

Brain Regions Involved in Arousal and Reward Processing are Associated with Apathy in Alzheimer's Disease and Frontotemporal Dementia

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Abstract.

Background: Apathy is a common and problematic symptom of several neurodegenerative illnesses, but its neuroanatomical bases are not understood.

Objective: To determine the regions associated with apathy in subjects with mild Alzheimer's disease (AD) using a method that accounts for the significant co-linearity of regional atrophy and neuropsychiatric symptoms.

Methods: We identified 57 subjects with mild AD (CDR = 1) and neuropsychiatric symptoms in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. We performed a multivariate multiple regression with LASSO regularization on all symptom subscales of the Neuropsychiatric Inventory and the whole-brain ROI volumes calculated from their baseline MRIs with FreeSurfer. We compared our results to those from a previous study using the same method in patients with frontotemporal dementia (FTD) and corticobasal syndrome (CBS).

Results: Of neuropsychiatric symptoms, apathy showed the most robust neuroanatomical associations in the AD subjects. Atrophy of the following regions were independently associated with apathy: the ventromedial prefrontal cortex; ventrolateral prefrontal cortex; posterior cingulate cortex and adjacent lateral cortex; and the bank of the superior temporal sulcus. These results replicate previous studies using FTD and CBS patients, mostly agree with the previous literature on apathy in AD, and correspond to the Medial and Orbital Prefrontal Cortex networks identified in non-human primates.

¹Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Conclusion: The current study, previous studies from our laboratory, and the previous literature suggest that impairment of the same brain networks involved in arousal, threat response, and reward processing are associated with apathy in AD and FTD.

Keywords: Apathy, Alzheimer's disease, frontotemporal dementia, magnetic resonance imaging, neuropsychiatry

INTRODUCTION

Apathy has had different specific definitions, but at the core of these definitions is a state of decreased motivation [1–3]. Because motivation is fundamentally an internal state that has proven hard to quantify and is subject to anosognosia (a lack of awareness of symptoms) measurements of apathy have generally relied on observations by an informant of a decrease in goal-directed activities and activities that were previously rewarding for the patient [3]. Apathy is a common and often disabling symptom of many different neurodegenerative illnesses including Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease, and dementia with Lewy bodies. Neuropsychiatric symptoms associated with dementia are a major problem that contributes to caregiver stress, cost, and poor patient prognosis [4, 5]. Apathy is the most common neuropsychiatric symptom in dementia, occurring in 25 to 88% of patients with AD and the vast majority of FTD patients [6–10].

Several studies have examined the neuroanatomical underpinnings of apathy in AD using magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (FDG-PET), and single-photon emission computed tomography (SPECT) (see [3] for a recent review). Decreased volume on structural imaging and decreased metabolism on functional imaging of several areas of the brain have been associated with apathy in AD, notably the anterior and posterior cingulate cortices, the orbitofrontal cortex, insula, putamen, and inferior temporal cortex, with a greater association with right-sided compared to left-sided structures [3]. Decreased diffusion tensor imaging fractional anisotropy of the anterior cingulate and genu of the corpus callosum, indicating impaired connectivity in neuronal tracts, have also been associated with apathy in patients with AD. Most of these studies in patients with AD did not control for cognitive deficits or other neuropsychiatric symptoms besides apathy [3].

Apathy is also a very common symptom of FTD. Apathy in FTD has been associated with atrophy in the right ventral striatum, the right temporal cortex,

and the left operculum-insula [11]. In other studies, atrophy of the dorsolateral prefrontal and lateral orbitofrontal cortex, right anterior cingulate cortex, right putamen, and right inferior parietal cortex were associated with apathy in FTD [9, 10]. On PET, apathy was associated with decreased orbitofrontal metabolism in FTD [12]. In a group of patients with mixed dementias, apathy was associated with decreased volume of the medial prefrontal cortex (PFC) [13]. There is evidence that FTD patients show a different pattern of symptoms of apathy than AD patients, with FTD patients showing greater reduced emotional output than AD patients [7]. In summary, in both FTD and AD, increased atrophy and/or decreased metabolism in the orbitofrontal cortex, anterior cingulate cortex, ventral striatum, insula, and inferior parietal cortex have been associated with apathy, more in the right hemisphere than the left.

