Published in final edited form as:

Int J Geriatr Psychiatry. 2014 November ; 29(11): 1116–1124. doi:10.1002/gps.4171.

THE SALIENCE NETWORK IN THE APATHY OF LATE-LIFE DEPRESSION

Genevieve S. Yuen¹, Faith M. Gunning¹, Matthew J. Hoptman^{2,3}, Bassem AbdelMalak¹, Amanda R. McGovern¹, Joanna K. Seirup¹, and George S. Alexopoulos¹

¹Weill Medical College of Cornell University, Weill Cornell Institute of Geriatric Psychiatry, NY

²Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY

³New York University School of Medicine, New York, NY

Abstract

Objective—Apathy is prevalent in late-life depression and predicts poor response to antidepressants, chronicity of depression, disability, and greater burden to caregivers. However, little is known about its neurobiology. Salience processing provides motivational context to stimuli. The aim of this study was to examine the salience network (SN) resting-state functional connectivity (rsFC) pattern in elderly depressed subjects with and without apathy.

Methods—Resting-state functional MRI data were collected from 16 non-demented, non-MCI, elderly depressed subjects and 10 normal elderly subjects who were psychotropic-free for at least two weeks. The depressed group included 7 elderly, depressed subjects with high comorbid apathy and 9 with low apathy. We analyzed the rsFC patterns of the right anterior insular cortex (rAI), a primary node of the SN.

Results—Relative to non-apathetic depressed elderly, depressed elderly subjects with high apathy had decreased rsFC of the rAI to dorsal anterior cingulate and to subcortical/limbic components of the SN. Depressed elderly subjects with high apathy also exhibited increased rsFC of the rAI to right dorsolateral prefrontal cortex and right posterior cingulate cortex when compared to non-apathetic depressed elderly.

Conclusions—Elderly depressed subjects with high apathy display decreased intrinsic rsFC of the SN and an altered pattern of SN rsFC to the right DLPFC node of the central executive network when compared to elderly non-apathetic depressed and normal, elderly subjects. These results suggest a unique biological signature of the apathy of late-life depression and may implicate a role for the rAI and SN in motivated behavior.

Address all correspondence to: Genevieve S. Yuen, MD, PhD Weill Cornell Institute of Geriatric Psychiatry New York-Presbyterian Hospital – Westchester Division 21 Bloomingdale Road New York, NY 10605-1596 gsyuen@med.cornell.edu (T) 914-997-4047; 646-232-3464 (F) 914-682-6979.

FINANCIAL DISCLOSURES

Dr. Alexopoulos received grant support from Forest Pharmaceuticals and has been a member of speakers' bureaus of Astra Zeneca, Avanir, Forest, Merck, and Lundbeck. He holds equity of Johnson and Johnson. No other authors report biomedical financial interests or potential conflicts of interest.

Keywords

salience; amotivation; apathy; insula; atypical depression; geriatric; aging

INTRODUCTION

Apathy is common in depression, affecting more than 30% of individuals with major depression, and is most prevalent in depressed older adults (Chase, 2011, Forsell et al., 1993, Krishnan et al., 1995, Lampe and Heeren, 2004, Mehta et al., 2008). The syndrome of apathy is defined as a primary motivational impairment that in depression results in diminished goal-oriented behavior, lack of intellectual interest, and indifference or flattening of affect (Marin, 1990). These clinical signs translate into apathetic, depressed patients being poorly engaged in treatment, posing a greater burden to caregivers, and having increased risk of future functional and cognitive impairment (Chase, 2011, Feil et al., 2003, Holtta et al., 2012). In geriatric depression, apathy predicts poor response of depressive symptoms to treatment, chronicity of depression, and disability (Chaturvedi and Sarmukaddam, 1986, Lavretsky et al., 1999, Levkovitz et al., 2011, Marin et al., 2003, Yeager and Hyer, 2008).

