Positron Emission Tomography Metabolic Correlates of Apathy in Alzheimer Disease

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Background: Apathy is the most common neuropsychiatric manifestation in Alzheimer disease (AD). Clinical, single-photon emission computed tomography, magnetic resonance imaging, and pathologic studies of apathy in AD have suggested an association with frontal dysfunction, most supportive of anterior cingulate abnormalities, but without a definitive localization.

Objective: To examine the association between apathy and cortical metabolic rate on positron emission tomography in AD.

Design: Forty-one subjects with probable AD underwent [18F] fluorodeoxyglucose positron emission tomography imaging and neuropsychiatric and cognitive assessments. Global subscale scores from the Scale for the Assessment of Negative Symptoms in Alzheimer Disease were used to designate the absence or presence of clinically meaningful apathy. Whole-brain voxel-based analyses were performed using statistical parametric mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, England), which yielded significance maps comparing the 2 groups.

Results: Twenty-seven (66%) subjects did not have apathy, whereas 14 (34%) had apathy. Statistical parametric mapping analysis revealed significant reduced activity in the bilateral anterior cingulate region extending inferiorly to the medial orbitofrontal region (P < .001) and the bilateral medial thalamus (P = .04) in subjects with apathy. The results of the statistical parametric mapping analysis remained the same after individually covarying for the effects of global cognitive impairment, depressed mood, and education.

Conclusions: Apathy in AD is associated with reduced metabolic activity in the bilateral anterior cingulate gyrus and medial orbitofrontal cortex and may be associated with reduced activity in the medial thalamus. These results reinforce the confluence of evidence from other investigational modalities in implicating medial frontal dysfunction and related neuronal circuits in the neurobiology of apathy in AD and other neuropsychiatric diseases.

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WHILE COGNITIVE IMPAIRMENT is the hallmark of Alzheimer disease (AD), neuropsychiatric symptoms occur frequently and are very distressing to caregivers. Apathy is the most common behavioral manifestation in AD, reported to occur in 29% to 72% of patients,1,2 and may co-occur with depressed mood or appear independently.3 Clinical studies, single-photon emission computed tomography studies, magnetic resonance imaging studies, and pathologic correlations of apathy in AD have shown an association with frontal dysfunction without a definitive localization. Neuropsychologic findings in patients with AD support a link between apathy and frontal dysfunction, with greater executive deficits seen in those with apathy.4,5

One magnetic resonance imaging study showed that AD patients with apathy had greater bilateral anterior cingulate and left supplementary motor cortex atrophy.6 Two pathologic studies of apathy in AD demonstrated increased neurofibrillary tangle counts in the anterior cingulate cortex.7,8

We examined the association between apathy and cortical metabolic rate on positron emission tomography (PET) in AD. We postulated that apathy in AD is associated with hypometabolism in the medial frontal regions.

METHODS

SUBJECTS

We enrolled 41 subjects who met criteria from the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association Work Group13 for probable AD. Subjects were recruited from the Veterans Affairs Greater Los Angeles Healthcare System and
University of California, Los Angeles, outpatient memory disorders clinics.

Subjects completed a comprehensive clinical evaluation, including a detailed history, physical examination, behavioral and cognitive assessments, serum laboratory evaluation, and structural imaging of the brain. Diagnosis of probable AD was made by an experienced subspecialty physician and was confirmed after review of the clinical information by a senior clinical research investigator (D.L.S.). Subjects did not receive any psychotropic medications, except for 50 mg or less of trazodone daily as needed for sleep for 3 weeks prior to clinical and PET assessments. None of the subjects were taking cholinesterase inhibitors or memantine.

The study was approved by the institutional review boards at the Veterans Affairs Greater Los Angeles Healthcare System and the University of California, Los Angeles. Written informed consent was obtained from subjects or legally authorized representatives after study procedures and risks were fully explained in accordance with institutional review board guidelines.

CLINICAL DATA

The Scale for the Assessment of Negative Symptoms in Alzheimer Disease (SANS-AD) was administered to all subjects. The SANS-AD was developed to assess the following symptoms specifically in AD: affective blunting (6 subscale items and a global rating), avolition/apathy (3 subscale items and a global rating), and social/emotional withdrawal (4 subscale items and a global rating). Scores range from 0 to 6 for each item (0 = not at all, 1 = questionable, 2 = mild, 3 = moderate, 4 = marked, and 5 = severe).

To focus on the specific phenomenon of apathy, 2 groups were designated based on absence or presence of clinically meaningful apathy derived from SANS-AD global subscale scores. Subjects with a score of 2 or more in either the avolition/apathy or social/emotional withdrawal global ratings were designated as having apathy, while subjects with a score of less than 2 in both were designated as not having apathy. The affective blunting subscale score was not considered in the assignment, as these symptoms are outside the apathy construct used in this study.

