

## Resting State fMRI in Late-life Anxious Depression

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### Introduction

The Default-Mode Network (DMN) is an organized functional network of several brain regions active during the resting state and inhibited during the performance of active tasks [1]. It involves retrieval and manipulation of past events in an effort to solve problems and develop future plans [2]. Analysis of resting state activity in clinical conditions may enhance the understanding of the pathophysiological underpinning of mental illnesses [2]. Comorbid anxiety is common in mid-life and late-life depressive disorders [3]. Although there is a large body of literature examining the functional neuroanatomy of anxiety [4], the functional neuroanatomy of late-life anxiety is not well defined, which is striking because more than half of the cases of late-life depression (LLD) are accompanied by substantial anxiety [5]. Given the malignant effect of comorbid anxiety on short- and long-term treatment response in LLD [6], anxious depression appears to be not just a more severe form of depression but possibly a distinctive dimension with a unique neurobiological profile. In this study, we analyzed the default-mode network 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 LLD patients participated in this study: 11 LLD-HA patients (2 males, all right-handed, age = 68.09 ± 8.43 years, MMSE = 27.18 ± 4.21, HDRS = 22.27 ± 4.92) and 8 LLD-LA patients (6 males, 7 right-handed, age = 69.5 ± 4.99 years, MMSE = 28.75 ± 1.49, HDRS = 19.25 ± 3.06). Subjects were all cognitively unimpaired. Anxiety symptoms were measured using the Hamilton Anxiety Rating Scale (HARS) for 14/19 subjects and the Brief Symptom Inventory (BSI) anxiety subscale form 5/19 subjects. High anxiety was defined as a total HARS score of 15 or higher or a total BSI anxiety score of 1 or higher [7,8]. There is no significant difference in MMSE or HDRS between the LLD-HA group and LLD-LA group.

The subjects were scanned on a Siemens Trio 3T scanner (Siemens AG, Munich, Germany) using a 12-channel head array coil. Axial T1-weighted image was acquired with 3D MP-RAGE: 176 slices, 224 x 256 matrix, FOV = 224 x 256 mm<sup>2</sup>, 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, 128x128 matrix, FOV = 256 x 256 mm<sup>2</sup>, TR = 2000ms, TE = 34ms, flip angle = 90°, slice thickness = 3mm, no gap, 150 time frames. During the resting imaging, the subjects were instructed to remain still and relax with eyes closed.

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 3x3x3 element 6 connected 2.5D erosion was performed on the PCC from the AAL atlas on Colin27 (Fig. 1 a). This led to a smaller ROI centered in the PCC (Fig.1 b). The reference time-series for a given subject was computed by averaging the time-series across the centered PCC ROI. The reference time-series was then correlated with the time-series of each voxel in the brain using 3dDeconvolve (AFNI) to generate a whole-brain correlation map.

### Results

*Within-group:* For each group (LLD-HA and LLD-LA), the correlation maps were statistically compared to the baseline 0 using a 1-sample t-test (corrected  $p < 0.0001$ ). Due to power issue (different n per group), the mean default-mode correlation maps (rather than t-maps) are shown in Fig. 2 with  $r > 0.4$ .

*Between-group:* The correlation maps from LLD-HA and LLD-LA groups are statistically compared using 2-sample t-test ( $p < 0.05$  and cluster size of 77, Fig. 2(c)).

### Discussion and Conclusion

Overall, our results show that 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). 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 [2]. Thus, 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 [4]. 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 less prefrontal-based strategies such as reappraisal and reorganization of retrieved/perceived material. This feature might be correlated with the observed poorer response to top-down psychotherapeutic interventions in subjects with comorbid anxious-depression [9]. These results suggest a unique biological signature of the anxiety symptoms in the context of late-life depression.

### Reference

- [1] Raichle ME et al. PNAS 2001;98(2):676-82.
- [2] Greicius MD et al. PNAS 2003;100(1):253-8.
- [3] Kessler RC et al. Arch Gen Psychiatry. 1994;51(1):8-19.
- [4] Mobbs D et al. Science. 2007;317(5841):1079-83.
- [5] Beekman AT et al. Am J Psychiatry. 2000;157(1):89-95.
- [6] Andreescu C et al. Br J Psychiatry. 2007;190:344-9.
- [7] Derogatis LR et al. Psychol Med. 1983;13(3):595-605.
- [8] Lenze EJ et al. (submitted). 2008.
- [9] Lenze EJ. Curr Psychiatry Rep. 2003;5(1):62-7.

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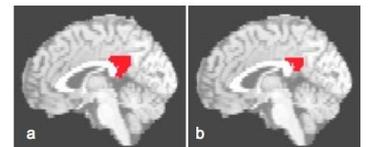


Fig. 1. Original PCC and the eroded centered ROI on Colin27.

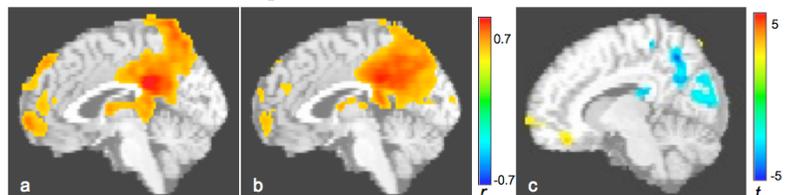


Fig. 2. Mean default-mode correlation maps for late-life depression patients with (a) low anxiety (LLD-LA) and (b) high anxiety (LLD-HA). Group comparison between LLD-LA and LLD-HA (c).