Donepezil Treatment and Changes in Hippocampal Structure in Very Mild Alzheimer Disease

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Objective: To compare longitudinal changes in the hippocampal structure in subjects with very mild dementia of the Alzheimer type (DAT) treated with donepezil hydrochloride, untreated subjects with very mild DAT, and controls without dementia.

Design: MPRAGE sequences were collected approximately 2 years apart on two 1.5-T magnetic resonance imaging systems, yielding 2 cohorts. Large-deformation high-dimensional brain mapping was used to compute deformation of hippocampal subfields.

Setting: A dementia clinic at Washington University School of Medicine.

Patients or Other Participants: Subjects came from 2 sources: 18 untreated subjects with DAT and 26 controls were drawn from a previous longitudinal study; 18 treated subjects with DAT were studied prospectively, and 44 controls were drawn from a longitudinal study from the same period.

Intervention: Patients were prescribed donepezil by their physician.

Main Outcome Measures: Hippocampal volume loss and surface deformation.

Results: There was no significant cohort effect at baseline; therefore, the 2 groups of control subjects were combined. The potential confounding effect of cohort/scanner was dealt with by including it as a covariate in statistical tests. There was no significant group effect in the rate of change of hippocampal volume or subfield deformation. Further exploration showed that compared with the untreated subjects with DAT, the treated subjects with DAT did not differ in the rate of change in any of the hippocampal measures. They also did not differ from the controls, while the untreated subjects with DAT differed from the controls in the rates of change of hippocampal volume and CA1 and subiculum subfield deformations.

Conclusions: Treatment with donepezil did not alter the progression of hippocampal deformation in subjects with DAT in this study. Small sample size may have contributed to this outcome.

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The effects of acetylcholinesterase (AChE) inhibitors on the symptoms of dementia of the Alzheimer type (DAT) can be highly variable. Although AChE inhibitors demonstrate modest overall benefits compared with placebo for stabilizing or slowing decline in mild to moderate Alzheimer disease (AD), summary estimates show small effect sizes. It is not currently possible to identify those who will respond to treatment prior to treatment. Cognitive improvements associated with AChE inhibitor treatment are often only temporary and when declines in cognition resume, they proceed similarly in patients who have received treatment and placebo. Moreover, there is no obvious neural mechanism by which AChE inhibitors might exert neuroprotective effects. Neuromorphometric measures are increasingly being studied as potential biomarkers for improved antemortem diagnosis of DAT and detection of disease modification following treatment. Using large-deformation high-dimensional brain mapping, we reported previously that reduced hippocampal volumes and inward deformations of the CA1 and subiculum subfields were present in subjects with very mild DAT and were correlated with a poorer response to donepezil hydrochloride treatment. However, while volumetric magnetic resonance imaging of the whole brain or medial temporal lobe structures is now being considered as a possible outcome measure in therapeutic trials for patients with DAT and mild cognitive impairment, few studies have as-
sessed the effects of treatment with AChE inhibitors on changes in brain structure, such as hippocampal degeneration, associated with the disease pathophysiology.

In this study, we used large-deformation high-dimensional brain mapping to compare changes in hippocampal volume and surfaces proximal to the CA1 and subiculum subfields between healthy older adults and 2 groups of subjects with DAT: 1 group treated with donepezil in an open-label study and a second group from a study prior to the availability of donepezil and that was therefore untreated. Although a prospective randomized study of this kind is desirable, it would be unethical to withhold treatment with an approved treatment for patients with DAT for a period sufficient to assess the effects of treatment on brain structure. We tested the hypothesis that treatment with donepezil would alter the rate of hippocampal volume loss and surface deformation in patients with very mild DAT.

METHODS

SUBJECTS

Subjects in this study were drawn from 2 sources. The first source was a previously published prospective longitudinal study in 18 subjects with very mild DAT and 26 subjects without dementia. These subjects with DAT had been enrolled in the study prior to the widespread use of donepezil and were therefore untreated.

The second source of subjects included 18 donepezil-treated patients with very mild DAT who were participating in a longitudinal study of the treatment of mild DAT with donepezil. The treating clinicians for these subjects were dementia specialists at the Memory Diagnostic Center at Washington University School of Medicine. These patients received baseline clinical assessments within 30 days of treatment initiation and every 3 months thereafter for a maximum of 2 years. Forty-four age-matched, community-dwelling, elderly subjects without dementia were selected as a control group from an ongoing longitudinal study of memory and aging at the Washington University School of Medicine Alzheimer’s Disease Research Center from the same period.

Exclusion criteria for all subjects included genetic mutations linked to familial forms of dementia or clinical diagnoses of other neuropsychiatric disorders (eg, Lewy body disease, vascular dementia, depression) that could have confounded the diagnosis of DAT.

