18F-Fluorodeoxyglucose Positron Emission Tomography Cortical Metabolic Activity Associated with Distinct Agitation Behaviors in Alzheimer Disease

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Objective: This study aimed to investigate the neurobiologic correlates of two distinct clusters of agitation symptoms to identify the unique biologic substrates underlying agitated behaviors. Methods: Eighty-eight outpatients with mild to moderate Alzheimer disease (AD) were recruited from the VA Greater Los Angeles Healthcare System Geropsychiatry Outpatient Program. A cross-sectional investigation was conducted of the relationship between cerebral glucose metabolism measured via 18F-fluorodeoxyglucose positron emission tomography and agitated symptoms from the Neuropsychiatric Inventory (NPI) in patients with AD. Two empirically derived clusters of agitation symptoms were investigated: an Agitation factor comprising agitation/aggression and irritability/lability items of the NPI, and a Behavioral Dyscontrol factor comprising elation/euphoria, disinhibition, aberrant motor behavior, sleep, and appetite items of the NPI. Mean cerebral metabolism for patients who scored positively on each of the two factors was compared with mean cerebral metabolism for those who did not. Results: Patients with AD who scored positively on the Agitation factor showed reduced glucose metabolism of the right temporal, right frontal, and bilateral cingulate cortex. In contrast, the Behavioral Dyscontrol factor did not show specific neurobiologic correlates. Conclusion: Symptoms encompassed within the Agitation factor have distinct neurobiologic underpinnings. The precipitants, course, and outcomes related to these symptoms may be unique from other neuropsychiatric symptoms characteristic of AD. Special attention to treatment of agitated behaviors involving anger, aggressiveness, hostility, and irritability/emotional lability is warranted, because they appear to reflect a clinically relevant symptom cluster with unique underlying neurobiologic correlates. (Am J Geriatr Psychiatry 2017; □□□□–□□□□)

Key Words: Alzheimer disease, agitation, FDG-PET, cerebral metabolism
INTRODUCTION

Agitated behaviors in Alzheimer disease (AD) are very common, affecting approximately 20% of outpatients and 40%–60% of care-home residents.\(^1\) Agitation, a subset of agitated behavior that involves overt threats, gestures, or violence, occurs in approximately 10%–25% of patients with AD.\(^1\)\(^,\)\(^3\) Agitated behaviors are most common in moderate to severe dementia and persist throughout the course of AD, contributing to increased distress and disability, caregiver burden,\(^4\) emergency department visits, acute hospitalizations, long-term institutionalization, and mortality.\(^5\)

Despite the frequency with which agitated behaviors occur in AD, agitation is a poorly understood syndrome. Agitation refers to a wide range of behaviors encompassing both an internal psychological state and observable behaviors\(^6\) that occur in the context of fluctuating environmental stimuli.\(^3\) These factors contribute to the heterogeneity of the syndrome and add to the challenge of characterizing its phenomenology and improving diagnosis and treatment. Consequently, the term “agitation” is applied broadly and inconsistently across clinical settings and research studies.\(^3\)\(^,\)\(^6\)\(^,\)\(^7\) The definition of agitation is often constrained by the specific instrument used to measure this symptom. Thus, inferences made from research are often study specific and related to the behaviors specifically captured by the study’s instrument of choice.

Agitation may result from a combination of social, psychological, and biologic factors, all of which interact to affect the presentation of the syndrome. Studies using various imaging modalities, including single positron emission tomography,\(^6\) magnetic resonance imaging,\(^9\)\^-\(^12\) \(^1\)\(^8\)F-fluorodeoxyglucose positron emission tomography (FDG-PET),\(^13\) and resting state functional connectivity,\(^14\) cite a wide range of brain regions and neural systems associated with agitated/aggressive behaviors including temporal, frontal, parietal, anterior cingulate, insular, and hippocampal regions.\(^8\)\^-\(^9\)\(^,\)\(^13\)\^-\(^15\) A few studies also investigated neurochemical or focal neuropathology relationships with agitation through brain autopsy specimens\(^16\)\^-\(^19\) or cerebrospinal fluid markers\(^20\) and report that agitated behaviors are associated with decreased cholinergic markers in frontal and temporal cortices, decreased serotonin, and higher levels of tau/phosphorylated tau or neurofibrillary tangles in the frontal cortex (for review, see Rosenberg et al.\(^7\)). The studies have used different instruments and conceptual frameworks to define agitation, often using one single item as the measure of interest. This limits the generalizability of findings and compromises the ability to define the neural correlates of specific agitated behaviors. To our knowledge, a study investigating the neurobiologic correlates of distinct subtypes of agitated behaviors has not been conducted.

