Published in final edited form as:
J Affect Disord. 2013 July ; 149(0): 398–405. doi:10.1016/j.jad.2012.11.023.

Functional Connectivity in Apathy of Late-life Depression: A Preliminary Study

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Abstract

Background—Apathy is common in late-life depression and is associated with disability and poor antidepressant response. This study examined whether resting functional connectivity (FC) of the nucleus accumbens (NAcc) and the dorsal anterior cingulate (dACC) with other structures can distinguish apathetic depressed older patients from nonapathetic depressed patients and normal subjects.

Keywords

functional connectivity; apathy; late life depression

INTRODUCTION

The geriatric psychiatry literature is replete with descriptions of apathy syndromes of depression. Terms such as “masked depression” and “depression without sadness” have been used in clinical texts to describe depressive syndromes accompanied by apathy and often reference is made to their high frequency in late life (Fisch, 1987; Gallo et al., 1997).

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Conflicts: Dr. Alexopoulos has received grant support from Forest Pharmaceuticals; has consulted to Hoffman-LaRoche, Lilly, Pfizer, and Otsuka; and has served at the speakers’ bureaus of Astra Zeneca, Avanir, Forest, Merck, Novartis, and Sunovion. No other authors report conflicts of interest.

Contributors: Dr. Alexopoulos conceptualized and designed and oversaw the conduct of the study, obtained funding and wrote the first draft of the manuscript. Dr. Hoptman oversaw acquisition of MRI data. Drs. Lim and Hoptman guided image analysis and provided consultation on data interpretation. Drs. Gunning and Yuen performed processing and analysis of MR images and contributed to revisions of the manuscript for important technical and intellectual content. Ms. Kanellopoulos and Ms. Seirup developed and managed the research database and performed statistical analyses in SPSS and SAS and contributed to the interpretation of data. All authors contributed to the manuscript and have approved the final version.

Apathy in depression has been defined as “lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress” (Marin, 1990; Marin et al., 1991; Starkstein and Leentjens, 2008). Lack of motivation is the superordinate dimension of apathy that influences emotional, cognitive and behavioral functions. On an emotional level, apathy is expressed as diminished emotional responses to desirable or undesirable events and lack of concern about their consequences. On a cognitive level, apathy leads to loss of interest in novel activities and in planning. Finally, on a behavioral level, apathy presents as lack of engagement and effort in productive activities.

Apathy affects 19–88% of non-demented individuals with major depression, and is most prevalent in depressed older adults (Forsell et al., 1993; Lampe and Heeren, 2004; Mehta et al., 2008). An epidemiologic study showed that a motivational disturbance was more common in older adults than a mood disturbance (Forsell et al., 1993). In a clinical sample of older adults with unipolar major depression, loss of interest was most common in older patients with first episode in late than in early life (Krishnan et al., 1995).

Apathy can be distinguished from the rest of the symptoms and signs of the depressive syndrome. Scores of the Apathy Evaluation Scale (AES) were not significantly correlated with depressive symptoms and signs (Marin et al., 1993) in a mixed sample consisting of normal elders and of patients with major depression, hemispheric stroke, and Alzheimer’s disease. Further, different relationships were identified between apathy (AES) and depression (HAM-D) scores among elderly patients with different diagnoses (Marin et al., 1994). For example, patients with right hemisphere stroke had similar levels of apathy and depression, but apathy and depression scores were not correlated. Low apathy and high depression scores were reported in left hemisphere stroke. Finally, no correlation was found between apathy and depression in a study of patients with five neurodegenerative disorders using the Neuropsychiatric Inventory, whose depression subscale does not include apathy items (Levy et al., 1998).

The few available studies suggest that apathy is associated with poor treatment response of depression. In adults with major depression, apathy at entry predicted poor response of depressive symptoms to treatment (Chaturvedi and Sarmukaddam, 1986). Similarly, severe apathy at baseline predicted a poor remission rate of both depression and apathy in drug-resistant patients with major depression treated with deep transcranial magnetic stimulation targeting the nucleus accumbens and the ventral tegmentum (Levkovitz et al., 2011). Finally, in elderly patients with major depression apathy at treatment end was correlated with poor outcome of antidepressant treatment (Lavretsky et al., 1999).

