Metabolic Patterns Associated With the Clinical Response to Galantamine Therapy

A Fludeoxyglucose F 18 Positron Emission Tomographic Study

Michael S. Mega, MD, PhD; Ivo D. Dinov, PhD; Verna Porter, MD; George Chow, MD; Erin Reback, BA; Paras Davoodi, BA; Susan M. O’Connor, RNC; Michele F. Carter, BS, RN; Herminia Amezcua, BS; Jeffrey L. Cummings, MD

Background: Regional brain correlates of treatment with cholinesterase inhibitors in those with Alzheimer disease are unknown.

Objective: To map brain metabolism associated with the treatment response to galantamine with fludeoxyglucose F 18 positron emission tomography in patients with Alzheimer disease.

Design: This is a hypothesis-driven, prospective, open-label study of 19 patients with mild to moderate Alzheimer disease examined before and after treatment with the cholinesterase inhibitor galantamine. Clinical examinations included the cognitive portion of the Alzheimer Disease Assessment Scale, the Mini-Mental State Examination, and the Neuropsychiatric Inventory. Imaging was performed using fludeoxyglucose F 18 positron emission tomography. The positron emission tomographic data, registered to a probabilistic anatomical atlas, were subjected to a voxel-based analysis of 3 subgroups: total patient analysis, cognitive analysis, and behavioral analysis. Subvolume thresholding corrected random lobar noise to produce 3-dimensional significance maps.

Results: The total group analysis showed an increase in left caudate metabolism with no significant change in clinical outcomes for the total group with treatment. Subgroup analysis of cognitive and behavioral responders demonstrated a significant activation of a striatal-thalamofrontal network with galantamine treatment that was not present in patients whose condition worsened or was unchanged by therapy. In cognitive subgroups, change in left anterior cingulate metabolism significantly correlated with change in the cognitive portion of the Alzheimer Disease Assessment Scale ($r=0.70, P=.02$); in behavioral subgroups, right cingulate metabolic change significantly correlated with improvement in depression and right ventral putamen metabolic change with improvement in apathy ($r=0.63, P<.05$ for both).

Conclusion: Cognitive and behavioral responders to galantamine therapy show clinically related improvements in prefrontal network metabolism along with thalamic activation.

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The challenge for functional neuroimaging in dementia treatment is identifying statistically significant patterns that are clinically meaningless. Past voxel-based studies of cholinesterase inhibitors in Alzheimer disease (AD) have combined patients with various outcomes, assuming that the average group response overwhelms the spectrum of individual response. This assumption may be invalid. Cognitive improvement, defined as a 4-point or greater improvement on the cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-cog), occurs in 12% to 60% of patients across cholinergic agents, while behavioral improvement, defined as a 4-point or greater improvement on the Neuropsychiatric Inventory (NPI), occurs in 41% of patients; thus, with cholinergic treatment, the condition in nearly half of patients worsens or remains unchanged. Few studies control for this diversity of treat-
ment response; we controlled the spectrum of response by examining subgroups of patients achieving a priori clinical criteria.

We first explored the general metabolic effect of galantamine, a relatively weak cholinesterase inhibitor but a potent nicotinic receptor modulator. We then mapped functional patterns associated with cognitive and behavioral responses to galantamine by testing 3 hypotheses. Previously, a baseline ventrolateral prefrontal deficit in patients with severe irritability, disinhibition, and euphoria was associated with behavioral improvement to cholinergic therapy. We tested this finding prospectively. Hypothesis 1 was that compared with nonresponders and the unchanged group, behavioral responders to galantamine will have significant ventrolateral prefrontal hypometabolism at baseline that improves with treatment, accompanied by improved irritability, disinhibition, and euphoria.

Cognitive improvement with a cholinergic agent may be associated with heteromodal executive and attentional network activation. Although the pharmacologic mechanism is different across cholinergic agents, there may be similar functional anatomical features associated with their clinical response. Hypothesis 2 was that cognitive responders to galantamine treatment will have significant increases in anterior cingulate and dorsolateral frontal metabolism associated with their clinical response.

As a nicotinic receptor modulator, galantamine lowers cell resting membrane potential, thereby facilitating firing. The thalamus has high concentrations of nicotinic receptors; α4/β2 receptors predominate on the thalamocortical glutaminergic efferents within frontal-subcortical circuits. If galantamine’s clinical effect occurs from nicotinic modulation, then thalamic activation in responders might occur. Hypothesis 3 was that compared with nonresponders and the unchanged group, responders will have significantly increased thalamic metabolism with galantamine treatment.