Given heterogeneity in methodologic approaches to defining agitation, translating findings to clinical settings where targeted treatment interventions can be implemented is difficult. Currently, pharmacologic treatments for agitated behaviors in patients with AD remain largely ineffective and carry a large side-effect profile,\(^21\) although exceptions have been reported\(^22\) (also see the review by Seitz et al.\(^23\)). To promote treatments targeted toward specific agitated behaviors, it is necessary to elucidate the biologically based phenotypes of agitation.

The purpose of this study was to determine whether specific behavioral subgroups of agitation are related to distinct patterns of cortical dysfunction measured via FDG-PET. Our goal was to identify patterns of cortical metabolic dysfunction associated with two empirically derived symptom clusters of agitated behaviors.\(^24\) We hypothesized that each of the two symptom clusters would be associated with unique patterns of cortical dysfunction in patients with AD, reflecting distinct biologically based phenotypes of agitated behaviors. Exploratory analyses were conducted to investigate neurobiologic correlates of individual agitated behaviors to investigate whether each item captures distinct aspects of agitation.

METHODS

Participants

Participants (N = 88) were recruited from the VA Greater Los Angeles Healthcare System Geropsychiatry Outpatient Program. Patients were excluded if they had a history of head trauma with loss of consciousness, a systemic illness or other neurologic condition accounting for cognitive impairment, a history of psychotic disorder unrelated to dementia, or a psychoactive substance use disorder. All patients underwent clinical evaluations including a complete history, psychiatric assessment, neurologic examination, cognitive assessment,
and structural neuroimaging with computed tomography or magnetic resonance imaging. The final diagnosis of probable AD was confirmed by a board-certified geriatric psychiatrist (D.L.S.) using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorder Association criteria, which are consistent with the National Institute on Aging-Alzheimer’s Association criteria. Patients taking psychotropic medications other than selective serotonin reuptake inhibitors (21/88 taking selective serotonin reuptake inhibitor) were excluded. Those on a stable dose of cholinesterase inhibitor were included (32/88: 29 taking donepezil, 3 taking galantamine). Because of study recruitment methods (i.e., new patients presenting to clinics for the first time), most participants in the study were not taking a cholinesterase inhibitor medication.

The institutional review board reviewed and approved the study. Consent to participate was documented according to institutional review board guidelines.

Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) measures the severity and frequency of 12 different psychiatric and behavioral symptoms or domains (anxiety, depression/dysphoria, elation, apathy/indifference, disinhibition, aberrant motor behavior, sleep disturbance, appetite/eating disorder, delusions, hallucinations, agitation/aggression, irritability/lability). Ratings are informant-based.

For the purposes of the current study we investigated two different dimensions of agitation revealed by a large-scale study that implemented principal component analysis to NPI ratings of patients with AD. The first component, a two-item factor of Agitation, comprises the irritability/lability and agitation/aggression items. The latter item includes predominantly oppositional and aggressive behaviors. The second component, a Behavioral Dyscontrol factor, consists of elation/euphoria, disinhibition, aberrant motor behavior, sleep, and appetite items. To calculate each individual’s NPI factor scores, we summed the frequency × severity (fxs) score (an overall index of symptom severity) for the individual items comprising each factor. Participants were classified as scoring positively on each symptom cluster if they scored an fxs greater than zero. Given the extensive overlap between symptoms of delusions and agitation, we also included the NPI delusion item’s fxs score as a covariate to isolate regional metabolic activity uniquely related to agitation.

FDG-PET Image Acquisition

Throughout the course of the study, three different tomographs with similar imaging characteristics were used to scan patients: 46 patients were scanned with a 953/31 tomographic scanner (Siemens, Siemens Medical Solutions, Hoffman Estates, IL), 23 with an Advance PET-CT (GE, General Electric, Fairfield, CT), and 19 with a Gemini TF PET-CT (Philips, Amsterdam, North Holland). The in-plane resolution was approximately 4 mm at full-width half maximum for all three scanners; the axial slice thickness varied across scanners and ranged from 2 to 4 mm. FDG was synthesized at the VA Greater Los Angeles Healthcare System PET Imaging facility. Participants received 5–10 mCi of FDG intravenously. After a 40-minute uptake phase, participants were placed in the PET scanner with the imaging plane parallel to the canthomeatal plane. Metabolic data were acquired for 30–40 minutes.

