; k_E=527; t=6.6;df=11) Left frontal superior gyrus: (−18/50/30; k_E=527;t= 5.6; df=11) Left lingual gyrus: (−15/−76/−7; k_E=60; t=5.68; df=11) *Left inferior frontal gyrus [BA46]: (−44/40/16; k_E=52, t=5.2; df=11; p=0.00014, threshold p<0.00012)*
	PVN		Middle frontal gyrus [BA6]: (−24/−12/52; k_E=577; t=4.25; df=54)	Left OFC [BA11]: (−26/28/−18; k_E=35; t=6.4; df=11) Right supramarginal gyrus [BA40]: (51/−32/42; k_E=601; t=6.6; df=11) Left insula [BA13]: (−42/−20/10, k_E=74; t=5.79; df=11) Right middle frontal gyrus [BA8]: (32/13/42; k_E=246; t=5.4; df=11)	Left medial frontal gyrus [BA9]: (−15/33/30; k_E =224; t=5.3; df=11) Left lingual gyrus [BA18]: (−9/−76/−5, k_E =187; t=5.3; df=11)
Worry Reappraisal	Left anterior insula	Left medial frontal gyrus [BA6]: (−8/−16/54, k_E=469; t=4.61; df=54) dACC [BA24]: (−6/−12/43; k_E=469; t=3.85; df=54) Right superior frontal gyrus: (18/44/34; t=4.44; k_E=80) Middle frontal gyrus: (28/−14/48; k_E=289; t=4.26; df=54)	Left temporal pole [BA38]: (−48/16/−12; k_E=187; t=4.49; df=54) Left hippocampus: (−30/−38/0; k_E=285; t=4.28; df=54) Right superior frontal gyrus [BA6]: (18/20/60; k_E=126; t=4.20; df=54)	Left anterior cingulate [BA32]: (−7/35/28; k_E=202; t=12.7; df=11) Left middle temporal gyrus: (−44/4/−37; k_E=294; t=9.1; df=11) Right temporal pole [BA38]: (42/16/−38; k_E=75; t=7.4; df=11)	Cerebellar vermis: (−1/−44/−6; k_E=138; t=8.5; df=11)

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Condition	Seed	Controls vs. GAD (x/y/z; k_E)		Pre- vs. post-treatment GAD (x/y/z; k_E)	
		Controls > GAD	**GAD > Controls**	**Pre > Post**	**Post > Pre**
	Left BA46 (dlPFC)	Right medial frontal gyrus [BA9]: (12/40/26; k_E=173; t=4.41; df=54) Right superior frontal gyrus [BA10]: (9/59/−7; k_E=146; t=3.46; df=54)	Left fusiform gyrus: (−18/−34/−16; k_E=91; t=4.59; df=54)	Left fusiform gyrus: (−40/−42/−16; k_E=301; t=11.6; df=11) Left rectus [BA11]: (−1/21/−24; k_E=155; t=9.1; df=11) Left limbic lobe (Uncus): (−32/−2/−34; k_E=107; t=8.4; df=11)	Right supramarginal gyrus [BA40]: (46/−36/60; k_E=166; t=13.2; df=11) Right superior frontal gyrus [BA11]: (18/51/−18; k_E=52; t= 7.2; df=11) Right inferior frontal gyrus [BA47]: (54/19/0.6; k_E=101; t= 6.9; df=11) Middle cingulate gyrus: (7/−32/41; k_E=102; t=6.6; df=11) Right cuneus: (12/−98/16; k_E=66; t=7.7; df=11)
	BNST		Left medial frontal gyrus: (−18/56/0; k_E=52; t=4.08; df=54)	Left frontal middle gyrus [BA6]: (−25/7/63; k_E=203; t=7.4; df=11)	Right lingual gyrus [BA19]: (24/−68/−2.70; k_E=355; t=8.9; df=11) *Right frontal superior gyrus [BA10]: (34/62/16; k_E= 179, t=5.4; df=11; p=0.0003, threshold p<0.00017)*
	PVN		Right amygdala: (22/−4/−18; k_E=217; t=4.88; df=54)	Right transverse temporal gyrus [BA41]: (55/−24/12, k_E=97; t= 6.5; df=11) Left putamen: (−24/−4/4, k_E=56; t=7.1; df=11) *Middle cingulate gyrus [BA31]: (−6/−30/40, k_E=125, p=0.0002, threshold p<0.00017*; t= 4.5; df=11)	*Right superior frontal gyrus: (21/55/14, k_E=115, p=0.0002, threshold p<0.00017;* t=5.7; df=11)

BA = Brodmann Area; BNST = bed nucleus of the stria terminalis; dACC = dorsal anterior cingulate cortex; GAD = generalized anxiety disorder; OFC = orbitofrontal cortex; PVN = periventricular nucleus of the hypothalamus. In italics, results that did not survive multiple comparison correction. All other results are significant are a corrected $p \leq 0.05$. t=T-test (peak-level); df= degrees of freedom

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Table 4

Proposed deficits in emotion regulation in late-life GAD

Domain	Deficit	Functional connectivity findings
Emotion Generation (Worry Induction)	Excessive attribution of negative affective value to worry statements	Greater Insula-OFC connectivity during worry induction in pre-treatment GAD (compared with non-anxious participants and with post-treatment GAD)
	Excessive attribution of threat	Greater BNST-Insula connectivity during worry induction in GAD
Emotion Regulation (Worry reappraisal)	Failure to reappraise worry	Lower insula-prefrontal connectivity during worry reappraisal in GAD
		Lower prefrontal connectivity (BA46-BA10/BA9) in GAD during worry reappraisal
		Greater prefrontal connectivity in post-treatment GAD during worry reappraisal
	Rigid executive network control	Similar nodes connected during both induction and reappraisal of worry in GAD
	Increased stress response during reappraisal	Greater BNST-subgenual cingulate connectivity in pre-treatment GAD during worry induction
		Greater PVN-Amygdala connectivity in pre-treatment GAD during worry reappraisal