Published in final edited form as:

Am J Geriatr Psychiatry. 2011 November ; 19(11): 980–983. doi:10.1097/JGP.0b013e318227f4f9.

THE DEFAULT MODE NETWORK IN LATE-LIFE ANXIOUS DEPRESSION

Carmen Andreescu¹, Minjie Wu², Meryl A. Butters¹, Jennifer Figurski¹, Charles F. Reynolds III¹, and Howard J Aizenstein^{1,2,*}

¹ Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, United States

² Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA, United States

³ Magnetic Resonance Research Center, University of Pittsburgh Medical Center, Pittsburgh, PA, United States

Abstract

Objectives—The aim of this exploratory study is to examine the default-mode network (DMN) functional connectivity pattern in elderly depressed subjects with and without comorbid anxiety.

Methods—Functional MRI data were collected for 11 elderly depressed subjects with high comorbid anxiety and 8 elderly depressed subjects with low anxiety. We analyzed the resting connectivity patterns of the posterior cingulate cortex. We compared the DMN activity in the elderly depressed subjects with high versus low comorbid anxiety.

Results—Depressed elderly with high comorbid anxiety had increased functional connectivity in the posterior regions of the DMN and decreased functional connectivity in the anterior regions of the DMN.

Conclusion—Elderly depressed subjects with high anxiety display a dissociative pattern of connectivity in the DMN when compared with elderly depressed subjects with low anxiety. These results suggest a unique biological signature of the anxiety symptoms in the context of late-life depression.

BACKGROUND AND OBJECTIVES

The Default-Mode Network (DMN) is a functional network of medial brain regions (posterior cingulate, medial prefrontal cortex, medial temporal cortex) active during the resting state and inhibited during the performance of effortful tasks (1). The DMN is active when subjects are engaged in internally focused tasks including memory retrieval, envisioning the future and conceiving the perspectives of others. Several studies have reported disruptions of the DMN in autism, major depressive disorder, Alzheimer's disease and schizophrenia.

* corresponding author.

Declaration of interest:

Carmen Andreescu, Minjie Wu, Jennifer Figurski and Meryl A. Butters do not have any potential conflict to acknowledge. Howard Aizenstein has received research support from Novartis Pharmaceuticals. Charles F. Reynolds III has received research support from Pfizer Inc., Eli Lilly and Co., Bristol Meyers Squibb, Forest Pharmaceuticals, and Wyeth Pharmaceuticals.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Comorbid anxiety is common in late-life depressive disorders (2). Although there is a large body of literature examining the functional neuroanatomy of anxiety, the functional neuroanatomy of anxiety comorbid with depression is not well defined. To our knowledge, there are no published data regarding the effect of anxiety on the late-life depression, which is striking as more than half of the cases of late-life depression (LLD) are accompanied by substantial anxiety (2). Given the malignant effect of comorbid anxiety on short- and long-term treatment response in LLD (3), anxious depression appears to not be just a more severe form of depression but possibly a distinctive dimension with a unique neurobiological profile.

In a previous analysis, our group has described a specific pattern of activation in the dorsal anterior cingulate and the posterior cingulate of depressed elderly subjects with increased anxiety during the performance of a Stroop-like cognitive task (4). Defining anxiety-related changes in DMN in the context of late-life depression would contribute further to the delineation of the neurobiological profile of anxious depression.

Thus, we performed a post-hoc, secondary exploratory analysis aiming to describe the DMN functional connectivity pattern in two groups: late-life depression subjects with high comorbid anxiety (LLD- HA) and late-life depression subjects with low comorbid anxiety (LLD-LA).

METHODS

Nineteen depressed elderly subjects were recruited from a late-life depression treatment study. Major depressive disorder was diagnosed with the Structured Clinical Interview for DSM-IV (SCID) and the 17-item Hamilton Depression Rating scale (HDRS). Cognitive function was assessed with the Mini Mental State Examination (MMSE) and the Dementia Rating Scale. Subjects were cognitively unimpaired. Anxiety symptoms were measured using the Hamilton Anxiety Rating Scale (HARS) for 15/19 subjects and the Brief Symptom Inventory (BSI) anxiety subscale form 4/19 subjects. High anxiety was defined as a total HARS score of 15 or higher, or a total BSI anxiety score of 1 or higher (5).