CLINICAL ASSESSMENT

The subjects were assessed at the time of magnetic resonance scanning (within a month). The Clinical Dementia Rating (CDR) scale was given to assess the presence and, if present, the severity of dementia symptoms. The CDR scale rates the presence or absence of cognitive impairment. A CDR of 0 indicates no dementia and scores of 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia, respectively. Clinical Dementia Rating assessments have been shown to have high interrater reliability when used at our Alzheimer’s Disease Research Center and in multicenter studies of DAT. Only subjects with DAT with a CDR of 0.5 or 0 were included in this study.

ApoE allele status was known in 100 of the 106 subjects. Fifty-nine of these 100 subjects had no ApoE4 alleles, 34 had a single ApoE4 allele, and 7 subjects had 2 ApoE4 alleles. In the group of treated subjects with DAT, 3 had no ApoE4 alleles, 7 had a single ApoE4 allele, and 2 had 2 ApoE4 alleles.

COGNITIVE ASSESSMENT

The subjects’ cognitive function performance was assessed independently and blinded of the clinical assessment in a comprehensive neuropsychological battery that included measures of episodic memory, semantic memory, speeded psychomotor performance, visuospatial ability, and attention. This battery was used previously to describe the pattern of cognitive deficits in 407 individuals with very mild and mild DAT (CDRs of 0.5 and 1), and 3 factors (temporal factor, parietal factor, frontal factor) relating to the frequency of β-amyloid plaques in the temporal, parietal, and frontal lobes were revealed. A general factor score was also computed. In the present study, these 4 factor scores were calculated for each of the subjects using unit weightings of z scores based on means and standard deviations derived from the prior study. Mini-Mental State Examination scores were not available for the untreated subjects with DAT at the time of study. We therefore examined the Short Blessed Test and Wechsler Memory Scale logical memory scores as an additional comparison of the characteristics of treated and untreated subjects with DAT.

IMAGING AND BRAIN MAPPING

The subjects from the first source were scanned approximately 2 years apart on a 1.5-T Vision system (Siemens Medical Systems, Erlangen, Germany), using a standard head coil and an MPRAGE sequence (repetition time=9.7 milliseconds, echo time=4.0 milliseconds, flip angle=8°, 1 × 1 × 1 mm3 voxel resolution, scan time=11.0 minutes) to collect one 3-dimensional T1-weighted volume. The subjects from the second source were scanned approximately 1.5 years apart on a different 1.5-T Siemens Vision system, using a standard head coil and identical MPRAGE sequence as earlier mentioned with slightly different protocols (repetition time=9.7 milliseconds, echo time=4.0 milliseconds, flip angle=10°, 1 × 1 × 1.25 mm3 voxel resolution, scan time=6.5 minutes) to collect multiple (2-4) 3-dimensional T1-weighted image volumes. The scans for each subject were aligned with the first scan and averaged to create a low-noise image volume. Landmark-based, large-deformation high-dimensional diffeomorphic mapping (large-deformation high-dimensional brain mapping) was used to generate the surfaces of the hippocampus in baseline scans. For longitudinal mapping, baseline and follow-up scans were first registered using a 9-parameter affine transformation (rigid-body rotation and translation plus cardinal axis stretch) to adjust for changes in head position and scanner drift. Next, the landmarks that were placed in the baseline scans were transferred to the follow-up scans by applying the affine transformations to the baseline landmarks. Then, the large-deformation high-dimensional brain mapping procedure was applied to all of the follow-up scans (See Wang et al, Appendix A, for rationale for this approach).

MEASUREMENT OF CHANGES IN HIPPOCAMPAL STRUCTURE

Left and right hippocampal volumes in each subject were calculated as the volumes enclosed by the hippocampal surfaces. An average hippocampal surface constructed from 86 healthy subjects was used as a reference surface, from which perpendicular deformation of each subject’s hippocampal surface was calculated at each surface point. Hippocampal surface zones corresponding to underlying subfields (ie, CA1, subiculum, and...
STATISTICAL ANALYSIS

Rates of change (per year) of the clinical, cognitive, and hippocampal measures for each subject were calculated by dividing the difference at the 2 assessments by the interval. Group differences in the rates of change of hippocampal volume and subfield deformation were examined with general linear models using SAS 9.1,27 where left and right sides were treated as repeated measures. Appropriate post hoc contrasts were used to examine pairwise group differences in the rates of change for treated subjects with a CDR of 0.5 vs a CDR of 0, untreated subjects with a CDR of 0.5 vs a CDR of 0, and, particularly, treated vs untreated comparisons. The analyses were also performed with sex as an additional covariate since the subjects with a CDR of 0 were mostly female (26 men, 44 women) while the subjects with a CDR of 0.5 were predominantly male (21 men, 15 women) (χ²=4.4; P=.11). Similar analyses were performed on the rates of change of psychometric scores (without hemisphere).