There is little knowledge of the functional neuroanatomy of apathy in depression despite the abundant geriatric psychiatry literature documenting the phenomenon of apathy syndromes in depression (Alexopoulos et al., 2013, Lavretsky et al., 2007, Lavretsky et al., 2008). Given the malignant effect of comorbid apathy on clinical outcomes and treatment response, apathetic depression appears to not be just a more severe form of depression but possibly a distinctive dimension with a unique neurobiological profile.

Functional brain network models are useful to understanding psychopathology in that they consider how functions of neural systems distributed across the entire extent of the brain, instead of a single brain area, together generate the constellation of cognitive and affective symptoms that constitute a disorder. Multiple studies focus on dysfunction within or between three particular networks in the manifestation of affective and psychotic disorders: (1) the default mode network (DMN) with key nodes in posterior cingulate and ventromedial prefrontal cortex; (2) the central executive network (CEN) with nodes in the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC); and (3) the salience network (SN) with anterior insula (AI), ventrolateral prefrontal cortical, and anterior cingulate cortical (ACC) nodes (Menon, 2011). While the DMN is active when individuals are engaged in internally focused tasks such as autobiographical memory and self-referential processes, the CEN is active during the performance of cognitively demanding tasks.

The SN nodes have robust connections to several limbic areas and subcortical structures—amygdala, ventral striatum/nucleus accumbens, hypothalamus, dorsomedial thalamus, periaqueductal gray, and substantia nigra/ventral tegmental area. As such, the SN is conceptualized as a bottom-up processor of salient experiences—whether cognitive, homeostatic, or emotional—that subsequently recruits other large-scale networks to influence ensuing behavior in response to the salient stimulus (Menon and Uddin, 2010, Seeley et al., 2007). For example, SN may receive emotional information from limbic inputs suggesting a need for an adaptive response, wherein the SN disengages DMN and engages

CEN in mediating attention, working memory and other higher cognitive processes in problem-solving. The right anterior insula (rAI) is the primary SN node, is deployed first upon the detection of salient stimuli (Downar et al., 2000, Ham et al., 2013), and acts as the major causal hub that triggers subsequent CEN versus DMN node activation (Sridharan et al., 2008, Supekar and Menon, 2012). Salience processing has been theorized to attribute motivational value to a stimulus and thus promote approach toward or retreat from a stimulus (Berridge et al., 2009).

In a previous resting-state fMRI analysis, our group described a pattern of high resting-state functional connectivity (rsFC) within the default mode network and low rsFC within the cognitive control network that distinguished depressed from normal elderly subjects (Alexopoulos et al., 2012). We also described the finding in apathetic, depressed elderly of an altered pattern of rsFC between nucleus accumbens, dorsal anterior cingulate, insula and other subcortical structures associated with reward and related behavioral responses (Alexopoulos et al., 2013). The current study was a re-analysis of the same subject sample used in the prior studies but focuses on different hypotheses and therefore on different networks.

This study examined the rsFC of the right anterior insula (rAI) and the salience network in depressed elderly patients with and without apathy and in psychiatrically normal subjects. Based on prior findings and the literature cited above, we conceptualized the SN as a system that provides motivational context to stimuli. We therefore conceptualized the apathy of late-life depression as the behavioral expression of abnormal rsFC of the SN and hypothesized that apathetic, depressed would exhibit decreased intra-network rsFC of the salience network.

METHODS

Subjects

We studied depressed and psychiatrically normal adults aged 60 years and older. The depressed group included consecutively recruited subjects who met DSM-IV criteria for unipolar major depression without psychotic features, had a score ≥ 18 on the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and were right-handed. Normal comparison subject requirements were: no history of any psychiatric disorder, HDRS <7 , and right-handedness. All subjects signed written informed consent approved by the Institutional Review Boards of Weill-Cornell Medical College and of the Nathan Kline Institute.