METHODS

CLINICAL EXAMINATION

This open-label study enrolled 22 patients who presented for an examination for dementia, met all study criteria, and agreed to scanning with fludeoxyglucose F 18 positron emission tomography (PET) after signing an informed consent approved by the Human Subjects Protection Committee. All met the criteria for probable AD. A Mini-Mental State Examination (MMSE) score of 13 or more, had a total NPI score of 4 or more, had no psychiatric or non-AD neurological illness, were stable while receiving concomitant medications for 1 month, were proficient in English, were 50 years or older, and had a live-in caregiver. Exclusion criteria included abnormal structural neuroimaging results, a hematocrit of less than 50% of normal, uncontrolled systemic illness, alcoholism or substance abuse within the year, or use of drugs that might interfere with the fludeoxyglucose F 18 PET assessment. The ADASCog and MMSE measured cognition, and the NPI assessed behavior. As in past studies, we defined clinical responders as achieving a 4-point or more improvement from baseline on the ADASCog or NPI while nonresponders worsened by 4 points or more and the unchanged group had a ±3-point change. These criteria reflect the change in placebo groups (±3-point change over 2-6 months) followed up with the NPI or ADASCog in double-blind, multicenter, clinical trials. Because of the few subjects and nonnormal distribution for all clinical data, a bootstrap analysis evaluated significance, as previously described.

SCANNING AND IMAGE PROCESSING

Scanning with fludeoxyglucose F 18 PET occurred at baseline and after 8 weeks of galantamine therapy. The patient’s family informed consent for scanning, and the patient assented to the procedure. While in the scanner in a dimmed room, the patient received a 5-mCi (18.5 × 10⁶ Bq) intravenous injection of fludeoxyglucose F 18, according to a protocol previously described. All of these early-stage patients could lie motionless without the need for sedation. Image resolution after reconstruction had a maximum of 3.6-mm full width at half maximum. A calculated attenuation correction was used. Details of the fludeoxyglucose F 18 PET method have been given. Spatial normalization was accomplished via 12-parameter affine registration to the AD probabilistic atlas, followed by linear-intensity normalization to the global mean intensity of the pretreatment and posttreatment groups. Subvolume thresholding computed statistical maps of the subtraction results. When no regional hypothesis was tested, Bonferroni correction was used, as previously described. Correlations among clinical and metabolic change were derived from Pearson product moment correlation coefficients of the differences in both follow-up scores minus baseline clinical scores and normalized metabolic intensities across subjects.

RESULTS

Of 22 patients, 19 tolerated a biweekly increase from 8 mg/d of galantamine to a maximum constant dose of 16 to 24 mg/d for at least 4 weeks, yielding a total of 8 weeks of therapy. These 19 patients were analyzed in the first part of the study, which explored the general metabolic pattern associated with the entire group’s treatment response. There were no significant changes in any of the clinical measures (either total score or subscores) for the entire treatment group during the treatment period. The mean ADASCog scores at baseline and posttreatment were 27.5 and 22.6, respectively; the mean MMSE scores at baseline and posttreatment were 23.7 and 25.3, respectively; and the mean NPI scores at baseline and posttreatment were 10.2 and 11.1, respectively.

Figure A shows the brain regions surviving a Bonferroni correction that were significantly hypometabolic after treatment compared with baseline. The left caudate was the only area with significantly increased metabolism after treatment to survive a Bonferroni correction (Figure 1B).

The baseline demographic and clinical characteristics for the cognitive and behavioral subgroups are presented in Table 1; no significant differences were found across baseline profiles within the 2 subgroups. Because 2 nonresponders were insufficient for an analysis of cognition-related brain changes, the 6 cognitive responders were examined against a demographically similar group.
of 6 cognitively unchanged patients (Table 1). In the behavioral subgroup, 18 patients were examined because of elimination of one patient who did not score at least 4 points on the baseline NPI. Clinical change scores for cognitive and behavioral groups are presented in Table 2 and Table 3, respectively. Cognitive response did not guarantee behavioral response—only 2 cognitive responders were also behavioral responders.

Figure 1. Statistical maps of regions surviving Bonferroni correction for the total patient group (N=19). A, Regions with significant decreased metabolism after galantamine treatment compared with baseline. B, Regions with significant increased metabolism after galantamine treatment compared with baseline. R indicates right side; L, left side.