RESULTS

The groups of 18 untreated subjects with a CDR of 0.5 (mean [SD] age, 73.7 [4.4] years; 11 men, 7 women) and 26 untreated subjects with a CDR of 0 (mean [SD] age, 73.0 [7.0] years; 12 men, 14 women) from the first source of subjects had similar ages and sex distributions. The groups of 18 treated subjects with a CDR of 0.5 (mean [SD] age, 74.0 [5.2] years; 10 men, 8 women) and 44 treated subjects with a CDR of 0 (mean [SD] age, 74.7 [5.4] years; 14 men, 30 women) from the second source had similar ages but somewhat different sex distributions. The 2 groups of subjects without dementia did not differ in age (tmax=−0.68; P=.50) or sex distribution (χ²=1.4; P=.23).

The 2 groups of subjects without dementia did not differ in baseline hippocampal volume (left: tmax=−0.81; P=.42; right: tmax=−0.26; P=.80) or CA1 (left: t=−0.78; P=.44; right: t=−0.41; P=.68) or subiculum (left: t=−0.84; P=.40; right: t=−1.4; P=.17) subfield deformation; however, they differed in the right remainder subfield deformation (t=−4.4; P<.001), but not the left (t=−0.57; P=.59). The 2 groups of subjects without dementia differed in the rates of change of left hippocampal volume (t=2.24; P=.03) and left and right CA1 subfield deformation (left: t=2.28; P=.03; right: t=2.32; P=.02). The 2 groups of subjects without dementia were combined for use as a single comparison group, and cohort source was used as a covariate in all subsequent statistical analyses. We present subject sample characteristics and hippocampal measures for the combined control cohorts and the 2 DAT groups in Table 1 and Table 2 and separately for the 2 control cohorts in Table 3. We observed that for both baseline measures and their rates of change, the variances remained about the same whether the 2 cohorts of control subjects were combined or not.

There was a group difference in the between-scan interval (F 1,103=4.5; P=.01), with the treated subjects with a CDR of 0.5 having a shorter mean [SD] interval (1.55 [0.42] years) compared with the untreated subjects (1.96 [0.37] years; least squares means contrast P=.06) as well as the combined group of subjects without dementia (2.05 [0.71] years; contrast P=.004). Therefore, rates of change of the hippocampal volume and subfield deformations were used in statistical analyses as opposed to using the hippocampal volume and subfield deformations at each point in a repeated-measures type of analysis of variance.

Statistical comparison results for the hippocampal and psychometric measures are shown in Table 4 and Table 5, with sex and cohort used as covariates. Effect sizes (Cohen d) are also provided for the hippocampal measures (unadjusted for the covariates). At baseline, the main group effect was significant for hippocampal volume and left and right CA1 and left and right subiculum subfield deformations. Contrasts showed that while both untreated and treated groups differed from the subjects without dementia, the treated and untreated DAT groups did not differ from each other in any of these measures (as expected at baseline).

Longitudinally, there was no overall main group effect after Bonferroni corrections in the rates of change for any of the hippocampal measures. Exploratory examination of the contrasts showed that the untreated subjects with a CDR of 0.5 differed from the healthy subjects without dementia in the rates of change of hippocampal volume and CA1 and subiculum subfield deformations. The...
Contrast scores at baseline. While the untreated and treated sub-
currents without dementia, the 2 groups of subjects with a CDR of 0.5 differed from each other in the rates of change in any of the factors. However, the untreated and treated subjects with dementia of the Alzheimer type did not differ from each other in the rates of change in any of the factors.

Abbreviations: SBT, Short Blessed Test; WLM, Wechsler Memory Scale logical memory.

a Results of general linear models where cohort and sex were used as covariates. For the comparison of rates of change, using baseline measures as an additional covariate is also reported. The untreated and treated subjects with dementia of the Alzheimer type differed from the healthy subjects without dementia in the rates of change of the general and parietal factors. However, the untreated and treated subjects with dementia of the Alzheimer type did not differ from each other in the rates of change in any of the factors.  

b Significant or near-significant effects after Bonferroni corrections.

All neuropsychological battery factor scores and the Short Blessed Test and Wechsler Memory Scale logical memory scores showed main effects of group at baseline. Contrasts showed that while untreated and treated subjects with a CDR of 0.5 differed from the healthy subjects without dementia, the 2 groups of subjects with a CDR of 0.5 did not differ from each other in any of these scores at baseline. While the untreated and treated sub-

treated subjects with a CDR of 0.5 did not differ from the healthy subjects without dementia or the untreated subjects with a CDR of 0.5. Using each measure’s baseline values as an additional covariate did not alter the results.