Exclusion criteria for the depressed group were: (1) history of other axis I psychiatric disorders prior to depression onset; (2) Mini-Mental State Examination (MMSE) score <24 (Folstein et al., 1975); (3) Mild Cognitive Impairment (MCI) according to criteria described by Petersen et al. (Petersen et al., 1999); (4) severe medical illness (i.e., metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke) within the 3 months preceding the study; (5) neurological disorders (i.e., dementia, delirium, history of head trauma, Parkinson's disease, and multiple sclerosis); (6) diseases often associated with depression (i.e., endocrinopathies other than diabetes, lymphoma, and

pancreatic cancer); (7) treatment with drugs associated with depression (i.e., steroids, α -methyl-dopa, clonidine, reserpine, tamoxifen, and cimetidine); and (8) metal implants. Exclusion criteria for non-depressed participants were the same as above.

Assessment

Major depressive disorder was diagnosed with the SCID-R, administered at entry to the study. Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Apathy was quantified using the self-rated Apathy Evaluation Scale (AES), a psychometrically validated instrument in older normal individuals and psychiatric patients (Clarke et al., 2007, Marin et al., 1991). Overall cognitive impairment was examined in a clinical interview and was rated with the MMSE (Folstein et al., 1975) and the Dementia Rating Scale (DRS) (Mattis, 1988). Memory was rated with the Hopkins Verbal Learning Test-Revised (Brandt, 2001), response inhibition with the Stroop Color Word Test (Golden, 1978) and visual attention and task switching with Trails A and Trails B (Reitan, 1985).

Depressed subjects underwent a 2-week, drug-washout phase in which they were tapered off all antidepressant and anxiolytic medications, including benzodiazepines. No normal subjects were taking psychotropic medication.

Image acquisition

MRI scans were acquired on a 1.5T Siemens Vision System at the Center for Advanced Brain Imaging of the Nathan Kline Institute. All subject scans were obtained within one to two weeks of assessment by SCID-R for the presence of major depression. All depressed patients were psychotropic-free for at least two weeks prior to the MRI scan. Data were processed and analyzed at the Weill-Cornell Brain Imaging Analysis Laboratory. Anatomic imaging included a turbo dual echo scan and high-resolution whole brain images acquired using a 3D T1-weighted MPRAGE for coregistration with fMRI data. fMRI data were acquired using BOLD contrasts in a single-shot multi-slice echo planar image (EPT; TR=2000 ms, TE=50 ms, flip-angle=90 degrees, matrix=64 × 64, FOV=224 mm, 5 mm slice thickness, 22 slices, no gap, 180 acquisitions), which allowed whole brain coverage. During scans, subjects were instructed to keep their eyes closed, stay as motionless as possible, think of nothing in particular, and remain awake. Adherence to these instructions was verified by verbal contact immediately after the resting-state scan.

Image processing

Resting-state data were processed following the procedure of Biswal et al. (Biswal et al., 2010) using the 1000 Functional Connectomes scripts (http://www.nitrc.org/projects/fconn_1000). To eliminate T1 relaxation effects, the first 10 images were discarded, leaving 170 images. Images were then motion-corrected and time-shifted using AFNI (Cox, 1996). Data were corrected for motion by aligning each volume to the mean image volume using Fourier interpolation in AFNI. Six motion parameters were calculated. Movement in each of the three cardinal directions (X, Y, and Z) and rotational movement around three axes (pitch, yaw, and roll) were included for each individual. Time series were smoothed using a 6-mm full width-half maximum (FWHM) Gaussian kernel, temporally filtered (.005-.1 Hz), and

normalized to MNI152 stereotactic space ($2 \times 2 \times 2 \text{ mm}^3$) using FSL (<http://www.fmrib.ox.ac.uk/fsl>). All subject data were visually inspected to ensure accurate normalization.