Little is known about the neurobiology of apathy of depression. The current views on the neurobiology of apathy are based on studies of neurodegenerative disorders and stroke. Akinetic mutism, an extreme form of apathy, has been described in a variety of conditions involving the ventral striatum (nucleus accumbens, ventromedial caudate), dorsal anterior cingulate cortex, ventral globus pallidus, and medial thalamus (Bonelli and Cummings, 2007). In Parkinson’s disease, apathy was inversely correlated with dopamine and norepinephrine transporter binding (^{11}C-RTI-32) in the ventral striatum (Remy et al., 2005). In frontotemporal dementia, apathy was associated with abnormal metabolism in the ventral striatum, ACC, orbitofrontal cortex, and caudate (Chase, 2011). In Alzheimer’s disease, apathy was correlated with neurofibrillary tangle density in the ACC (Marshall et al., 2006), while MRI studies found correlations of apathy with grey matter of the ACC, frontal cortex, head of caudate and putamen (Apostolova et al., 2007; Bruen et al., 2008; Chase, 2011). Functional imaging studies showed that apathy is associated with abnormal metabolism in the ACC and other frontal and orbital regions with less consistent abnormalities in temporal and medial thalamic areas. In stroke and traumatic brain injury, right sided lesions led to

greater apathy than left sided lesions (Andersson et al., 1999). Overall, an average of 61% of patients with focal frontal lobe lesions had apathy while apathy was identified in 40% of patients with basal ganglia lesions (Chase, 2011). Among those with subcortical lesions, damage of the caudate nucleus, globus pallidus, and mediodorsal thalamic nuclei were most frequently associated with apathy. Taken together, these studies suggest that apathy may be associated with abnormalities of the ventral striatum, ACC, and basal ganglia.

This study investigated functional connectivity at rest (FC) in depressed elderly patients with and without apathy and in psychiatrically normal subjects. FC is based on the observation that spontaneous blood oxygen level dependent (BOLD) signal fluctuations among brain regions similarly modulated by specific tasks tend to be correlated (Biswal et al., 1995; Cordes et al., 2001; De Luca et al., 2005; Fox and Raichle, 2007; Fox et al., 2009; Lowe et al., 1998). FC during rest is thought to reflect important interrelationships among structures with related functions. Most of the brain's energy (>85%) is consumed to maintain a functionally differentiated state at rest (Fox and Raichle, 2007). Studies using different methodology suggest that BOLD activity during a resting state is mainly driven by "intrinsic activity", which remains consistent across different resting conditions (Fransson, 2005; Raichle and Mintun, 2006), task performance (Fair et al., 2007; Fransson, 2006; Greicius et al., 2004; Sapir et al., 2005; Sun et al., 2007; Waites et al., 2005), sleep (Fukunaga et al., 2006; Horovitz et al., 2008), and anesthesia (Peltier et al., 2005; Vincent et al., 2007).

This study conceptualized apathy of late-life depression as the behavioral expression of abnormal FC of the nucleus accumbens (NAcc) and the dorsal anterior cingulate (dACC) with brain structures related to mood regulation. This view was based on apathy studies on neurodegenerative disorders and on current views on the neurobiology of depression, which postulate abnormal interactions between reward structures, including the NAcc, and prefrontal regions (Phillips et al., 2003). Accordingly, this study compared FC between apathetic depressed elders with depressed elders without apathy and with normal elderly control subjects.

METHODS

Subjects

We studied depressed and psychiatrically normal adults aged 60 years and older. The depressed group consisted of consecutively recruited subjects who met DSM-IV criteria for unipolar major depression without psychotic features and had a score of 18 or greater on the 24-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The normal comparison subjects were recruited through advertisement and were required to have no history or presence of any psychiatric disorder. The subjects signed written informed consent approved by the IRBs of Weill-Cornell Medical College and of Nathan Kline Institute. The consent form informed subjects that there would be a placebo phase during the study, but did not specify the time of the placebo phase.

Individuals were excluded if they had: 1) Mini-Mental State Examination score < 24 (Folstein et al., 1975) or met the Mild Cognitive Impairment (MCI) criteria of Petersen et al (Petersen et al., 1999) during the clinical interview; 2) presence of delirium, history of stroke, head trauma, multiple sclerosis, or brain degenerative diseases; 3) metastatic cancer, brain tumors, unstable cardiac, hepatic, or renal disease, myocardial infarction, or stroke within the 3 months preceding the study; 4) diseases frequently associated with depression, i.e. lymphoma, pancreatic cancer, or endocrinopathies other than diabetes; 5) treatment with drugs associated with depression, i.e. steroids, alpha-methyl-dopa, clonidine, reserpine,

tamoxifen, or cimetidine; and 6) metal implants. Depressed subjects with history of other axis I psychiatric disorders prior to the onset of depression were excluded.

Assessment

DSM-IV diagnosis was based on the SCID-R (First, 2002), administered at entry to the study. Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Overall cognitive impairment was rated with the Mini Mental State Examination (MMSE) (Folstein et al., 1975) and the Dementia Rating Scale (Mattis, 1988). Memory was rated with the Hopkins Verbal Learning Test-Revised (Brandt and Benedict, 2001), response inhibition with the Stroop Color Word Test (Golden, 1978) and visual attention and task switching with Trails A and Trails B (Reitan and Wolfson, 1985). Apathy was assessed with the Apathy Evaluation Scale (Marin et al., 1991) and dysexecutive behavior with the Frontal Systems Behavior Scale (FrSBe) (Grace et al., 2001). Disability was evaluated with the World Health Organization Disability Assessment Scale (WHODAS-II) (Epping-Jordan and Ustun, 2000).