Table 1. Baseline Demographic and Clinical Characteristics of the Cognitive and Behavioral Subgroups*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cognitive Subgroups</th>
<th>Behavioral Subgroups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders</td>
<td>Unchanged Group</td>
<td>Responders</td>
</tr>
<tr>
<td>Male-female ratio</td>
<td>2:4</td>
<td>2:4</td>
<td>2:4</td>
</tr>
<tr>
<td>Age, y</td>
<td>73.9 (3.9)</td>
<td>78.3 (2.7)</td>
<td>77.4 (4.7)</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.3 (0.6)</td>
<td>15.5 (0.3)</td>
<td>14.8 (0.5)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>23.3 (1.1)</td>
<td>24.2 (1.5)</td>
<td>25.2 (1.2)</td>
</tr>
<tr>
<td>ADAS-cog score</td>
<td>32.5 (4.7)</td>
<td>26.5 (4.4)</td>
<td>25.7 (5.5)</td>
</tr>
<tr>
<td>NPI score</td>
<td>14.3 (3.7)</td>
<td>10.0 (2.1)</td>
<td>14.8 (2.9)</td>
</tr>
</tbody>
</table>

Abbreviations: ADAS-cog, cognitive portion of the Alzheimer Disease Assessment Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

*Data are given as mean (SEM) unless otherwise indicated. No significant difference was found in any domain.

Table 2. Change Scores for the 2 Patient Groups in the Cognitive Analysis*

<table>
<thead>
<tr>
<th>Test</th>
<th>Responders Unchanged Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>2.0 (1.6) 1.1 (0.9)</td>
</tr>
<tr>
<td>NPI total</td>
<td>–1.3 (1.6) 2.3 (4.9)</td>
</tr>
<tr>
<td>ADAS-cog†</td>
<td>–8.3 (1.3) –2.3 (0.2)</td>
</tr>
<tr>
<td>Learning‡</td>
<td>–2.0 (0.6) –0.8 (0.5)</td>
</tr>
<tr>
<td>Naming</td>
<td>0.3 (0.2) 0.3 (0.3)</td>
</tr>
<tr>
<td>Recall</td>
<td>–1.0 (0.5) 0.5 (0.8)</td>
</tr>
<tr>
<td>Commands</td>
<td>–0.2 (0.2) –0.2 (0.4)</td>
</tr>
<tr>
<td>Drawing</td>
<td>–0.2 (0.2) 0.2 (0.2)</td>
</tr>
<tr>
<td>Praxis</td>
<td>–0.3 (0.3) –0.3 (0.2)</td>
</tr>
<tr>
<td>Orientation</td>
<td>–1.3 (0.8) –0.8 (0.6)</td>
</tr>
<tr>
<td>Recognition</td>
<td>–2.0 (0.6) –0.8 (0.6)</td>
</tr>
<tr>
<td>Language</td>
<td>–0.5 (0.2) –0.2 (0.2)</td>
</tr>
<tr>
<td>Comprehension</td>
<td>–0.2 (0.2) 0.2 (0.2)</td>
</tr>
<tr>
<td>Fluency</td>
<td>–0.5 (0.3) 0.0 (0.2)</td>
</tr>
<tr>
<td>Instructions</td>
<td>–0.2 (0.3) –0.2 (0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.

*Data are given as mean (SEM).
†P<.001 across the 2 cognitive groups compared with their baseline and change scores.
‡P<.02 in responders compared with their baseline score.