MPRAGEs were segmented using FSL's FAST software (Zhang et al., 2001), and these segmentations were normalized to MNI152 space using the transformations for the MPRAGE. White matter, cerebrospinal fluid, and total brain signal time series were extracted using masks derived from the MPRAGE segmentation. These time series, along with time series for the 6 motions parameters were used as nuisance regressors in a general linear model. In the first level analyses, these time series were residualized from the preprocessed resting-state data.

Functional connectivity analysis

To calculate time series, we used FSL's FLIRT program to transform each subject's resting-state data into MNI152 space using a 12 DOF linear affine transformation. Next, we calculated the spatial mean time series for the seed region of interest (ROI), the right anterior insula. This ROI was defined as a set of voxels contained in an 8-mm sphere centered at the peak of an activation cluster (MNI coordinates: 39, 23, -4) identified by Menon and colleagues in studies of the rAI as the main causal hub of the SN (Sridharan et al., 2008, Supekar and Menon, 2012). Individual subject analyses were carried out with GLM of FSL's FEAT toolbox using seed-based regression approaches on the residualized resting-state data (Biswal et al., 2010, Hoptman et al., 2010). The time series for the rAI seed was entered as a predictor. Individual subject-level, Z-statistic images were generated for the rAI seed.

Data analysis

Mann-Whitney and chi-square tests were used to identify demographic and clinical variables that distinguished depressed versus normal subjects and that distinguished apathetic depressed versus non-apathetic depressed versus normal subjects. Group level analyses of FC were conducted using FLAME (FMRIB's Local Analysis of Mixed Effects), to produce thresholded z-score maps of activity associated with each seed. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$ (Worsley et al., 1992). These maps revealed networks for each group (controls (N=10), depressed patients with high apathy (N=7), depressed patients with low apathy (N=9). In addition, difference maps for direct group comparisons were performed. Two-tailed significance tests were used in all comparisons.

RESULTS

Subjects

Twenty-six older adults were studied. Of these, 16 were non-demented, non-MCI subjects (mean: 69 years, SD: 5.5) with non-psychotic, unipolar major depression (baseline MADRS mean: 23.5, SD: 4.0) and 10 were normal subjects (mean age: 68.6 years, SD: 7.0). There were no significant differences in education, overall cognitive impairment (MMSE, DRS), memory (HVLT-R), or performance in a response inhibition task (Stroop Color Word)

between depressed and normal subjects. Depressed subjects, however, had higher depression scores (MADRS: $z=4.2$, $p < 0.0001$).

Depressed subjects were divided into apathetic (AES ≥ 36.5) and non-aphathetic (AES < 36.5) groups (Clarke et al., 2007). There were no significant differences in demographics, severity of depression, overall cognitive impairment, memory, and response inhibition between apathetic and non-aphathetic depressed subjects at baseline (Table 1). There was also no significant difference in blood pressure measurements across groups. All depressed subjects were scanned at the end of a 2-week psychotropic washout phase. No normal subjects were taking psychotropic medication.

Functional connectivity with Right Anterior Insula seed

With the rAI seed, apathetic depressed, non-aphathetic depressed, and normal elderly subjects demonstrated significant functional connectivity at rest within a network that included the anterior insula, ventrolateral prefrontal cortex, anterior cingulate cortex, caudate, thalamus, nucleus accumbens, amygdala, and hippocampus (Figure 1).

Relative to non-aphathetic depressed elderly patients, apathetic depressed elders had lower rsFC of the rAI with the right dorsal anterior cingulate cortex (BA 32, MNI coordinates 10, 12, 38), right nucleus accumbens (MNI coordinates 6, 6, -6), left caudate (MNI coordinates -16, 14, 14), left thalamus (MNI coordinates -14, -26, -4), bilateral amygdala (MNI coordinates 26/-24, -14, -12), and bilateral hippocampus (MNI coordinates 22/-26, -14, -24/-18) (Figure 2a-e). Apathetic depressed also had lower rsFC of the rAI with bilateral posterior parietal cortex, including the supramarginal gyrus (BA 5, MNI coordinates 10, -32, 62; BA 40, MNI coordinates -38, -30, 62) than non-aphathetic depressed patients (Figure 2f).