These studies have helped to elucidate the neuroanatomical bases of apathy in individual neurodegenerative diseases, but several questions remain. Different neurodegenerative disorders affect disparate regions of the brain. Is apathy associated with the same brain regions in all neurodegenerative disorders, or does the neuroanatomy of apathy vary by disorder? Do the clinical syndromes of apathy differ depending on the brain regions involved and can we distinguish different clinical syndromes of apathy? A barrier to answering these questions has been the significant co-linearity of both brain atrophy and apathy in neurodegenerative illnesses. Atrophy in one region is associated with atrophy in adjacent regions and apathy overlaps with other neuropsychiatric syndromes such as depression [14]. To address these questions and issues, we examined the brain regions associated with apathy in mild AD using multivariate regression that accounts for the co-linearity of neuropsychiatric and imaging measures. We then compared our results to a previous study by our group examining apathy in FTD and CBS patients using the same method [15] with the goal of determining if the same or different regions are associated with apathy in these neurodegenerative disorders.

MATERIALS AND METHODS

Subjects

The data were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>), after receiving permission from ADNI administration, on January 2, 2015. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. For up-to-date information, see <http://www.adni-info.org>. All participants received structural brain MRI scans on 1.5-Tesla scanners from GE Healthcare (Waukesha, WI) or Siemens Medical Solutions (Erlangen, Germany) according to the standardized ADNI protocol with multiple procedures to minimize variation between study sites. For further information on the ADNI study, including subject recruitment methods and MRI parameters, please see [16] and <http://clinicaltrials.gov/show/NCT00106899>. ADNI has been approved by the Institutional Review Boards of all participating institutions. Informed written consent was obtained from all participants at each site.

We screened all of the patients who had participated in ADNI1 to find patients who had a Clinical Dementia Rating (CDR) = 1, had been administered the Neuropsychiatric Inventory (NPI), had at least one neuropsychiatric symptom (defined as a total NPI score ≥ 1), and a structural 1.5T MRI scan. We did not use FDG-PET or 3T MRI scans because only a subset of the subjects had these scans. We limited our recruitment to ADNI1 for consistency in the imaging data as the MRI field strength and FreeSurfer algorithm were changed between ADNI1 and ADNI2. Each subject was limited to one baseline datapoint (i.e., if a subject met inclusion criteria at multiple ADNI visits, only their first of these visits was used) and the MRI data were inspected for quality and the subject removed if the data showed poor quality. This resulted in 57 subjects. See Table 1 for subject characteristics.

Measures

The NPI was administered to all subjects participating in ADNI. This is a scale in which a

Table 1
Subject characteristics

N	57
Age mean (SD)	76.5 (9.1)
Total MMSE mean (SD)	22.8 (2.2)
Total NPI mean (SD)	3.1 (2.4)
% with NPI-Q Apathy ≥ 1	26%
Mean apathy score in subjects with apathy (SD). Range is 1 (mild) to 3 (severe)	1.6 (0.7)

knowledgeable informant is interviewed on the development of a range of neuropsychiatric symptoms by the patient [17]. The NPI-Q, assessing only symptom presence and severity, was used in this study. It has a range of 0 (symptom not present) to 3 (symptom present and severe). In our previous study of FTD and CBS patients, we used the full NPI that assesses severity \times frequency of a symptom, giving a larger range of scores. We analyzed the following data from ADNI1: NPI subscales, the total Mini-Mental State Examination (MMSE) score [18], age, and volumes of 64 MRI regions-of-interest (ROIs) (32 on the right and left). Volumes were calculated using FreeSurfer version 4.4 by researchers at the University of California, San Francisco from T1-weighted images per ADNI protocols.

Analyses

To test the effect of volume loss on the NPI scores, we then entered the NPI subscales and the whole-brain ROI volumes calculated from FreeSurfer into a multivariate regression. For model selection, we used Least Absolute Shrinkage and Selection Operator (LASSO) regularization. Multivariate regression with LASSO regularization achieves sparsity in the estimated model by interpreting variables with non-zero regression coefficients as truly associated with the dependent variable. The model we considered was $y_{ip} = a_p + \sum_{j=1}^Q \beta_{jp} x_{ij} + \varepsilon_{ip} = 1, \dots, n, p = 1, \dots, P$ where n was the number of individuals, Q was the number of ROIs, and P was the number of non-imaging outcome measures. The possible confounding variables age and total MMSE [18] score were adjusted prior to the analysis by fitting linear regression. We applied multivariate linear regression with LASSO regularization using the *lars* R package for model selection [19, 20], and the model coefficients were corrected for multiple comparison [21]. This is the same method that we used in [15].