PET Image Analysis

PET data were analyzed in Matlab R2012a (MathWorks, Natick, MA) using SPM2 (Wellcome Trust Centre for Neuroimaging, London, UK). PET images were normalized to The Montreal Neurological Institute space using a trilinear interpolation, resampled to 2 × 2 × 2-mm voxels, and smoothed with a 6-mm full-width half maximum smoothing kernel.

We conducted Student two-sample t tests in SPM to investigate differences in cerebral metabolism between individuals who scored > 0 and those who scored zero on each of the factors. Images were normalized to the global mean using proportional scaling, and a threshold mask of 0.8 was set to remove signal from structures outside of gray matter. Result maps were thresholded at p < 0.01 at the voxel level. Findings were considered significant at the cluster level at p < 0.05 corrected using the family-wise error procedure.

In separate analyses we covaried for factors of no interest. The design specification and statistical procedures used were identical to that described in the previous paragraph. To control for global cognition, we covaried for scores on the Mini-Mental State Exam (MMSE).
In a second set of analyses, we covaried for each individual’s fxS score from the delusion item of the NPI to further isolate regions associated only with agitation. Mean signal within significant clusters was extracted for each individual using the volume-of-interest tool in SPM2. We conducted follow-up Spearman’s correlation analyses to investigate the strength of the relationship between volume-of-interest metabolic data and fxS values.

Additionally, as an exploratory analysis to further investigate the neural substrates underlying specific aspects of agitation, we submitted four individual NPI items (agitation, irritability, aberrant motor behaviors, and disinhibition) that comprise a four-item Agitation factor to additional t tests to explore whether unique neural substrates underlie each of these items or whether they are capturing similar constructs.

RESULTS

Eighty-eight patients with probable AD were included in the study. Participant characteristics and NPI score frequencies within the sample are presented in Table 1. Of the 88 patients, 50 were assigned a score > 0 on the Agitation factor and 38 received a score of zero. Similarly, 50 were assigned a score > 0 on the Dyscontrol factor and 38 received a score of zero. Thirty-four of 88 participants scored > 0 on both the Agitation factor and Dyscontrol factor (38%).

Patients scoring > 0 on the Agitation factor versus those who scored zero were similar on age, education, MMSE score, illness duration, and medication use (all p ≥ 0.10). There was a significantly smaller proportion of women in the >0 Agitation group (χ²[1, N = 88] = 6.5, p = 0.01; Fisher’s exact test, p = 0.01). Patients with Behavioral Dyscontrol > 0 did not differ from patients who scored zero on age, education, illness duration, MMSE score, gender breakdown, and medication use (all p ≥ 0.07).

Agitation Factor t Test: SPM Analysis

Results of the SPM analysis revealed significantly lower metabolic activity for patients who scored > 0 on the Agitation factor than for patients who did not in three significant clusters (all p ≤ 0.003). The largest cluster spanned the middle and superior gyri of the right temporal lobe. Lower metabolic activity was also found in the middle and posterior bilateral cingulate and right frontal lobe (lateral prefrontal and frontal pole). Although associations were observed with other brain regions (e.g., parahippocampal gyrus), these did not reach the statistical threshold of the analysis.

Results did not change when MMSE was entered into the analysis as a covariate. Given a significant difference in gender breakdown between individuals who scored > 0 on the Agitation factor and those who did not, data were reanalyzed covarying for gender, and findings did not change. Additionally, the pattern of findings remained when data were reanalyzed with only individuals not taking a cholinesterase inhibitor medication (N = 56). When the NPI delusion item fxS score was included as a covariate in the model, the cluster in the right frontal lobe was no longer significant; however, metabolism in the middle and posterior bilateral cingulate and right temporal lobe remained significantly different between the groups, with the >0 group showing lower metabolic rates in these regions.

Results of the Agitation factor analyses are presented in Table 2 and Figure 1.