MRI

MRI Data Acquisition—MRI scans were acquired on a 1.5T Siemens Vision MR system at the Center for Advanced Brain Imaging (CABI) of the Nathan Kline Institute. 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 (EPI; TR = 2000 ms, TE = 50 ms, flip-angle = 90 degrees, matrix=64×64, FOV = 224mm, 22 5mm slices, no gap), which allowed whole brain coverage.

Image Processing—Resting state (awake, closed eyes) data were processed following the procedure of Biswal et al (Biswal et al., 2010). To eliminate T1 relaxation effects, the first 10 images were discarded. Images were then motion corrected and time shifted using AFNI (Cox, 1996). Next, time series were smoothed using a 6-mm full width-half maximum (FWHM) Gaussian kernel, temporally filtered (.005Hz–.1Hz), and normalized to MNI152 stereotaxic space using FSL (http://www.fmrib.ox.ac.uk/fsl). MPRAGEs were segmented using FSL's FAST software, and these segmentations were normalized to MNI152 space using the transformations for the MPRAGE.

FC analysis—To calculate timeseries 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 each seed ROI. Using seeds that were anatomically defined, we placed one seed in each hemisphere of the NAcc and one seed was placed in each hemisphere in the dACC.

For each seed, individual participant analyses was carried out with GLM of FSL's FEAT toolbox using the seed-based regression approaches (Biswal et al., 2010; Hoptman et al., 2010). The timeseries for each seed as well as CSF, white matter, total brain matter, and motion parameters were entered as predictors. Next, individual subject-level, Z-statistic images were extracted.

Data Analysis

Initially, chi square and Mann-Whitney tests were used to identify demographic and clinical variables distinguishing depressed from normal subjects and depressed subjects who achieved remission from those who remained symptomatic. 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 apathy at baseline (N = 7), depressed patients without apathy at baseline (N = 9). In addition, difference maps for direct group comparisons (e.g., depressed patients with apathy vs. depressed patients without apathy were performed; controls vs. depressed patients with apathy; controls vs. depressed patients without apathy). 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 statistically significant differences in education (years), overall cognitive impairment (MMSE, DRS), memory (HVLT-R), and response inhibition (Stroop) between depressed and normal subjects. However, depressed subjects had higher depression (MADRS: $z=4.2$, $p<0.0001$) scores than normal subjects. Depressed subjects divided into an apathetic (AES ≥ 36.5) and a non-apathetic (AES<36.5) group. There were no statistically significant differences in demographics, severity of depression, and cognitive functions between apathetic and non-apathetic depressed subjects at baseline with the exception of apathy (AES) in which apathetic patients had had more abnormal scores (Table 1). Depressed subjects were scanned at the end of a 2-week psychotropic washout phase. None of the normal subjects was on psychotropic agents.

Functional Connectivity

NAcc Seeds—For both the left and the right NAcc seeds, both depressed and non-depressed subjects demonstrated significant FC within a network that included the striatum, the caudate, the amygdala, the thalamus, and the orbitofrontal cortex (OFC). Overall, apathetic depressed patients had lower FC of the NAcc with the right amygdala, basal ganglia (caudate, putamen), globus pallidus, and thalamus and higher FC with the dACC and dorsomedial prefrontal cortex (dmPFC) than non-apathetic patients. Voxel and MNI stereotaxic space coordinates appear in the Appendix.

Left NAcc: For the left NAcc seed, apathetic patients exhibited lower FC than non-apathetic patients with the right amygdala, putamen, and globus pallidus, and the left caudate (Figure 1a). Apathetic patients had higher FC than non-apathetic patients with the left dorsal ACC and dmPFC (Figure 1b).

When apathetic patients and healthy control subjects were directly compared, apathetic patients had lower FC with the right inferior gyrus, right amygdala, bilateral putamen and globus pallidus, and left hippocampus and superior frontal gyrus (Figure). Apathetic patients had higher FC with the left OFC and middle frontal gyrus. Non-apathetic patients had less pronounced differences in FC from healthy controls, i.e. lower FC with the dACC and higher FC with the inferior frontal gyrus.

Right NAcc: For the right NAcc seed, apathetic patients showed lower FC than non-apathetic patients with the right amygdala, putamen and globus pallidus, and with the left caudate (Figure 2a). Apathetic patients exhibited higher FC than non-apathetic patients with the dmPFC and the left dACC (Figure 2b).