RESULTS

Apathy was detected (i.e., had an NPI value equal to or greater than 1) in 26% of the subjects. The results of the multiple regression are presented in Fig. 1. Figure 1 represents whole-brain associations between the measures of neuropsychiatric symptoms (the NPI subscales) and ROI volumes in our subjects. Cold colors represent negative associations (i.e., the score on the NPI subscale increases, representing more severe neuropsychiatric symptoms, as the regional volume decreases). Hot colors represent the converse. To understand the selective associations, we applied biclustering on the estimated coefficients that LASSO selected using hierarchical cluster analysis with complete linkage. Significant associations are noted as colored boxes on the heat map in Fig. 1. All of the associations with apathy in Fig. 1 are neg-

ative, i.e., as the volume in the region decreases, apathy increases. The color scale represents standardized coefficients, which are equivalent to partial correlation coefficients. The multivariate multiple regression we performed resulted in sparse associations between regional volumes and neuropsychiatric symptoms (Fig. 1). Of the neuropsychiatric symptoms, apathy has the most anatomic associations (Fig. 1). Table 2 lists the partial correlations between apathy (the NPI scale with the strongest anatomical associations) and ROI volume. The associations remained significant at 5% level even after multiple comparison correction. These associations group into four regions (Fig. 1 and Table 2): ventromedial PFC; ventrolateral PFC; posterior cingulate cortex and adjacent lateral cortex; and bank of the superior temporal sulcus. These regions are represented graphically in Fig. 2.

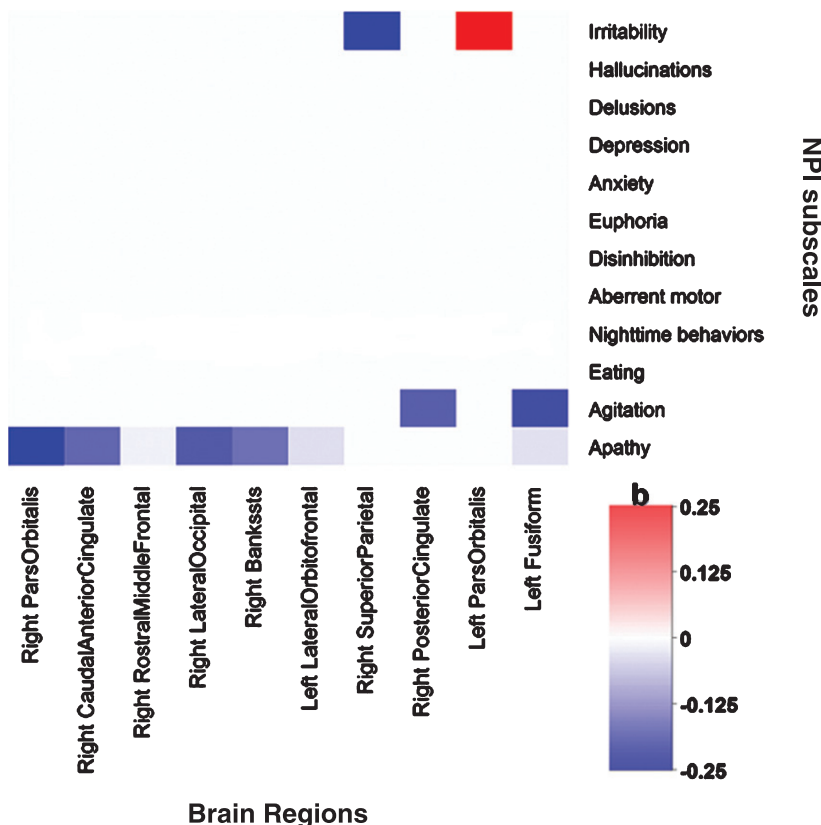


Fig. 1. Whole brain association between Freesurfer ROI volumes and neuropsychiatric symptoms, as measured by the Neuropsychiatric Inventory (NPI), in 57 ADNI subjects with mild AD. Cold colors represent negative associations. Hot colors represent the converse. The color scale represents standardized coefficients, which are equivalent to partial correlation coefficients. Only ROIs with significant positive or negative associations with the NPI or NPI subscales are shown in the figure. Right Pars Orbitals – Apathy (corrected $p=0.0131$), Right Superior Parietal – Irritability (corrected $p=0.0042$), and Left Pars Orbitalis – Irritability (corrected $p=0.0007$) associations survived after multiple comparison correction. “Bankssts”, banks of the superior temporal sulcus.