Behavioral Dyscontrol Factor t Test: SPM Analysis

There were no significant differences in metabolic activity for individuals who were classified as having Behavioral Dyscontrol compared with those who were not. Rerunning the SPM analysis excluding sleep and appetite from the Behavioral Dyscontrol factor also did not yield any significant clusters.

Correlations between Regional Cortical Metabolism and Agitation Factor Scores

To demonstrate effect sizes and possible differential associations on subitems, we ran Spearman correlations between the Agitation factor’s fxS score, each individual item’s fxS score (agitation, irritability) of the Agitation factor, and regional cortical metabolism for the three significant clusters identified by the two-item Agitation factor t test in SPM2. The Agitation factor’s fxS score, the agitation item’s fxS score, and the irritability item’s fxS score were each significantly correlated (all p < 0.01) with cortical metabolism in all three volumes-of-interest: right temporal (r = −0.35, −0.33, and −0.29, respectively), right
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (Range) for Whole Sample</th>
<th>SD</th>
<th>Mean (SD) for Agitation Factor &gt; 0</th>
<th>Mean (SD) for Agitation Factor = 0</th>
<th>p Value</th>
<th>Mean (SD) for Dyscontrol Factor &gt; 0</th>
<th>Mean (SD) for Dyscontrol Factor = 0</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Age</td>
<td>78.4 (52–97)</td>
<td>8</td>
<td>78.0 (8.0)</td>
<td>79.0 (8.1)</td>
<td>0.55</td>
<td>79.1 (7.6)</td>
<td>77.6 (8.5)</td>
<td>0.37</td>
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<tr>
<td>Gender, % female</td>
<td>19</td>
<td>—</td>
<td>10</td>
<td>32</td>
<td>0.01†</td>
<td>16</td>
<td>24</td>
<td>0.26</td>
</tr>
<tr>
<td>Education (N = 86)</td>
<td>13.9 (6–24)</td>
<td>3.6</td>
<td>13.9 (3.2)</td>
<td>13.8 (4.1)</td>
<td>0.91</td>
<td>13.3 (3.5)</td>
<td>14.7 (3.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>MMSE</td>
<td>19.3 (3–30)</td>
<td>5.6</td>
<td>18.8 (5.8)</td>
<td>20.1 (5.3)</td>
<td>0.50</td>
<td>18.5 (5.9)</td>
<td>20.4 (5.2)</td>
<td>0.12</td>
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<tr>
<td>Illness duration, yr (N = 83)</td>
<td>3.2 (0–10)</td>
<td>2.4</td>
<td>3.6 (2.4)</td>
<td>2.7 (2.3)</td>
<td>0.10</td>
<td>3.1 (2.1)</td>
<td>3.4 (2.7)</td>
<td>0.55</td>
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<tr>
<td>Cholinesterase inhibitor, % taking</td>
<td>36</td>
<td>—</td>
<td>23</td>
<td>14</td>
<td>0.50</td>
<td>20</td>
<td>16</td>
<td>0.94</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor, % taking</td>
<td>24</td>
<td>—</td>
<td>16</td>
<td>8</td>
<td>0.33</td>
<td>15</td>
<td>10</td>
<td>0.62</td>
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<table>
<thead>
<tr>
<th>NPI Factors/Items</th>
<th>No. &gt; 0 (%)</th>
<th>Mean fxs in Whole Sample (Range)</th>
<th>Mean fxs in Those &gt; 0 on Factor/Item (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI agitation factor (2 items)</td>
<td>50 (57)</td>
<td>3.4 (0–24)</td>
<td>5.9 (1–24)</td>
</tr>
<tr>
<td>NPI agitation item</td>
<td>41 (47)</td>
<td>1.8 (0–12)</td>
<td>3.8 (1–12)</td>
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<tr>
<td>NPI irritability item</td>
<td>34 (39)</td>
<td>1.6 (0–12)</td>
<td>4.1 (1–12)</td>
</tr>
<tr>
<td>NPI Dyscontrol factor (5 items)</td>
<td>50 (57)</td>
<td>5.3 (0–43)</td>
<td>9.3 (1–43)</td>
</tr>
<tr>
<td>NPI elation/euphoria item</td>
<td>5 (6)</td>
<td>0.1 (0–4)</td>
<td>2.2 (1–4)</td>
</tr>
<tr>
<td>NPI disinhibition item</td>
<td>23 (26)</td>
<td>1.2 (0–12)</td>
<td>4.6 (1–12)</td>
</tr>
<tr>
<td>NPI elation/euphoria item</td>
<td>18 (20)</td>
<td>1.1 (0–12)</td>
<td>5.2 (1–12)</td>
</tr>
<tr>
<td>NPI sleep item</td>
<td>16 (18)</td>
<td>1.0 (0–12)</td>
<td>5.6 (2–12)</td>
</tr>
<tr>
<td>NPI appetite item</td>
<td>27 (31)</td>
<td>1.9 (0–12)</td>
<td>6.2 (1–12)</td>
</tr>
<tr>
<td>Overlap of factors, %</td>
<td>38</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NPI delusions item</td>
<td>28 (32)</td>
<td>1.4 (0–12)</td>
<td>4.4 (1–12)</td>
</tr>
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</table>