When apathetic patients and controls were compared, apathetic patients showed lower FC with the putamen and the globus pallidus bilaterally. Non-apathetic patients had lower FC than controls with the OFC bilaterally.

dACC Seeds—For both the left and the right dACC seeds, both depressed and non-depressed subjects demonstrated significant FC within a network that included the dACC, left PFC, supramarginal, superior parietal, inferior parietal regions, and thalamus. Apathetic patients had lower FC of the dACC with frontal gyri and higher FC with the insula, middle frontal gyrus, and the OFC than non-apathetic patients.

Left dACC: For the left dACC seed, apathetic patients had lower FC than non-apathetic patients with both the superior and the inferior frontal gyruses bilaterally and the left middle frontal gyrus and the right superior parietal region (Figure 3a). Apathetic patients demonstrated higher FC than non-apathetic patients with the right insula, OFC, and the middle frontal gyrus (Figure 3b).

When compared with healthy controls, apathetic depressed patients had lower FC with the superior and the middle frontal gyrus bilaterally and with the left subgenual ACC. Relative to controls, apathetic depressed patients had higher FC with the dmPFC and the right insula. Non-apathetic patients had lower FC than healthy controls with the right OFC and left rostral ACC and higher FC with left superior frontal gyrus and right inferior frontal gyrus.

Right dACC: When the seed was placed in the right dACC, apathetic depressed patients demonstrated lower FC than non-apathetic depressed patients with the ventrolateral PFC bilaterally and the left superior frontal gyrus (Figure 4a). Apathetic patients exhibited higher FC than non-apathetic patients with right structures, i.e. middle frontal gyrus, OFC, and insula (Figure 4b).

Apathetic depressed patients had lower FC than healthy controls with left structures, i.e. subgenual ACC, caudate, and middle frontal gyrus and increased FC with the left dACC and the dorsomedial PFC. Non-apathetic patients had lower FC than healthy controls with the right OFC and vmPFC and higher FC with the left superior frontal gyrus and the right inferior frontal gyrus.

DISCUSSION

The principal finding of this study is that resting FC of the NAcc and the dACC distinguished older patients with apathy and major depression from depressed older patients without apathy and from normal older subjects. Apathetic depressed patients had lower FC of the NAcc with the amygdala, caudate, putamen, globus pallidus, and thalamus and increased FC with the dmPFC, the superior frontal cortex, and the insula than non-apathetic patients. Further, apathetic patients had lower FC of the dACC with dorsolateral and ventrolateral prefrontal cortices and higher FC with the insula and the OFC than non-apathetic patients.

To our knowledge this is the first study to identify abnormalities in resting FC distinguishing apathetic depressed older patients from non-apathetic depressed patients and normal subjects. A strength of this study is that its subjects were free of psychotropic drugs for at least two weeks. Its limitations include a small number of subjects, the lack of random sampling, and the use of a 1.5 T scanner; a more powerful scanner may have yielded additional findings because of its higher signal-to-noise ratio.

The structures on which this study focused are anatomically connected (Bonelli and Cummings, 2007). Specifically, the dACC (BA24) provides input to the ventral striatum, which includes the NAcc, olfactory tubercle, ventromedial caudate, and ventral putamen. Projections from the ventral striatum innervate the rostromedial globus pallidus interna and ventral pallidum and the rostrodorsal substantia nigra. The ventral pallidum provides input to the magnocellular mediodorsal thalamus, which in turn projects to the dACC thus closing the dACC-subcortical loop. An indirect loop has also been identified projecting from the ventral striatum to the rostral pole of globus pallidus externa, which connects to the medial subthalamic nucleus, and from there projections are sent to the ventral pallidum.

Along with anatomical connections, the functions of NAcc and dACC are directly related to motivational, cognitive, and behavioral functions of the kind found impaired in apathetic states. The NAcc is a central node in networks processing diverse reward functions and serves as an interface between limbic and motor processing. The NAcc is selectively activated during the perception of pleasant pictures and during imagery of pleasant, emotional scenes (Costa et al., 2010; Sabatinelli et al., 2007). The dACC is a processing station of top-down and bottom-up stimuli assigning appropriate control to other structures. It may play a special role in reward circuitry, particularly in reward-based decision making, learning, and the performance of novel, nonautomatic tasks (Bush et al., 2002).