The MR images were obtained at the time of subject enrollment. The fMRI resting state data was acquired using a simple sensory-motor task (finger tapping), a method frequently used, as finger tapping does not interfere with the activity in the DMN (6). The subjects were scanned on a Siemens Trio 3T scanner, using a 12-channel head array coil. Axial T1-weighted image was acquired with 3D MP-RAGE: 176 slices, 224×256 matrix, FOV = 224×256 mm², TR = 2300 ms, TE = 3.43 ms, TI = 900 ms, Flip angle = 9°, slice thickness = 1mm, no gap. Five-minute resting-state fMRI scans were performed with standard FID-EPI: 28 slices, 128×128 matrix, FOV = 256×256 mm², TR = 2000ms, TE = 34m, flip angle = 90°, slice thickness = 3mm, no gap, 150 time frames. During the resting imaging, the subjects were instructed to press a single key every time they saw the word “tap” on a screen. The stimulus appeared for 1 second at every 12 seconds.

The functional images were co-registered, normalized into MNI Colin27 using a fully deformable model, and then smoothed with a 6-mm Gaussian filter. A band-pass filter ([.01 . 1] Hz) was then used to extract the resting-state signal. A $3 \times 3 \times 3$ element 6 connected 2.5D erosion was performed on the PCC from the AAL atlas on Colin27. The reference time-series for a given subject was computed by averaging the time-series across the centered PCC ROI. For each subject, a reference resting-state time-series was extracted by averaging the time-series for all voxels within the PCC ROI. A correlation coefficient map was calculated with the reference time-series as the regressor of interest using 3dDeconvolve from Analysis of Functional NeuroImages (AFNI) (7). In the map, the correlation

coefficient at a given voxel shows the time-series correlation between that voxel and PCC ROI, which represents the resting state functional connectivity score at the voxel.

To determine the mean resting-state functional connectivity map for each group (high versus low anxiety depressed subjects), the correlation coefficient maps were statistically compared to the baseline using a 1- sample t-test. The resulting t-maps were then thresholded at a corrected $p < .001$ via Monte Carlo simulations (AlphaSim, AFNI (8), with the whole brain template as mask). A 2-sample t-test of the correlation coefficient maps (between high anxiety depressed subjects and low anxiety depressed subjects) was used to identify between-group differences in resting-state functional connectivity. The resulting t-maps were then thresholded at a corrected $p < 0.05$ via Monte Carlo simulations [AlphaSim, AFNI (8)].

RESULTS

We studied 11 subjects with high anxiety (2 males, all right-handed, age = 68.09 ± 8.43 years) and 8 subjects with low anxiety (6 males, 7 right-handed, age = 69.5 ± 4.99 years). The mean HRSD was 19.2 (± 5.9) for the high anxiety group and 19.0 (± 2.9) for the low anxiety group ($t=0.1$, $df=7$, $p=0.43$). The mean MMSE was 27.8 (± 1.72) for the high anxiety group and 28.7 (± 1.5) for the low anxiety group ($t=1.1$, $df=7$, $p=0.92$). Two subjects in the high anxiety group had a SCID diagnosis of anxiety disorder (one subject = Generalized Anxiety Disorder and Social Phobia, one subject = Obsessive-Compulsive Disorder). Three subjects in the low anxiety group had a SCID diagnosis of anxiety disorder (one subject = Specific Phobia, two subjects = Generalized Anxiety Disorder). 6/11 (54.5%) subjects with high anxiety had recurrent MDD; 3/8 (37.5%) subjects with low anxiety had recurrent MDD. The two groups did not differ with to age of onset of MDD [high anxiety group mean = 56.7 years, $SD = 15$; low anxiety group mean = 60.2 years, $SD = 12.1$, $t = 1.02$, $df = 7$, $p = 0.87$] or total duration of current depressive episode [high anxiety group mean (weeks) = 118.7, $SD = 114$, low anxiety group mean (weeks) = 217, 8, $SD = 190.9$, $t = 0.46$, $df = 7$, $p = 0.13$]. High anxiety depressed elderly had either a mean BSI anxiety score of 1.41 (± 0.35) or a mean HARS score of 18.3 (± 3.9). Low anxiety depressed elderly had either a mean BSI anxiety score of 0.41 (± 0.11) or a mean HARS score of 11.3 (± 1.9).

Within-group comparison

For each group, the correlation maps were statistically compared to the baseline using a 1-sample t-test (corrected $p < 0.001$, cluster size of 140). For each subject, we correlated the fMRI time-series from the PCC with the fMRI time-series in all the voxels in the brain. These within-subject individual voxels r-values were then averaged to obtain a mean default-mode correlation map, thresholded at $p < 0.001$, corresponding to a $r > 0.4$ ($df = 146$). The mean default-mode correlation maps are shown in Fig. 1 ($r > 0.4$). All groups demonstrated the expected default-mode network of activity, with significant medial prefrontal and anterior cingulate correlation (joint height and extent threshold of $p < 0.001$, via Monte Carlo simulations (AlphaSim, AFNI).