Notes: p Values reflect results of (1) independent samples t tests examining differences between groups on age (df = 86), education (df = 84), MMSE (df = 86), and illness duration (df = 81) and (2) χ² Fisher’s exact test [1, N = 88] examining group differences in gender breakdown, cholinesterase inhibitor use, and selective serotonin reuptake inhibitor use. MMSE: Mini-Mental State Exam; SD: standard deviation; cells with dashes: no data available.

†Significant difference between individuals with a score > 0 on the Agitation factor and those with a score of zero (p < 0.05).
frontal \((r_s = −0.36, −0.29, \text{ and } −0.34, \text{ respectively})\), and cingulate \((r_s = −0.35, −0.31, \text{ and } −0.31, \text{ respectively})\). Thus, overall, there were medium-sized associations between clinical symptoms and metabolic rate.

**Post-Hoc Exploratory Analyses**

To further understand the pathophysiology of specific agitated behaviors, we investigated the cortical metabolic correlates of scores on the agitation, irritability, aberrant motor behaviors, and disinhibition items. Results are presented in Table 3 and Figure 2. In comparing those who scored > 0 with those who did not on the agitation and irritability items, clusters of regions arose that overlap with those from analyses of the Agitation factor. Specifically, greater hypometabolism in the bilateral cingulate was found for the agitation item, greater hypometabolism in the right frontal lobe was found for the irritability item, and greater hypometabolism in the right temporal lobe was found for both items. Regional relationships unique to each individual item were also found. Lower metabolic activity in the occipital lobe was found in individuals who scored > 0 on the agitation single item. Additionally, lower metabolic activity in the right insula and right precentral and postcentral gyri were found in those scoring > 0 on the irritability single item. The SPM analysis of the two Behavioral Dyscontrol items did not reveal any differences between those with and without each symptom.

**DISCUSSION**

This study explored differences in patterns of cerebral metabolism in AD patients with and without agitation across two subtypes of agitated behaviors. Findings suggest that specific neurobiologic underpinnings mediate the expression of distinct agitated behaviors. The Agitation factor, comprising symptoms of aggressiveness/violence, anger, uncooperativeness, irritability/crankiness, emotional lability, and impatience, were associated with hypometabolism of core AD pathology including the bilateral posterior cingulate, right middle temporal gyrus, and right frontal cortex. Moreover, this was independent of degree of cognitive impairment. In contrast to the Agitation factor, there were no differences in cerebral metabolism between individuals who scored positively on the Behavioral Dyscontrol factor (elation/euphoria, disinhibition, aberrant motor behavior, sleep, and appetite items) and those who did not.

To our knowledge, only one previous study investigated associations between agitation and cerebral glucose metabolism in patients with AD. Similar to our findings, the authors reported correlations between an agitation/disinhibition factor score derived from the Neurobehavioral Rating Scale and hypometabolism in temporal and frontal lobes. Studies that have investigated the relationship between specific agitated behaviors and brain atrophy report associations in the...
frontal cortex, cingulate cortex, insula, amygdala, and hippocampus. These results are largely consistent with the present findings. Collectively, findings from the present study and previous studies implicate agitation with structural and functional dysfunction of regions associated with core AD pathology, suggesting the manifestation of agitated behaviors in AD is associated with the pathologic progression of the disease. In particular, the bilateral posterior cingulate and middle temporal gyrus, associated with the Agitation factor, have important neural connections with the amygdala, a region known for its association with aggressiveness and vulnerable to early effects of AD. Thus, the association between hypometabolism in these regions and agitation/aggression and irritability may reflect disease-related dysfunction of the amygdala.