Table 3. Change Scores for the 3 Patient Groups in the Behavioral Analysis*

<table>
<thead>
<tr>
<th>Test</th>
<th>Responders Unchanged Group Nonresponders</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>2.7 (1.5) 0.4 (1.0) 1.8 (0.9)</td>
</tr>
<tr>
<td>ADAS-cog†</td>
<td>–5.3 (1.7) –3.0 (1.7) –2.2 (0.9)</td>
</tr>
<tr>
<td>NPI total‡</td>
<td>–6.8 (0.9) –0.4 (0.7) 10.8 (2.8)</td>
</tr>
<tr>
<td>Delusions</td>
<td>–1.2 (1.1) –0.4 (0.3) 0.6 (0.5)</td>
</tr>
<tr>
<td>Hallucinations§</td>
<td>0.3 (0.3) –0.1 (0.1) 1.6 (0.9)</td>
</tr>
<tr>
<td>Agitation‖</td>
<td>0.0 (0.4) 0.4 (0.8) 1.8 (0.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>–2.2 (1.6) 0.6 (0.4) –0.2 (1.0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>–1.3 (0.7) –0.3 (0.4) 0.6 (1.8)</td>
</tr>
<tr>
<td>Euphoria¶</td>
<td>–0.2 (0.2) 0.0 (0.2) 0.8 (0.4)</td>
</tr>
<tr>
<td>Apathy‖</td>
<td>–1.5 (1.0) 0.0 (0.8) 2.8 (1.0)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.0 (0.0) –0.1 (0.5) 1.2 (1.1)</td>
</tr>
<tr>
<td>Irritability‖</td>
<td>–1.2 (1.2) –0.1 (0.6) 1.6 (0.6)</td>
</tr>
<tr>
<td>Abnormal motor</td>
<td>–1.5 (0.8) 0.9 (1.4) 0.0 (0.3)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 1.

*Data are given as mean (SEM).
†P<.05 in nonresponders compared with responders and in responders compared with their own baseline.
‡P<.01 across all 3 clinical groups.
§P<.05 in nonresponders compared with the unchanged group.
‖P<.05 in nonresponders compared with the unchanged group and responders, and with their own baseline.
¶P<.05 in nonresponders compared with responders.
Figure 2 presents the statistical maps of the hypothesis-driven analyses for the cognitive subgroups. Cognitive responders had a significantly increased metabolism after treatment in the left caudate-thalamofrontal circuit (anterior cingulate and prefrontal cortex) compared with their baseline data (right side [R]). This pattern of activation was not present after treatment in the cognitively unchanged group (left side [L]). Additional regions of increased metabolism were also found in the left inferior temporal and right inferior parietal lobule (not shown) for the cognitive responders after treatment.

Figure 3 presents statistical maps of the hypothesis-driven analyses for the behavioral subgroups. A, The right orbital-frontal cortex in the responders was hypometabolic compared with the unchanged patients (left), a finding not present in nonresponders at baseline compared with the unchanged group (not shown). Responders at baseline had bilateral orbital-frontal hypometabolism compared with nonresponders (right). B, After treatment, significantly increased metabolism was found in the right thalamus of the responders compared with the unchanged group (left) that was not present at baseline. Compared with their baseline, responders had significantly increased left caudate-thalamofrontal circuit metabolism with treatment (right). Responders also had greater bilateral anterior cingulate and left thalamic activation with treatment compared with nonresponders that was not present at baseline (not shown). R indicates right side.

Figure 4 presents the clinical correlates of the imaging findings in the subgroups. Across the cognitive responders and the unchanged group, metabolic changes in the left cingulate with treatment were significantly correlated ($r=0.70, P<.02$) with improvement on the ADAS-cog (Figure 4A). Similarly, changes in right cingulate metabolism with treatment were significantly correlated ($r=0.63; P<.05$) with change in depression (Figure 4B), while changes in the right ventral putamen were significantly correlated ($r=0.63; P<.05$) with change in apathy across behavioral responders and nonresponders (Figure 4C).

**COMMENT**

To our knowledge, this is the first study to correlate clinical outcomes with changes in metabolism in AD patients across the spectrum of clinical response: responders, the unchanged group, and nonresponders. Our first analysis of the total patient group underscores the importance of the subgroup analysis. The total group had no significant clinical benefit from treatment and metabolic maps were remarkable for decreases in cortical and subcortical metabolism. The only region to show increased metabolism was the left caudate. However, when clinical subgroups were examined separately, cognitive and behavioral responders demonstrated a significant activation of a striatal-thalamofrontal network with galantamine treatment that was not present in patients whose condition worsened or was unchanged by therapy (Figure 5). Our results suggest functional imaging studies of dementia therapy should analyze data into subgroups of clinical response.