Table 2

All significant (at $p < 0.01$ level) Spearman partial correlations between apathy and regional volume in 57 ADNI AD CDR = 1 subjects controlling for age and MMSE

Region	Structure	r	p^*
Ventromedial PFC	L Medial OFC	-0.39	0.003
	R caudal ACC	-0.43	0.001
Posterior cingulate cortex, retrosplenial cortex and adjacent lateral cortex	R PCC	-0.36	0.008
	L fusiform	-0.44	0.001
	R inferior parietal	-0.36	0.007
	R lateral occipital	-0.36	0.006
Ventrolateral PFC	R lingual	-0.37	0.005
	R pars orbitalis	-0.54	<0.001
	R pars triangularis	-0.36	0.007
	L lateral OFC	-0.38	0.004

*All p -values were less than 0.05 for all 10 ROIs after multiple comparison correction. PFC, prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex.

DISCUSSION

The current study demonstrates the following: 1) Apathy, among neuropsychiatric symptoms in AD, demonstrates robust neuroanatomical associations (Fig. 1); 2) Decreased volume in four brain regions is associated with apathy (Fig. 1, Table 2); and 3) Each

of the regions displayed in Fig. 1 provides an independent contribution to apathy in these early AD patients, given that, while complete elimination of collinearity is not possible, our statistical method attempts to account for neuroanatomic and neuropsychiatric collinearity. In our previous study of patients with FTD and CBS using similar methods, we also found that areas in the medial and lateral ventral PFC and caudal anterior cingulate were independently associated with apathy [15]. The FTD and CBS patients have less posterior atrophy, and it might thus be expected that they would not show the associations between apathy and posterior atrophy that the AD patients show in the current study. The association between parietal atrophy and apathy detected in the current study was also detected in a previous study using voxel-based morphometry in a larger number of FTD patients [9]. It thus appears that in both AD and FTD/CBS, degeneration of the lateral and medial ventral PFC (including the anterior cingulate cortex), bank of the superior temporal sulcus, and the posterior cingulate and adjacent cortex, more on the right than the left, is associated with apathy. This conclusion does not preclude the association of other brain regions

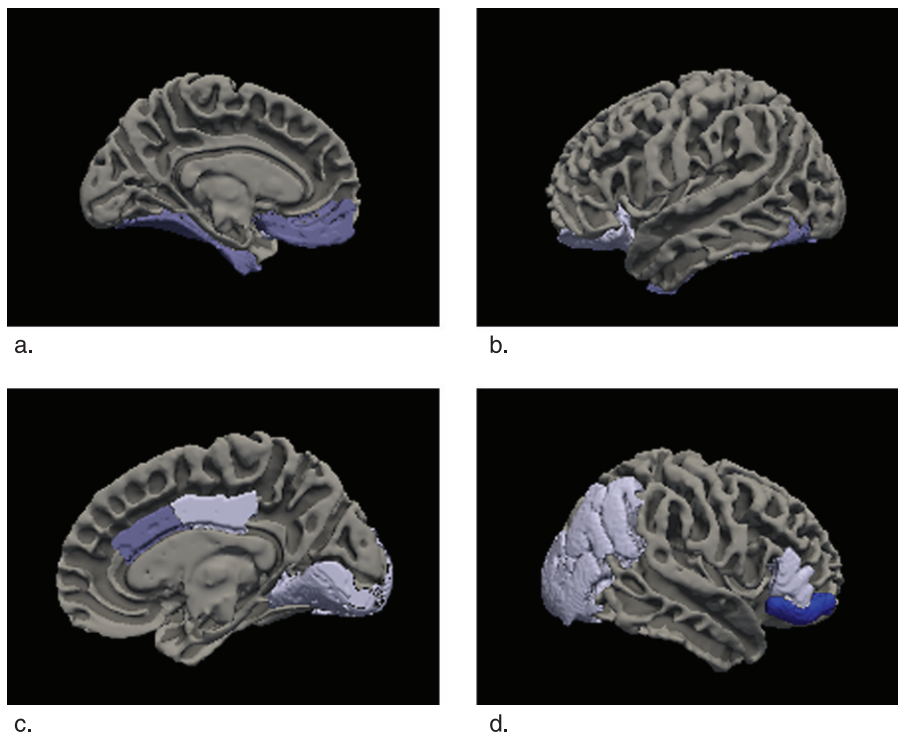


Fig. 2. A graphic representation of the correlation data presented in Table 2. Significant correlations between apathy and regional volume are represented on a model brain using Freesurfer. Left hemisphere is represented in a. and b., right hemisphere represented in c. and d. Similar to Fig. 1, cold colors represent stronger negative correlations.

with apathy. In Parkinson's and Huntington's diseases, apathy is associated with primarily subcortical degeneration [22–24]. Other authors have suggested that cortical and subcortical apathy syndromes differ in their clinical presentation and treatment based on the anatomic system involved [25], and that apathy itself is not a unitary construction whose components may have different anatomical associations [10].