Consistent with past studies, the insula was also uniquely associated with irritability in this study and may capture specific aspects of the item related to emotional dysregulation (e.g., “does the patient rapidly change moods...?”; “Is the patient cranky and irritable?”). These findings suggest that symptoms of agitation, and particularly irritability, in AD may be partly because of the ineffective regulation of emotions. Consistent with this conclusion, in their review of agitation studies, Rosenberg et al. suggested two separate neurobiologic mechanisms of agitation in AD, one because of deficits in affective regulation and one because of deficits in executive functioning. To the extent that patients diverge on these two symptom profiles of agitation, it would be useful for future studies to examine unique diagnostic and treatment implications of each.

The results of this study point to generally right-dominated associations between cortical metabolism and agitation and irritability items of the NPI. Some studies investigating agitation in AD also report similar associations between right-sided cortical dysfunction and agitation. For example, a study by Hsu et al. found a relationship between posterior atrophy (based on the posterior cingulate, parieto-occipital sulcus, sulci of the parietal lobes, and precuneus) and agitation only in the right hemisphere. Additionally, studies have reported aggressive behavior to have stronger associations with right hemisphere dysfunction than left hemisphere dysfunction in patients with schizophrenia and frontotemporal dementia, agitation has been associated with patients who have had

FIGURE 1. [a] SPM results of the t test comparing mean metabolic activity for individuals with a score > 0 on the Agitation factor with mean metabolic activity for those with a score of zero displayed on average brains in SPM2. [b] SPM results of the t test comparing mean metabolic activity for individuals with a score > 0 on the Agitation factor with mean metabolic activity for those with a score of 0 with NPI delusion item’s fxs score as a covariate, displayed on average brains in SPM2. Images show all brain regions at p < 0.01 uncorrected. Only clusters as described in Table 2 were significant at the corrected cluster level, and they are outlined and labeled with “C” and the corresponding cluster number from Table 2.
right hemisphere infarctions, and irritability has been associated with hypoperfusion in the right frontal gyrus in patients with dementia with Lewy bodies. Thus, several lines of evidence point to right hemisphere dysfunction as involved in the expression of agitated and aggressive behaviors across several different clinical disorders.

Although initial analyses of the Agitation factor revealed frontal lobe involvement, controlling for delusions removed this association, suggesting that frontal involvement in our sample of patients scoring positively on the Agitation factor may reflect the presence of delusions, which commonly co-occur in AD patients with agitation. Previous studies have found right frontal cortex dysfunction to be associated with delusional thoughts in AD, and the findings collectively suggest a partial dissociation between neural systems that contribute to delusions and those involved in agitated behaviors. The divergent neural contributions may at least partly explain the different clinical responses of agitation or psychosis in AD that are seen in trials of antipsychotic treatments and potentially aligns with findings regarding the modest to low efficacy of atypical antipsychotics in the treatment of agitation. Taken together, these findings suggest that optimal treatment of agitated behaviors and delusions may require different approaches.

Unlike the Agitation factor, the Behavioral Dyscontrol factor did not relate to metabolic dysfunction in our sample of patients with AD, suggesting that this cluster of symptoms does not represent a biologically based syndrome that is reflected in regional cortical hypometabolism. One potential reason for lack of differences may lie in the heterogeneity of the items comprising this factor, including repetitive and/or odd behaviors, sleep difficulty, changes to eating and/or appetite, weight loss or weight gain, and elation/euphoria. Given the heterogeneity of the factor, detecting focal regions of cortical hypometabolism may not be possible. Another consideration for lack of differences is the fact that individuals who did not score positively on the Behavioral Dyscontrol factor are not necessarily symptom free. For example, 32% of AD patients in our sample scored positively on the Agitation factor but did not score positively on Behavioral Dyscontrol and thus were included as control subjects in this analysis.