Three past studies have used functional imaging to evaluate cholinesterase inhibitor treatment in responders. Potkin et al found prefrontal and hippocampal metabolic increases from baseline in rivastigmine responders compared with decreases in nonresponders and placebo-treated patients over 26 weeks. However, qualitative, not quantitative, measures of treatment...
response were used. Vennerica et al. measured brain perfusion with rivastigmine treatment and defined response by global impressions of change, stable or improved NPI, or improvement of at least 2 points on the MMSE. After 6 months of treatment, responders improved by 1.8 points on the NPI and by 2.4 points on the MMSE. Responders showed increased bilateral anterior cingulate and left dorsolateral parietofrontal perfusion compared with baseline. Nonresponders lost 2.1 MMSE points and had a 3.9-point worsening on the NPI while demonstrating diffuse right greater than left perfusion declines across the entire brain. No examinations were done comparing responders with nonresponders in that study, nor were perfusion changes correlated with clinical scores. Nobili et al. also evaluated brain perfusion using a 2.9-point MMSE score decline per year as a rate cutoff for nonstable vs stable patients treated with either donepezil or rivastigmine over 15 months. No perfusion differences were found between the 2 groups at baseline or in the stabilized group at follow-up compared with baseline; but, at follow-up, the nonstable group had a left frontal defect compared with the stable group. No correlations were made among brain perfusion patterns and clinical scores.

We prospectively tested 3 hypotheses. The first was supported in that behavioral responders had significant correlations with clinical change. A, Changes in normalized positron emission tomography (PET) counts in the left cingulate (arrow) showed a significant correlation ($r=0.70$, $P<.02$) with cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-cog) change across cognitive responders and the unchanged group. B, Changes in normalized PET counts in the right cingulate (arrow) showed a significant correlation ($r=0.63$, $P<.05$) with improvement in depression across behavioral responders and nonresponders. C, Changes in normalized PET counts in the right ventral putamen, abutting the extended amygdala (arrow), showed a significant correlation ($r=0.63$, $P<.05$) with improvement in apathy across behavioral responders and nonresponders.

Figure 4. Normalized metabolic change correlates with clinical change. A, Changes in normalized positron emission tomography (PET) counts in the left cingulate (arrow) showed a significant correlation ($r=0.70$, $P<.02$) with cognitive portion of the Alzheimer Disease Assessment Scale (ADAS-cog) change across cognitive responders and the unchanged group. B, Changes in normalized PET counts in the right cingulate (arrow) showed a significant correlation ($r=0.63$, $P<.05$) with improvement in depression across behavioral responders and nonresponders. C, Changes in normalized PET counts in the right ventral putamen, abutting the extended amygdala (arrow), showed a significant correlation ($r=0.63$, $P<.05$) with improvement in apathy across behavioral responders and nonresponders. R indicates right side.
cantly lower metabolism in ventrolateral frontal regions at baseline that resolved with treatment compared with behaviorally unchanged patients (on the right), nonresponders (bilaterally), and their own baseline (on the left) after treatment. This baseline ventrolateral frontal defect was not found in cognitive responders compared with cognitively unchanged patients. These paralimbic changes occurred with significant NPI changes that distinguished the responders from the nonresponders: euphoria, irritability (as hypothesized), apathy, and agitation (not hypothesized). The pretreatment orbital-frontal defect in behavioral responders to galantamine treatment was similarly found in a separate group of patients showing behavioral response to donepezil, suggesting this baseline profile is shared by the class of cholinergic agents.

To test the specificity of this finding, future studies should select patients based on the degree of their baseline orbital-frontal defect and prospectively follow their treatment response.

The second hypothesis was supported in that cognitive responders significantly increased metabolism in heteromodal attention-executive networks with galantamine treatment. Cognitively unchanged patients did not demonstrate this pattern after treatment. Furthermore, normalized fludeoxyglucose F 18 PET changes in the left anterior cingulate significantly correlated with ADAS-cog change across the cognitive response spectrum. This underscores the clinical relevance of the left anterior cingulate in cognitive response to galantamine treatment, reflected in the language-based ADAS-cog. The anterior cingulate on the left augments attention and the efficiency of executive function via its monosynaptic connections with dorsolateral prefrontal and posterior parietotemporal association cortices (all regions were hypermetabolic in cognitive responders but not in the unchanged group after treatment).

The third hypothesis also was supported. For the cognitive and behavioral responders, there was an increase in anterior medial thalamic metabolism on the left with treatment compared with their baseline scans, which was not seen in either the behavioral nonresponders or the cognitively unchanged groups. Furthermore, in behavioral nonresponders, the left thalamus was hypometabolic at baseline and after treatment compared with the behaviorally unchanged patients. In the cognitive subgroup, bilateral baseline thalamic hypometabolism was present in the unchanged group vs the responders, while after treatment, behavioral responders showed a left thalamic metabolic increase compared with nonresponders (both results not shown). These robust findings support a role for the activation of a relatively normal thalamus in patients responding, either cognitively or behaviorally, to galantamine treatment, and suggest a modulatory role for galantamine on the nicotinic receptors that have their highest concentration in the thalamus, where α4/β2 receptors predominate on thalamocortical glutaminergic afferents that compose part of the frontal-subcortical circuits. The α7 subtype is predominate on the γ-aminobutyric acid cell bodies in the reticulare thalami, these cells play a pivotal role in gating ascending sensory input. The laterality of this effect in the left thalamus of both responder subgroups may reflect a synergy with the caudate and frontal cortex on the left, as seen in Figure 2 (top right) and Figure 3B (right).