Apathetic depressed patients had lower FC than non-apathetic patients of the NAcc with the amygdala, putamen, caudate and globus pallidus and higher FC with dACC and dmPFC than non-apathetic patients. The NAcc is part of the cortico-striato-thalamo-cortical loop. Significant sources of input to the NAcc come from the amygdala, and from dopaminergic fibers of the ventral tegmental area (VTA) via the mesolimbic pathway. The amygdala processes motivationally salient stimuli (Lindquist et al., 2012), while the VTA serves functions related to reward, motivation, and cognition. Thus the NAcc, amygdala, VTA is a complex for processing various aspects of reward related perception and behavior. The NAcc gives input to the ventral part of globus pallidus, which in turn projects to the thalamus and from there to the prefrontal cortex and the striatum. FC abnormalities in these networks may contribute to the perception and experience of rewards and contribute to apathy in late-life depression.

Apathetic depressed patients had lower FC of the dACC with the superior and inferior frontal gyri and higher FC with the insula, the middle frontal gyrus, and the OFC than non-apathetic patients. These prefrontal cortices are responsible for high level processing of working memory including monitoring and manipulation of information and maintenance of distinct stimuli including response mapping rules and adaptive decision making. The insula is connected with the ACC and is a node critical for the experience of basic emotions (happiness, sadness, aversion, fear, anger) and with emotional salience of body representation and the environment including environmental monitoring and response selection. The OFC plays a central role in integrating the affective value of reinforcers in overall perception, and in decision making and expectation (Kringelbach, 2005). Thus, the FC differences between apathetic and non-apathetic depressed patients are between the dACC, a central distribution node, and structures related to processing of both various emotions as well as complex behavioral responses.

Identifying the causes of apathy in late life depression is beyond the scope of this study. However, vascular compromise may contribute to apathy and may account in part for the poor antidepressant response of apathetic depressed patients. Consistent with our finding of low FC among medial frontal structures and the ventral striatum are findings suggesting that lesions in the basal ganglia and in frontal subcortical regions have been associated with apathy (Levy and Dubois, 2006; van Reekum et al., 2005). Healthy elders with apathy have

more subcortical white matter hyperintensities (WMH) than those without apathy (Yao et al., 2009). Apathy was associated with history of stroke/TIA as well as cardiovascular risk factors in a large probability sample of community residing elders (Ligthart et al., 2012). There was a dose-effect relationship between apathy and hypertension, type 2 diabetes mellitus, obesity, and C-reactive protein. Similarly, lower ankle-brachial blood pressure, an index of peripheral vascular disease, may be an independent risk factor for apathy (Sugawara et al., 2011). Among individuals older than 85 years, those with apathy had more vascular diseases at baseline and during a 5 year follow-up (van der Mast et al., 2008). Both apathy (Chaturvedi and Sarmukaddam, 1986; Lavretsky et al., 1999; Levkovitz et al., 2011) as well as increased WMH volume of (Sheline et al., 2008) (Gunning-Dixon et al., 2010) and low fractional anisotropy in areas, including frontal and frontal-subcortical white matter regions has been associated with low remission rate of late-life major depression (Alexopoulos et al., 2010; Alexopoulos et al., 2009; Alexopoulos et al., 2008). These abnormalities are principally located in areas likely to interrupt connections among frontal and ventral striatum structures and may be contributed to by cerebrovascular disease among other factors (Hoptman et al., 2009).

In conclusion, resting FC between the NAcc and the dACC on the one hand and structures related to processing of rewards and of related behavioral responses distinguished older apathetic depressed patients from non-apathetic depressed patients and from normal older subjects. In addition to replication, these findings point to the need for studies of the structural integrity and functional responses of NAcc and dACC networks in depressed older apathetic patients, who are often unresponsive to classical antidepressants and remain disabled and suffering.

Acknowledgments

Role of the funding source: Personnel and imaging cost of this work was supported by NIMH grants R01 MH65653, R01 MH079414, P030 MH085943, T32 MH019132 (GSA), K23 MH74818 (FGD) and the Sanchez Foundation. Escitalopram and placebo were provided free of cost by Forest Pharmaceuticals, Inc.

We thank Raj Sangoi (RT) (R) (MR) for his assistance in scanning the research participants and Eric Woods for participating in the clinical evaluation.

Appendix

Table 2

Regions showing group functional connectivity differences between apathetic and non-apathetic depressed patients.

Seed		Region	Voxels	Z	MNI Coordinates		
					X	Y	Z
Left Nucleus Accumbens	Apathy<No Apathy	R Inferior Frontal	407	4.13	56	30	−2
		R Ventral Striatum	221	4.97	22	18	−16
		R Putamen	174	4.07	26	14	−4
		L Caudate	94	4.21	−14	4	18
	Apathy>No Apathy	L Dorsal ACC	274	3.76	−8	20	32
		R Sup Frontal	108	3.85	20	42	28
Right Nucleus Accumbens	Apathy<No Apathy	R Amygdala	82	3.08	26	6	−18
		L Caudate	66	3.53	12	−4	18
		R Globus Pallidus	56	3.18	20	2	−6