The Mini-Mental State Examination (MMSE) was administered to all subjects to measure the severity of global cognitive impairment. The Neurobehavioral Rating Scale (NRS), a 28-item scale covering a wide range of behavioral and cognitive symptoms, was administered to all subjects. The NRS depressed mood item was used in our study; scores range from 0 to 6 (0 = not present at all, 6 = extremely severe dysphoria). This NRS item assesses the severity of depressed mood, which includes sadness, hopelessness, and dysphoria (as distinct from apathy or disinterest) and has been shown to be reliable in patients with dementia. The NRS delusions item was also used. Subjects underwent clinical assessment, including SANS-AD, MMSE, and NRS, immediately prior to PET imaging.

IMAGING DATA

The Siemens 933/31 tomographic scanner (Siemens Medical Solutions, Hoffman Estates, Illinois) was used to perform PET imaging of cerebral metabolic activity. The scanner has an inplane spatial resolution (full width at half maximum) of approximately 5 mm and an axial slice thickness of approximately 3 mm. Fluorodeoxyglucose was synthesized at the Veterans Affairs Greater Los Angeles Healthcare System PET imaging facility in accordance with the technique of Hamacher et al. Subjects received 5 to 10 mCi (1 Ci equals 3.7 × 10¹⁰ Bq) of [¹⁸F] fluorodeoxyglucose intravenously. During the 40-minute [¹⁸F] fluorodeoxyglucose uptake phase, subjects were at rest with eyes open and ears uncovered in a dimly lit room. After the uptake phase, subjects were positioned in the scanner with the imaging plane parallel to the canthomeatal plane. A thin restraining tape was placed across subjects’ foreheads to maintain head position. Metabolic data were then acquired during a period of approximately 40 minutes.

IMAGE AND DATA ANALYSIS

Whole-brain voxel-based analyses were performed using statistical parametric mapping software (SPM2; Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk/spm) in MATLAB 6.5 software (Mathworks, Natick, Massachusetts). For each subject, PET images were transformed to a standard template in Montreal Neurological Institute Talairach and Tourjouxs atlas space. Activity values were scaled proportionately and images were smoothed with a 6-mm gaussian filter.
Two sample statistical parametric mapping analyses yielded significance maps comparing relative regional activity in subjects with apathy and subjects without apathy. Stereotactic coordinates of peak voxel differences within clusters were determined in reference to the Talairach and Tournoux atlas. Clusters with \( P < .05 \) (uncorrected) were considered statistically significant.

Demographic variables, including age, cognitive symptom duration, education, sex, MMSE score, and NRS depressed mood item score, were screened for differences between subjects with and without apathy using \( t \) tests for continuous variables and \( \chi^2 \) test for sex. Demographic variables that were significantly different were individually included as predictor variables (covariates) in a 2-sample statistical parametric mapping analysis using a linear regression model to examine the independent effect of apathy on relative regional activity. Because of potential neurobiological interaction between apathy and depressed mood, the NRS depressed mood item score and the NRS delusions item score were also included as covariates, despite not being significantly different between the 2 groups.

**RESULTS**

Among enrolled subjects, 27 (66%) did not have apathy, while 14 (34%) had apathy. Table 1 presents the demographics and clinical scores for both groups. Mean MMSE score and years of education were lower in subjects with apathy compared with subjects without apathy (MMSE, \( t = 2.24, P = .03 \); education, \( t = 2.05, P = .048 \)).

Statistical parametric mapping analysis revealed significant reduced activity in the bilateral anterior cingulate region (Brodmann area 24) extending inferiorly to the medial orbitofrontal region (Brodmann area 11/12; cluster level, \( P < .001 \)) as well as in the bilateral medial thalamus (\( P = .04 \)) in subjects with apathy compared with subjects without (Table 2, Figure 1). With statistical parametric mapping correction for multiple clusters, the
findings in the anterior cingulate and the medial orbitofrontal cluster remained significant ($P = .002$), but the findings in the medial thalamus cluster were no longer significant ($P = .50$). While the peak voxel relationship was in the right hemisphere for each of these clusters, the clusters were bilateral and generally symmetric. In the statistical parametric mapping analysis to identify voxels with significant increased activity in subjects with apathy compared with those without apathy, there was increased activity in the left angular gyrus (Brodmann area 39; cluster level, $P = .01$) in subjects with apathy.

The results of the statistical parametric mapping analysis remained the same after covarying for the effect of MMSE score on activity (Table 3, Figure 2). The results of the statistical parametric mapping analysis also remained the same after individually covarying for the effects of age, education, cognitive symptom duration, NRS depressed mood item score, and NRS delusions item score on activity, except that the association between apathy and activity in the thalamus was no longer significant ($P = .55$) after covarying for age.