Relative to non-aphathetic depressed elderly patients, apathetic depressed patients had higher rsFC of the rAI with the right DLPFC (BA 9, MNI coordinates 38, 38, 36), right posterior cingulate cortex (BA 31, MNI coordinates 6, -36, 30), and left posterior cingulate/precuneus (BA 31/7, MNI coordinates 10, -46, 42) (Figure 3).

With the rAI seed, intra-network rsFC of the SN of non-aphathetic depressed subjects was indistinguishable from that of normal, elderly subjects. However, non-aphathetic depressed subjects exhibited increased rsFC of rAI to bilateral posterior cingulate cortex/precuneus (BA 31/7, MNI coordinates 10, -48, 44/-10, -50, 34) (Figure 4).

When compared directly to normal elderly subjects, rAI rsFC of apathetic depressed elderly patients had similar differences to those seen in the apathetic depressed versus non-aphathetic elderly comparison, i.e. decreased intrinsic SN rsFC and increased rAI rsFC with right DLPFC (BA9, MNI coordinates 40, 40, 34) and bilateral posterior cingulate cortex/precuneus (BA31/7 10, -38, 32 / 6, -38, 32; -12, -30, 42 / -10, -44, 44). In a comparison between the entire depressed cohort and normal elderly subjects, depressed subjects exhibited increased rsFC of rAI with bilateral precuneus (Figure 5).

DISCUSSION

The principal finding of this study is that apathetic depressed elders had distinct patterns of functional connectivity. In particular, apathetic depressed differentiated from non-apathetic depressed elderly patients and from normal, elderly subjects with a pattern of decreased intrinsic salience network resting-state functional connectivity and a pattern of increased functional connectivity of the right anterior insula of the SN with the right DLPFC node of the central executive network. A secondary finding was that both apathetic and non-apathetic depressed subjects differentiated from normal, elderly subjects with a pattern of increased rsFC of rAI with posterior cingulate cortex/precuneus nodes of the default mode network. To our knowledge, this is the first study to identify a relationship between the SN and the apathy of late-life depression.

These results expand upon prior reports that aberrant DMN and CEN activation and functional connectivity patterns underlie the biology of major depressive disorder. The DMN is active when subjects are engaged in internally focused tasks or self-referential thinking and is inhibited during the performance of cognitively demanding tasks (Raichle et al., 2001). Structures within the DMN have been found to be excessively active during depressive episodes (Sheline et al., 2009), and the degree of DMN activity may correlate with increased maladaptive rumination (Hamilton et al., 2011). Sheline and colleagues found a resting-state hyper-connectedness of the DMN in major depression (Sheline et al., 2010).

Prior work from our group further demonstrated a double dissociation of depressed elderly from normal elderly subjects with a pattern of high rsFC within the DMN and low rsFC within the cognitive control network (Alexopoulos et al., 2012). The current study was a re-analysis of the same sample used in the prior study but focused on different hypotheses and networks. In the current study, we observed that both apathetic and non-apathetic depressed subjects exhibited increased rsFC between the SN (rAI node) and the DMN (poster cingulate cortex/precuneus node) when compared to normal, elderly subjects. As the SN is thought to aid in shifting attention from internal to external stimuli, or disengaging DMN and engaging CEN, aberrant increased rsFC between SN and DMN may predispose individuals to a depression, core features of which may include difficulty in engaging in cognitively demanding tasks while ignoring irrelevant, negatively-valenced stimuli. Furthermore, the results from our current study demonstrate an impaired intrinsic rsFC of the SN which, when added to abnormalities in other networks related to depression, can manifest in a picture of a depression marked by high comorbid apathy.