The results of the current study mostly agree with the previous literature on AD and apathy. All of the brain regions found to be associated with apathy in the current study have been previously linked to apathy in AD [3]. However previous studies on AD have found brain regions associated with apathy that we did not detect in the current study, notably the insula and inferior temporal cortex. There are two possible, non-mutually exclusive, explanations. One is that these regions have been associated with apathy in AD, but do not contribute associations independent of the other regions, and so were not detected using our analytic approach. A second possibility is that they may have weaker associations with apathy and would be detected in a larger sample.

Do the brain regions found to be associated with apathy in the current study have anything in common? Three of the four regions (the ventromedial PFC, bank of the superior temporal sulcus, and posterior cingulate and adjacent cortex) correspond closely to a network identified in macaques, called the Medial Prefrontal Cortex (MPFC) Network [26, 27]. Research with anterograde and retrograde transmitters in macaques has identified several distinct networks involving the PFC [28–32]. One of these, the MPFC Network involves the agranular ventromedial PFC, parahippocampal cortex, posterior cingulate and adjacent cortex, and the rostral superior temporal gyrus and dorsal bank of the superior temporal sulcus [26]. This network has close reciprocal connections with subcortical structures including the amygdala, cochlear - pontine - spinal loops controlling rapid simple startle responses [33], and the peri-aqueductal gray [34]. This network is importantly involved in arousal and the response of animals and humans to threat and pain [35–37]. In the current study, and in previous studies from our laboratory in patients with FTD and CBS [9, 15], damage to the cortical components of this network is strongly associated with apathy.

The one brain region associated with apathy in the current study, as well as in our previous study of FTD and CBS patients using similar methods [15], that is not a component of the MPFC Network is

the ventral lateral PFC. This is a granular region in the Orbital Prefrontal Cortex (OPFC) Network. This network receives extensive sensory and limbic inputs through the uncinate fasciculus and input from areas involved in reward processing including the ventral tegmental area, nucleus accumbens, and ventral striatum [28, 29]. The OPFC Network plays important roles in olfactory and gustatory processing and reward and reinforcement learning in primates [38, 39], including assessing the rewarding or punishing nature of stimuli [32]. Lesions of the lateral ventral PFC in monkeys results in impaired reward learning, but preserved fear conditioning [40]. Neurodegeneration of the lateral ventral PFC is associated with the development of inappropriate repetitive behaviors [15]. The current and previous studies by our group [15] suggest that neurodegeneration of the ventrolateral prefrontal region of this network is associated with apathy, independent of the association between the MPFC Network and apathy. In the current study of AD patients and in our previous study of FTD and CBS patients, apathy is associated with neurodegeneration of the MPFC and OPFC Networks identified in non-human primates. As we discussed in a previous publication [15], and has been suggested by previous authors [10, 25], interference with several different brain functions (e.g., arousal/threat response, reward processing) and networks could lead to a similar clinical syndrome of apathy. Further research will determine if we can more finely distinguish clinical syndromes of apathy.

In summary, the current study, previous studies from our laboratory [9, 15], and the previous literature [3] suggest that similar brain areas are associated with apathy in AD and FTD, but that the specific involvement of those regions differs between the illnesses with the frontal regions associated with apathy more prominently involved in FTD and the more posterior regions with AD. The regions associated with apathy in the current study correspond well to networks identified in non-human primates to be involved in arousal/threat response and with reward processes. While multiple sites and scanners are used in ADNI, the organizers of ADNI have been very careful, indeed the model, about standardizing imaging protocols, data collection, and quality control across sites. The patients enrolled in ADNI, while well-characterized, had relatively mild apathy. It would be interesting to see if the same, or more, brain regions are associated with apathy in AD patients with more severe apathy. Given the

limitations of the study, replication in a larger sample is needed. Important questions that remain unanswered by the current study are: Can we clinically distinguish the syndromes of apathy associated with specific brain regions or networks (e.g., the MPFC and OPFC Networks) and are these syndromes differentially amenable to treatment?

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