Seed		Region	Voxels	Z	MNI Coordinates		
					X	Y	Z
	Apathy>No Apathy	L Dorsal ACC	106	2.97	−8	0	40
		L Dorsomedial PFC	97	3.01	−8	30	34
Left Dorsal Anterior Cingulate Cortex	Apathy<No Apathy	L Sup Frontal	532	3.60	−12	22	54
		R Mid Frontal	315	4.19	46	−2	48
		L Sup Parietal	134	4.09	−24	−66	58
		L Sup Frontal	78	3.08	−40	12	52
		L Inf Frontal	71	3.43	−58	26	12
	Apathy>No Apathy	R Mid Frontal	211	3.42	26	30	28
		R Insula	69	2.89	34	24	8
		R Orbital Frontal	65	3.56	30	30	−16
Right Dorsal Anterior Cingulate Cortex	Apathy<No Apathy	R Mid Frontal	315	4.03	46	4	48
		R Inf Frontal	148	3.88	38	−14	32
		L Sup Frontal	115	3.74	−4	20	60
		R Sup Frontal	113	3.74	10	18	52
		R Inf Frontal	77	4.05	18	83	32
	Apathy>No Apathy	R Mid Frontal	226	3.79	34	36	38
		R Orbital Frontal	134	3.38	31	83	30
		R Insula	71	3.34	38	4	14

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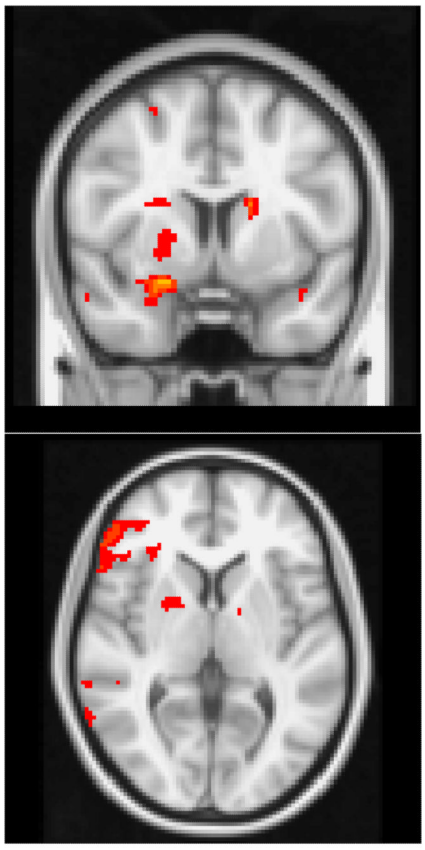

Figure 1a.

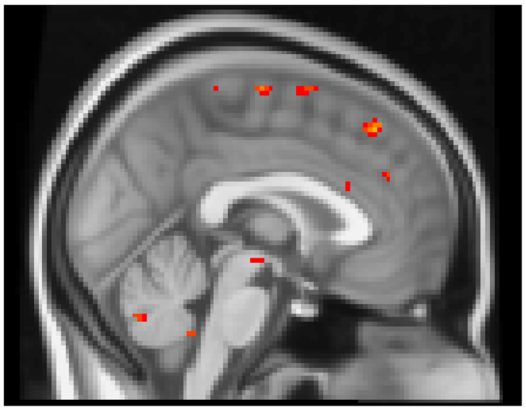

Figure 1b.

Figure 1.

T maps of the left nucleus accumbens resting state connectivity: 1a. Apathetic Patients <NonApathetic Patients; 1b. Apathetic Patients > NonApathetic Patients. Images were thresholded using clusters determined by z>2.3 and a corrected cluster significance threshold of p<0.05.

Figure 1a. Seed in the Left Nucleus Accumbens:
Apathetic Patients <NonApathetic Patients

Figure 1b. Seed in the Left Nucleus Accumbens:
Apathetic Patients > NonApathetic Patients

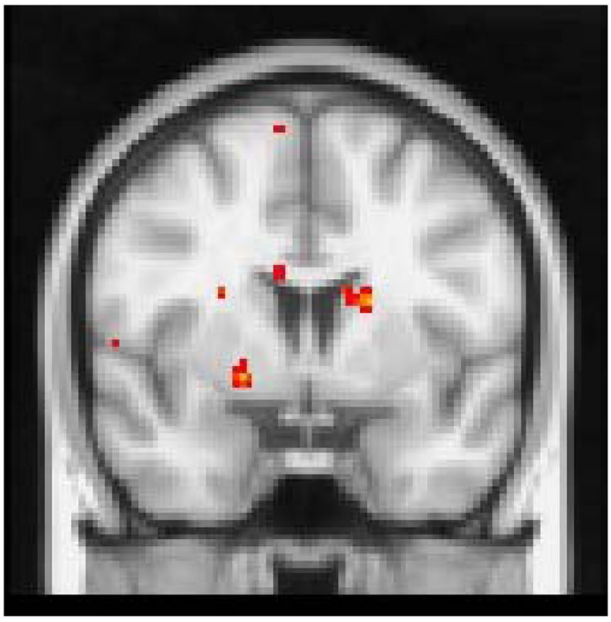

Figure 2a.