Salience processing provides motivational context to a stimulus and may thus be central to initiating motivated behavior. Conversely, aberrant salience processing may underlie the motivational disturbances or apathy that is frequent in depression and most prevalent in late-onset depression. Rodent models of reward and motivation by Berridge et al. demonstrate that incentive salience processing attributes motivational value to a stimulus and thereby promotes approach toward or retreat from a stimulus (Berridge et al., 2009). In a review of human brain lesions, Levy and Dubois conclude that apathy may result from failed affective encoding of an ongoing or forthcoming behavior (Levy and Dubois, 2006). That is, the

normal affective processing that indicates the motivational value of a behavior and that orients decision-making is disrupted. Patients with focal orbital and medial prefrontal cortical lesions, for instance, exhibit decreased emotional reactivity to reward, decreased ability to evaluate the positive or negative consequence of a choice on an affective level, and decreased goal-directed behavior (Bechara et al., 1994, Bechara et al., 2000). The SN with its robust connections to several limbic and subcortical structures has been conceptualized as a bottom-up processor of salient experiences that guide an individual's ensuing behavior (Seeley et al., 2007). Greicius and colleagues demonstrated that electrical brain stimulation the SN in human subjects with refractory epilepsy elicited motivated states and “the expectation of an imminent challenge coupled with a determined attitude to overcome it” (Parvizi et al., 2013). Rodents with lesions in homologs of this electrical stimulation site conversely gave up more easily during a task in which they had to climb over a barrier before reaching a food pellet (Rudebeck et al., 2006). Thus, the SN may serve as a key motivator or driver of behaviors. In our study, apathetic depressed elderly demonstrated lower rsFC of rAI to limbic/subcortical components of the SN. This can be understood as a neurobiological dysfunction contributing to the indifference and flattening of affect in response to emotional stimuli that is seen in apathetic individuals.

Increased rsFC of the rAI to right DLPFC in apathetic depressed elderly subjects is consistent with earlier findings on the function of the DLPFC. DLPFC has been shown to be involved in cognitive control for emotional information, such as when distracting emotional information needs to be ignored during an emotional Stroop task (Etkin et al., 2006, Ochsner and Gross, 2005), and disengagement from negative stimuli (Vanderhasselt et al., 2011). Greater tonic or resting activity in right DLPFC measured by electroencephalography has been correlated with greater behavioral inhibition in response to threat (Shackman et al., 2009). While ignoring emotional information or disengaging from negative stimuli might seem an advantageous compensatory strategy to curtail a depressive state, the combination of increased rsFC between SN and DLPFC and decreased intrinsic SN rsFC may result in a maladaptive apathetic state.

These findings should be considered preliminary and viewed in the context of the study's limitations. These include the small number of subjects and the use of a 1.5 T scanner. A higher field scanner may have revealed additional abnormalities that characterize apathy in depression. Also, when imaging the aging brain, it is possible that individual differences in atrophy may negatively impact spatial normalization steps in image processing that affect subsequent image analysis results. For this reason, all subject data were visually inspected individually to ensure accurate normalization. Moreover, because we did not observe differences in atrophy (whole brain, gray or white matter) across the separate groups, this should not have had a systematic impact on our results. In addition, this study was limited to examining the resting-state. The SN and CEN are typically activated together during goal-directed cognitive tasks. A future direction includes probing whether dynamic interaction between SN and CEN during performance of such a task distinguishes apathetic from motivated states.

In conclusion, we observed that decreased intrinsic salience network rsFC and increased rsFC of the rAI to right DLPFC distinguishes apathetic depressed elderly from non-apathetic

depressed and from normal, elderly subjects. If confirmed, these findings may serve as a unique biological signature of the apathy of late-life depression and implicate a role for the rAI and the salience network in motivated behavior. Given the malignant effect of comorbid apathy on clinical outcomes and treatment response in late-life depression, identifying the network abnormalities of this meaningful dimension of the depressive disorder can provide novel targets for treatment development.