The strongest evidence linking a drug's clinical effect on regional brain function is provided when significant correlations between clinical test and imaging data are found. The metabolic change from baseline in the left cingulate significantly correlated with ADAS-cog improvement across both cognitive response subgroups (r = 0.70; P = .02), while the right cingulate metabolic change from baseline significantly correlated with improvement in depression across behavioral responders and nonresponders (r = 0.63; P < .05). The laterality of this effect is perhaps reflective of the mood relative influence of the right hemisphere vs the language-based resources engaged by the ADAS-cog. The right ventral putamen, abutting the extended amygdala, also correlated significantly with improvement in apathy across behavioral responders and nonresponders (r = 0.63, P < .05). The ventral putamen receives dopaminergic projections from the ventral tegmental area, modulation of these limbic projections occurs via presynaptic nicotinic receptors. An increase in motivation to engage motorically or emotionally may result from this ventral pallidal activation.

Figure 5. Surface mapping of right medial and lateral frontal regions of increased metabolism in behavioral responders compared with nonresponders after galantamine treatment supports frontal-subcortical network activation associated with clinical response to treatment.
Caution should be used in interpreting the results of this small open-label study. Two patients did not tolerate dose advancement; thus, a selection bias may have occurred. Also, no placebo group was used to contrast the treatment effect. It may be that the placebo effect has a brain metabolic correlate in AD. Although we designed this study to prospectively test focused hypotheses, voxel-based image analysis is prone to type I errors. Larger patient groups should be assessed to determine if these findings are robust. Future studies might use principal component analysis of clinical data linked to the striatal-thalamofrontal network found herein to prospectively test the specificity of this treatment response. Until such prospective studies are accomplished, no evidence exists to support PET as a biomarker in clinical trials for screening or developing drugs.

In summary, to our knowledge, this is the first study to correlate treatment outcome to brain metabolism across the spectrum of clinical response in AD. Cognitive and behavioral responders to galantamine show improvements in striatal-thalamofrontal circuit metabolism, and treatment-related changes in cognition, depression, and apathy are significantly associated with specific regional metabolic changes. Whether this striatal-thalamofrontal activation pattern is a hallmark of general cholinergic treatment in AD patients will require further testing.

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Author Affiliations: Alzheimer’s Disease Center and Center on Aging, Providence Health System, Portland, Ore (Dr Mega); Laboratory of Neuro Imaging and Department of Statistics (Dr Dinov), Department of Neurology (Drs Porter and Cummings and Ms Reback, Davoodi, O’Connor, Carter, and Amezcua), Alzheimer’s Disease Research Center (Ms Reback, Davoodi, O’Connor, Carter, and Amezcua and Dr Cummings), and Department of Psychiatry and Biobehavioral Sciences (Dr Cummings), The David Geffen School of Medicine at UCLA, Los Angeles, Calif; and Department of Neurology, Tarzana Regional Medical Center, Los Angeles (Dr Chow).

Correspondence: Michael S. Mega, MD, PhD, Alzheimer’s Disease Center and Center on Aging, Providence Health System, 10150 SE 32nd Ave, Portland, OR 97222 (michael.mega@providence.org).

Author Contributions: Study concept and design: Mega. Acquisition of data: Mega, Porter, Chow, Reback, Davoodi, O’Connor, Carter, and Amezcua. Analysis and interpretation of data: Mega, Dinov, and Cummings. Drafting of the manuscript: Mega. Critical revision of the manuscript for important intellectual content: Mega, Dinov, Porter, Chow, Reback, Davoodi, O’Connor, Carter, Amezcua, and Cummings. Statistical analysis: Mega and Dinov. Obtained funding: Mega. Administrative, technical, and material support: Dinov, Chow, Reback, Davoodi, O’Connor, Carter, Amezcua, and Cummings. Study supervision: Mega. Editing of the manuscript for clarity of presentation: Cummings.

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