Findings from the present study have several important clinical implications. For one, symptoms encompassed within the Agitation factor may have precipitants, course, and outcomes unique from other neuropsychiatric symptoms characteristic of AD. Special attention to treatment of agitated behaviors involving anger, aggressiveness, hostility, and irritability/emotional lability is warranted because they appear to reflect a clinically relevant symptom cluster with unique underlying neurobiologic correlates. Additionally, the mechanism for treating symptoms within the Behavioral Dyscontrol factor may differ from the treatment of aggressive/hostile and irritable behavior. Given that the Agitation factor symptoms appear to have a spe-

<table>
<thead>
<tr>
<th>Region</th>
<th>Cluster Size (K)</th>
<th>Cluster p Value, FWE-Corrected</th>
<th>Peak Coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI agitation single item</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>Right temporal, middle, and superior gyri</td>
<td>3834</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C2</td>
<td>Right calcarine cortex</td>
<td>4524</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NPI irritability single item</strong></td>
<td></td>
<td></td>
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<tr>
<td>C1</td>
<td>Right temporal, middle, and superior gyri</td>
<td>5905</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right insula</td>
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<td></td>
<td></td>
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<tr>
<td>Right precentral and postcentral gyri</td>
<td></td>
<td></td>
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<tr>
<td>Right frontal, middle, and inferior</td>
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</tbody>
</table>

**Notes:** Statistics shown for the peak voxel within each cluster. Degrees of freedom for t tests = 86. C: Cluster; FWE: family-wise error; MMSE: Mini-Mental State Exam; x, y, z: Montreal Neurological Institute coordinates.
specific underlying neurobiology, targeting such a set of specific symptoms in treatment-development programs may be most rewarding.

The findings from this study can help inform improved definitions of agitation by providing a neurobiologic structure to the observed symptoms and their correlates with other neuropsychiatric syndromes in AD. Recently, a consensus definition of agitation was put forth by the International Psychogeriatric Association Agitation Work Group. The provisional definition of agitation requires a patient to have cognitive impairment and emotional distress and disability resulting from agitated behavior(s), which is reflected by at least one of three observable behaviors: excessive motor activity, verbal aggression, or physical aggression. Considerations arise when evalu-
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ating this definition in the context of findings from this study. For example, given a lack of distinct neural correlates underlying aberrant motor activity in our study, the inclusion of excessive motor activity as one of three observable behaviors may be conceptually reasonable from a clinical standpoint but may compromise the specificity of the diagnosis.

The current study is an important first step toward identifying a unified syndrome of agitation by investigating the neurobiologic substrates of distinct agitated behaviors; however, the study is not without limitations. Our definition of agitation is inevitably constrained by the items used to reflect agitated behaviors on the NPI. To minimize this issue we used empirically derived symptom clusters of agitated behaviors that helped capture other aspects of agitation within the NPI instrument beyond the agitation/aggression item alone. Additionally, although reliability of the NPI has been demonstrated, it is a caregiver-rated assessment and thus prone to varying interpretations by caregivers. Replication of these findings with instruments that use other rating approaches is imperative to validate the results of the present study. Another potential limitation of the study is our dichotomous approach to classifying patients. This was done for several reasons. First, a high number of participants did not exhibit any symptoms across the two factors (i.e., scores of 0). Second, the NPI queries for presence or absence of symptoms before asking more detailed questions, and, third, we believe this reasonably represents clinical situations in which agitation symptoms are considered present or not. Nevertheless, agitated symptoms exist on a continuum of both frequency and severity and dichotomizing them will inevitably reduce variance, thus missing potentially important associations. Additionally, the high saturation of zero scores on NPI items may have impacted the Spearman correlations reported. Another important consideration is that we did not account for cortical atrophy, and some reported associations may be driven by regional atrophy rather than functional changes. Regardless of whether findings are because of atrophy or functional neural changes, findings highlight brain regions that are relevant for the expression of agitated behaviors. A final limitation relates to our sample; mainly, that it was male-dominated and most participants were not taking cholinesterase inhibitor medication despite being in mild to moderate stages of AD. Examining these questions with more representative and larger population-based samples is important.

The results of the present study highlight the importance of understanding the neurobiologic substrates of distinct agitated behaviors. Future studies geared toward understanding, diagnosing, and treating agitated behaviors should consider stratifying results by the specific symptoms and subsets of agitation to delineate the aspects that contribute to a unique syndrome distinct from other neuropsychiatric syndromes. Additionally, considering interactions with other neuropsychiatric symptoms or dementia features and interactions of agitation with environmental stimuli and caregiver behavior is important to fully understand optimal management for agitated behaviors in AD. The present study speaks to the value of multimodal neuroimaging to develop biologically informed phenotypes of agitated behaviors in AD.

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