Acknowledgments

Personnel and imaging cost were supported by NIMH grants R01 MH65653, R01 MH079414, P030 MH085943, T32 MH019132 (GSA), K23 MH74818 (FMG) and the Sanchez Foundation. The authors thank Raj Sangoi RT (R) MR for his work as chief MR technologist.

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Figure 1. t-maps of the resting-state functional connectivity of the salience network for (a) apathetic depressed elderly; (b) non-aphathetic depressed elderly; (c) normal elderly adults. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Seed region of interest was in the right anterior insula.

Figure 2.

t-maps of right anterior insula resting-state functional connectivity for Apathetic depressed patients < Non-apathetic depressed patients in (a) right dorsal anterior cingulate cortex, (b) right nucleus accumbens, (c) left caudate, (d) left thalamus, (e) bilateral amygdala and hippocampus, (f) bilateral posterior parietal cortex. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Seed region of interest was in the right anterior insula.

Figure 3.

t-maps of right anterior insula resting-state functional connectivity for Apathetic depressed patients > Non-apathetic depressed patients in (a) right dorsolateral prefrontal cortex, (b) right posterior cingulate cortex, and (c) left posterior cingulate cortex/precuneus. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Seed region of interest was in the right anterior insula.

Figure 4. t-maps of right anterior insula resting-state functional connectivity for Non-apathetic depressed patients > Normal elderly subjects in (a) right and (b) left posterior cingulate cortex/precuneus. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Seed region of interest was in the right anterior insula.

Figure 5. t-maps of right anterior insula resting-state functional connectivity for Depressed patients > Normal elderly subjects in (a,b) bilateral posterior cingulate cortex/precuneus. Images were thresholded using clusters determined by $z > 2.3$ and a corrected cluster significance of $p < 0.05$. Seed region of interest was in the right anterior insula.

Table 1

Demographic and clinical characteristics of older patients with major depression with high (AES ≥36.5) and low (AES<36) apathy and normal elders.

Variable	Apathetic depressed (N=7) Mean (SD)	Non-apathetic depressed (N=9) Mean (SD)	Normal elders (N=10) Mean (SD)
Age	69.9 (4.9)	68.3 (6.1)	68.6 (7.0)
Education	17.0 (2.8)	17.3 (2.1)	16.3 (3.8)
AES ^a	43.6 (5.3) *	30.1 (4.2)	22.5 (2.7) **
MADRS ^b	25.6 (4.4)	21.9 (3.0)	2.1 (1.3) ***
MMSE ^c	28.9 (1.1)	29.3 (0.7)	28.5 (0.97)
DRS ^d	134.9 (5.3)	137.8 (3.3)	137.3 (3.9)
Stroop color word	33.9 (11.5)	36.4 (8.3)	38.5 (6.8)
Trails A	38.3 (7.7)	33.5 (9.9)	30.0 (11.1)
Trails B	96.8 (44.1)	81.2 (18.2)	75.7 (25.3)
HVLT-R ^e Immediate recall	25.4 (5.2)	28.2 (4.0)	25.5 (5.1)
HVLT-R Delayed recall	9.1 (2.2)	9.1 (2.2)	9.5 (2.2)
Systolic blood pressure (mm Hg)	126.0 (15.4)	121.1 (7.5)	130.2 (16.0)
Diastolic blood pressure (mm Hg)	73.6 (11.0)	67.6 (12.0)	75.8 (5.7)

Mann-Whitney comparisons

Normal elders vs. Apathetic depressed $p < 0.001$

* Apathetic depressed vs. Non-apathetic depressed $p < 0.001$

** Normal elders vs. Non-apathetic depressed $p < 0.002$

*** Normal elders vs. Non-apathetic depressed $p < 0.001$

^a Apathy Evaluation Scale

^b Montgomery Asberg Depression Rating Scale

^c Mini Mental State Exam

^d Dementia Rating Scale

^e Hopkins Verbal Learning Test-Revised