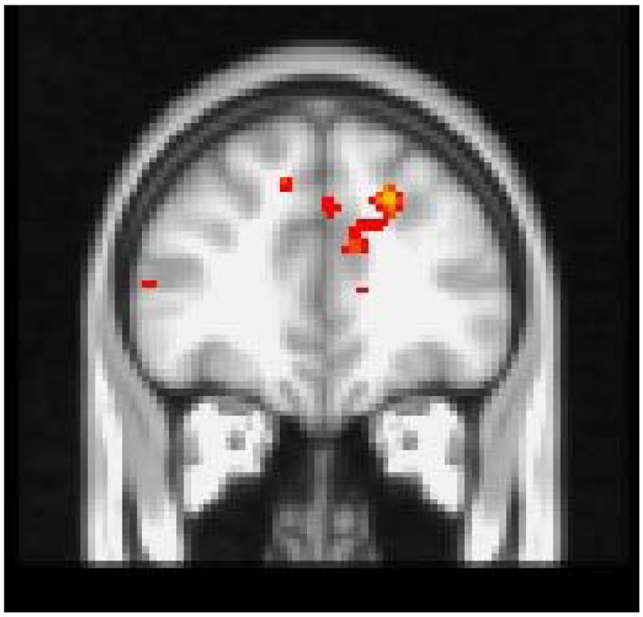

Figure 2b.

Figure 2.

T maps of the right nucleus accumbens resting state connectivity: 2a. Apathetic Patients <NonApathetic Patients; 2b. Apathetic Patients > NonApathetic Patients. Images were thresholded using clusters determined by z>2.3 and a corrected cluster significance threshold of p<0.05.

Figure 2a. Seed in the Right Nucleus Accumbens:
Apathetic Patients < NonApathetic Patients

Figure 2b. Seed in the Right Nucleus Accumbens:
Apathetic Patients > NonApathetic Patients

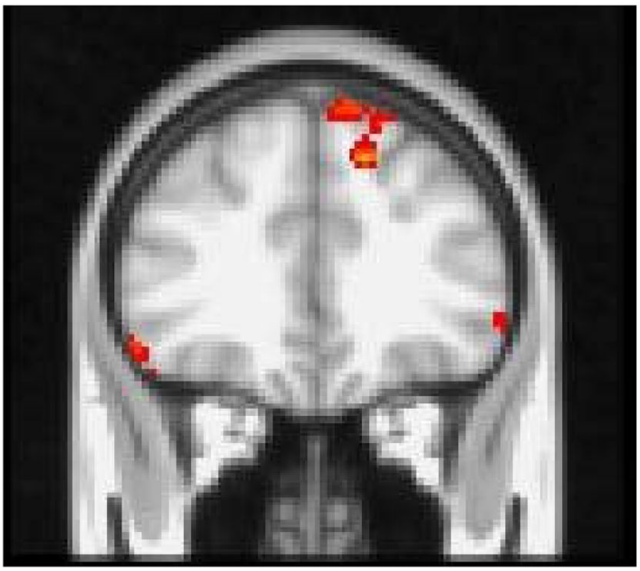

Figure 3a.

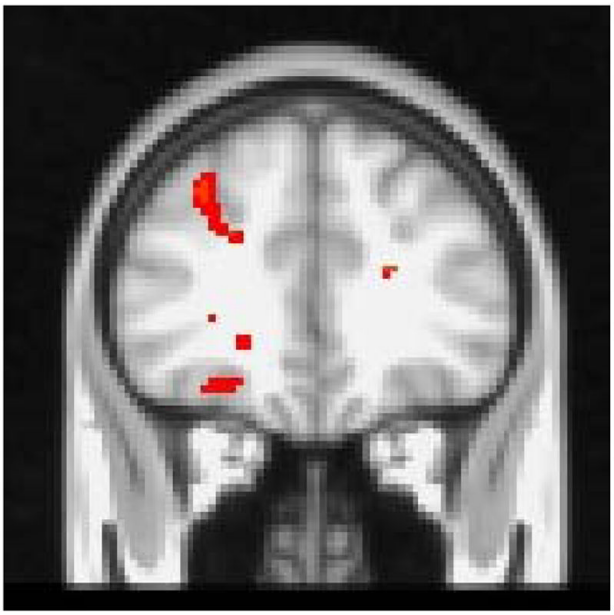

Figure 3b.