Between-group comparison

The correlation maps from LLD-HA and LLD-LA groups were statistically compared using 2-sample t-test [$p < 0.05$ and cluster size of 77, Fig. 1(c)]. This shows that compared with low anxiety depressed subjects, depressed subjects with increased anxiety have significantly higher functional connectivity in the posterior regions of the DMN, including precuneus, and significantly lower DMN activation in rostral ACC, mPFC and OFC (see Fig 1).

CONCLUSION

Overall, our results show that, during the performance of a simple sensory-motor task, elderly depressed subjects with high anxiety display a dissociative pattern of connectivity in the DMN when compared with elderly depressed subjects with low anxiety. Thus, depressed subjects with high anxiety had increased connectivity in the posterior regions of the DMN (including the occipital and parietal associative areas) and decreased connectivity in the anterior regions of the DMN (the rostral ACC, medial prefrontal and orbito-prefrontal cortex). Our results are limited by the lack of a control group. Nonetheless, these results can be interpreted in the context of the hypothesized role of the DMN: retrieval and manipulation of information and past events in an effort to solve problems and develop future plans (9). Thus, we can speculate that the increased connectivity in the posterior areas of the DMN suggests that subjects with increased anxiety maintain a “higher alert”, scanning both the environment (occipital areas) and themselves (parietal areas) excessively, in an effort to detect external or internal potential sources of threat. Increased bias-to-threat is one of the salient features of anxious subjects. At the same time, the decreased connectivity with the frontal areas indicates that, compared with depressed subjects with low anxiety, depressed subjects with increased anxiety utilize fewer prefrontal-based strategies such as reappraisal and reorganization of retrieved/perceived material to self-regulate. This feature might be correlated with the observed poorer response to top-down psychotherapeutic interventions in subjects with comorbid anxious-depression (10). These results suggest a unique biological signature of the anxiety symptoms in the context of late-life depression.

Acknowledgments

This work is supported in part by NIH grants K23 MH086686, P30 MH071944, R01 MH037869, T32MH019986, RO1MH076079, R01 072947, P30 AG024827, the National Alliance for Research on Schizophrenia and Depression (NARSAD) Young Investigator Award, the John A. Hartford Foundation Center of Excellence in Geriatric Psychiatry and the University of Pittsburgh Medical Center (UPMC) endowment in Geriatric Psychiatry.

The Authors would like to thank Dr. Lei K. Sheu for her help with the revised manuscript.

REFERENCES

1. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98(2):676–82. [PubMed: 11209064]
2. Beekman AT, de Beurs E, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000; 157(1):89–95. [PubMed: 10618018]
3. Andrescu C, Lenze EJ, Dew MA, Begley AE, Mulsant BH, Dombrovski AY, et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *Br J Psychiatry*. 2007; 190:344–9. [PubMed: 17401042]
4. Andrescu C, Butters M, Lenze EJ, Venkatraman VK, Nable M, Reynolds CF, et al. fMRI Activation in Late-life Anxious Depression: A potential Biomarker. *International Journal of Geriatric Psychiatry*. 2009 (in press).
5. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med*. 1983; 13(3):595–605. [PubMed: 6622612]
6. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A*. 2004; 101(13):4637–42. [PubMed: 15070770]
7. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29(3):162–73. [PubMed: 8812068]
8. Ward, B. AFNI AlphaSim documentation. Biophysics Research Institute, Medical College of Wisconsin; Milwaukee, WI: 2000. Simultaneous inference for fMRI data..

9. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A*. 2003; 100(1):253–8. [PubMed: 12506194]
10. Lenze EJ. Comorbidity of depression and anxiety in the elderly. *Curr Psychiatry Rep*. 2003; 5(1): 62–7. [PubMed: 12686004]

Figure 1.

Mean default-mode correlation maps for late-life depression patients with (a) low anxiety LLD-LA; (corrected $p < 0.001$, $df=146$, cluster size of 140) – medial frontal [Talairach coordinates $x=6$, $y=61$, $z=4$], pregenual anterior cingulate [Talairach coordinates $x=6$, $y=39$, $z=4$]; (b) high anxiety LLD-HA; (corrected $p < 0.001$, $df=146$, cluster size of 140) medial frontal gyrus [Talairach coordinates $x=6$, $y=58$, $z=12$]. Group comparison between LLD-LA and LLD-HA, ($p < 0.05$, $df=17$, cluster size of 77) (c) subgenual cingulate [Talairach coordinates $x=10$, $y=30$, $z=-8$], medial frontal gyrus [Talairach coordinates $x=-8$, $y=61$, $z=8$]