### Table 3. Location, Cluster Level, and Peak Voxel Coordinates of Hypometabolism in AD Subjects With Apathy, With MMSE as a Covariate

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Level</th>
<th>Voxel Level</th>
<th>Peak Voxel Talairach Coordinate</th>
<th>No. of Voxels</th>
<th>$P$ Value</th>
<th>$t$ Test $P$ Value</th>
<th>$t$ Test Score</th>
<th>$X$</th>
<th>$Y$</th>
<th>$Z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral anterior cingulate and medial orbitofrontal cortex</td>
<td>6772</td>
<td>&lt;.001</td>
<td>4.62 &lt;.001</td>
<td>6772</td>
<td>&lt;.001</td>
<td>4.62 &lt;.001</td>
<td>10 44 -26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral thalamus</td>
<td>922</td>
<td>.02</td>
<td>3.78 &lt;.001</td>
<td>922</td>
<td>.02</td>
<td>3.78 &lt;.001</td>
<td>4 -16 8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination.

Figure 2. A, Statistical parametric map (glass-brain view) for the 2-sample $t$ test for proportionally scaled [18F] fluorodeoxyglucose positron emission tomographic activity comparing Alzheimer disease subjects with apathy to Alzheimer disease subjects without apathy after covarying for Mini-Mental State Examination score. Voxels shown are those for which the apathy group has significantly lower activity than the without-apathy group ($P < .01$, uncorrected). The red v's show crosshair position in B. B, Significant voxels are also displayed on a standard magnetic resonance image with a view of the anterior cingulate gyrus and medial orbitofrontal cortex (the thalamus is not seen on this image). The scale shows the value of the $t$ statistic.

### COMMENT

Apathy in AD is associated with reduced metabolic activity in the bilateral anterior cingulate gyrus, medial orbitofrontal cortex, and medial thalamus. The relationship with medial thalamus metabolic activity was less robust and no longer significant when corrected for multiple clusters and age. The frontal subcortical circuit implicated in apathy involves the anterior cingulate, nucleus accumbens, globus pallidus, substantia nigra, midline thalamic nuclei, and medial dorsal nucleus of the thalamus; reduced neuronal activity in several of these regions was observed in our study in subjects with AD.

The medial orbitofrontal region has reciprocal connections with the anterior cingulate and medial dorsal nucleus of the thalamus, which is reinforced by the results of the current study and may be important in assigning internal relevance to external stimuli that a person encounters. The nucleus basalis of Meynert in the basal forebrain has cho-
linergic projections to the frontal limbic cortical regions, medial dorsal nucleus of the thalamus, and midline thalamus. Dysfunction of neural systems in these projection fields (perhaps related to reduced cholinergic tone) may be related to the development of apathy in AD. In fact, donepezil, a cholinesterase inhibitor, has been shown to reduce neuropsychiatric symptoms in AD, particularly apathy and hallucinations.

Positron emission tomographic imaging has not been used previously to address apathy in AD. The results of the current study reinforce the confluence of evidence from other investigational modalities in implicating medial frontal dysfunction in the neurobiology of apathy in AD and other neuropsychiatric diseases and suggest that the specific neurophysiologic contributions to apathy occur across neuropsychiatric disorders.

In the current study, medial frontal dysfunction in AD subjects with apathy was independent of severity of global cognitive impairment, age, cognitive symptom duration, and education, underscoring the clinical and physiologic importance of behavioral symptoms in AD. Apathy has also been shown to be phenomenologically distinct from depression. The current study extends this distinction to regional brain function and suggests that neurobiologic correlates of apathy in AD are independent of depressed mood and delusional thoughts. This finding contributes to a better understanding of neuropsychiatric syndromes in AD.

The limitations of this study are as follows: first, the construct of apathy is variable and research findings will depend on the specific assessment instrument used. The results of the current study apply to the apathy construct used here. Second, the extent of apathy varies in patients with AD. However, in the current study, a dichotomous analysis was performed (comparing groups with and without apathy) because of the skewed distribution. Finally, many neuropsychiatric symptoms are seen in AD. However, only depressed mood and delusional thoughts were covaried for in the current study to assess the apathy relationship independent of dysphoria, which may co-occur in some patients.

In conclusion, apathy in AD—independent of severity of global cognitive impairment, age, cognitive symptom duration, education, and depressed mood—is associated with reduced metabolic activity in the bilateral anterior cingulate gyrus and medial orbitofrontal cortex and may be associated with reduced activity in the medial thalamus. These results suggest a specific neurobiologic basis for the expression of apathy in AD. This finding also supports the validity of a medial frontal subcortical circuit related to apathy and helps define the role of distinct neural functional systems associated with particular clinical phenotypes across neuropsychiatric disorders.

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Author Contributions: Dr Sultzer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Marshall, Monserratt, and Mandelkern.

Critical revision of the manuscript for important intellectual content: Marshall, Harwood, Mandelkern, Cummings, and Sultzer.

Statistical analysis: Marshall, Monserratt, Mandelkern, and Sultzer.

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REFERENCES

New Initiatives: Clinical Trials and Videos

We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. Open-label studies will also receive our special attention. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient’s neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.