Figure 3.

T maps of the left dorsal anterior cingulate cortex (ACC) resting state connectivity: 3a. Apathetic Patients <NonApathetic Patients; 3b. Apathetic Patients > NonApathetic Patients. Images were thresholded using clusters determined by z>2.3 and a corrected cluster significance threshold of p<0.05.

Figure 3a. Seed in the Left Dorsal ACC:
Apathetic Patients < NonApathetic Patients

Figure 3b. Seed in the Left Dorsal ACC:
Apathetic Patients > NonApathetic Patients

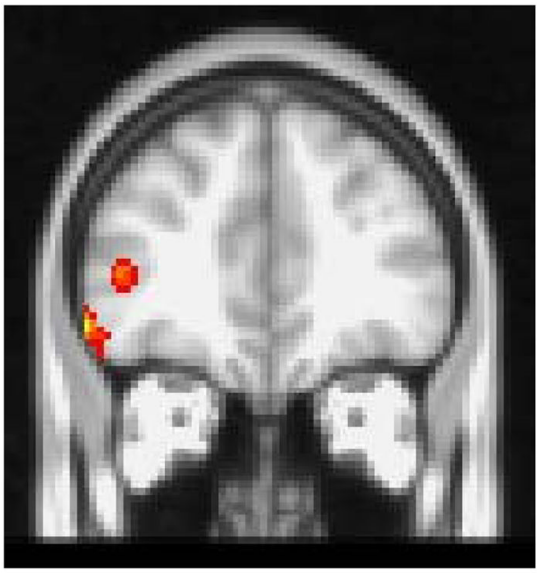

Figure 4a.

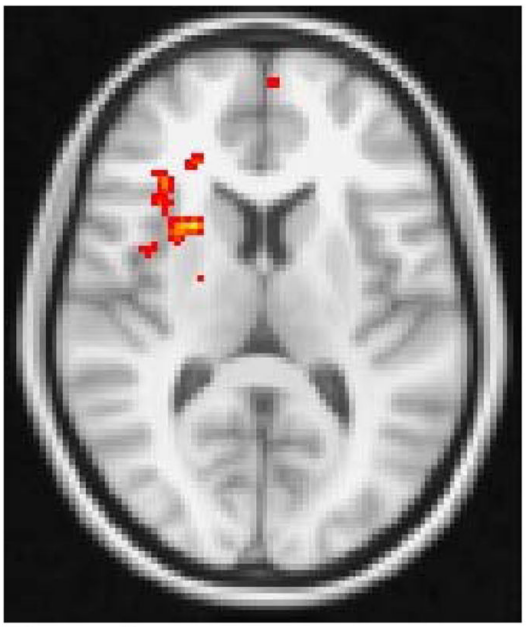

Figure 4b.

Figure 4.

T maps of the right dorsal anterior cingulate cortex (ACC) resting state connectivity: 4a. Apathetic Patients <NonApathetic Patients; 4b. Apathetic Patients > NonApathetic Patients. Images were thresholded using clusters determined by z>2.3 and a corrected cluster significance threshold of p<0.05.

Figure 4a. Seed in the Right Dorsal ACC Seed:
Apathetic Patients < NonApathetic Patients

Figure 4b. Seed in the Right Dorsal ACC Seed:
Apathetic Patients > NonApathetic Patients

Table 1

Characteristics of Older Patients with Major Depression with High (AES[1]≥36.5) and Low (AES<36.5) Apathy Scores and Normal Elders.

Variable	Apathetic Depressed (N=7)	Non-Apathetic Depressed (N=9)	Normal Elders (N=10)
	Mean (SD)	Mean (SD)	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[1]-Patient Self-Rated	43.6 (5.3)*	30.1 (4.2)	22.5 (2.7)**
MADRS[2]	25.6 (4.4)	21.9 (3.0)	2.1 (1.3)***
MiniMental State Exam	28.9 (1.1)	29.3 (0.7)	28.5 (0.97)
DRS[3] Total	134.9 (5.3)	137.8 (3.3)	137.3 (3.9)
DRS Initiation/Perseveration	33.9 (4.4)	36.0 (0.7)	35.9 (1.1)
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[4] 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)

[1] Apathy Evaluation Scale;

[2] Montgomery Asberg Depression Rating Scale;

[3] Dementia Rating Scale;

[4] Hopkins Verbal Learning Test-Revised;

Mann-Whitney comparisons:

* Apathetic Depressed vs. Non-Apathetic Depressed p<0.001,

** Normal Elders vs. Non-Apathetic Depressed p = 0.002,

*** Normal elders vs. Apathetic Depressed p = 0.001, Normal Elders vs. Non-Apathetic Depressed p < 0.001.