Patterns of rates of change on the hippocampal surfaces in subjects with a CDR of 0.5 treated with donepezil, untreated subjects, and subjects without dementia are visualized in Figure 1. Comparisons of rates of change among subjects with a CDR of 0.5 treated with donepezil, untreated subjects, and subjects without dementia are visualized in Figure 2. We observed that compared with controls, while the 2 groups with a CDR of 0.5 showed

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rates of change in similar regions of the CA1 subfield, the untreated subjects with a CDR of 0.5 showed additional difference in the subiculum that the untreated subjects with a CDR of 0.5 did not; however, these differences were not significant between these 2 groups of subjects with a CDR of 0.5.

Since the presence of 1 or more ApoE4 alleles has been shown previously to predict a poorer response to AChE inhibitors,5,6 we examined the rates of change in the psychometric and hippocampal measures separately for the 3 treated subjects with DAT with no ApoE4 allele and 9 treated subjects with DAT with 1 or 2 ApoE4 alleles. Because of the small sample size, Wilcoxon exact tests were used. The comparisons showed that while the rates of decline for Mini-Mental State Examination (P = .04) and Wechsler Memory Scale logical memory (P = .03) scores and inward deformation in the left subiculum (P = .02) were significantly more severe in subjects with 1 or more ApoE4 alleles as compared with the 3 subjects without any ApoE4 allele, none of the other psychometric or hippocampal measures showed any significant difference in the rates of change.

Progressive hippocampal volume loss, assessed using magnetic resonance imaging, is a characteristic neuroanatomical feature of AD. However, it is unknown whether treatment with medications marketed for the

Table 4. Hippocampal Measurements at Each Visita

<table>
<thead>
<tr>
<th>Group</th>
<th>Left Volume, mm³</th>
<th>Left CA1, mm³</th>
<th>Left Subiculum, mm³</th>
<th>Left Remainder, mm³</th>
<th>Right Volume, mm³</th>
<th>Right CA1, mm³</th>
<th>Right Subiculum, mm³</th>
<th>Right Remainder, mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>2126 (355)</td>
<td>-0.095 (0.42)</td>
<td>-0.0053 (0.23)</td>
<td>-0.053 (0.19)</td>
<td>2617 (409)</td>
<td>2.7 (2,101)</td>
<td>-0.24 (0.18)</td>
<td>0.086 (0.20)</td>
</tr>
<tr>
<td>Treated</td>
<td>1996 (387)</td>
<td>-0.14 (0.51)</td>
<td>-0.10 (0.23)</td>
<td>-0.22 (0.13)</td>
<td>2328 (539)</td>
<td>2.6 (2,101)</td>
<td>-0.25 (0.18)</td>
<td>-0.17 (0.25)</td>
</tr>
<tr>
<td>Untreated</td>
<td>1714 (210)</td>
<td>-0.60 (0.29)</td>
<td>-0.13 (0.24)</td>
<td>-0.32 (0.22)</td>
<td>2184 (370)</td>
<td>2.9 (2,101)</td>
<td>-0.28 (0.18)</td>
<td>-0.25 (0.25)</td>
</tr>
</tbody>
</table>

Table 5. Statistical Test Results of Hippocampal Measuresa

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>P Value (Effect Size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>11 (2.101)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CA1</td>
<td>7.5 (2.101)</td>
<td>.001</td>
</tr>
<tr>
<td>Subiculum</td>
<td>11 (2.101)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Remainder</td>
<td>4.1 (2.101)</td>
<td>.002</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>2.7 (2.101)</td>
<td>.001</td>
</tr>
<tr>
<td>CA1</td>
<td>2.48 (2.101)</td>
<td>.001</td>
</tr>
<tr>
<td>Subiculum</td>
<td>3.42 (2.101)</td>
<td>.001</td>
</tr>
<tr>
<td>Remainder</td>
<td>1.08 (2.101)</td>
<td>.001</td>
</tr>
<tr>
<td>Rates of change, slope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>1.9 (2.99)</td>
<td>.06</td>
</tr>
<tr>
<td>CA1</td>
<td>1.9 (2.99)</td>
<td>.06</td>
</tr>
<tr>
<td>Subiculum</td>
<td>2.2 (2.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Remainder</td>
<td>1.12 (2.99)</td>
<td>.30</td>
</tr>
</tbody>
</table>

aFor surface deformations, negative values for these measures represent inward variation of the surface while positive values for these measures represent outward variation of the surface. Individual rates of change (per year) of the hippocampal volume and subfield deformation were calculated by dividing the raw difference at the 2 points by the interscan interval.

bSignificant or near-significant effects.
Figure 1. Visualization of the pattern of longitudinal change on the hippocampal surfaces in subjects without dementia and subjects with very mild dementia of the Alzheimer type, either treated with donepezil hydrochloride or untreated. Top panels show the left and right hippocampi viewed from the top (dorsal surface), while bottom panels show the left and right hippocampi viewed from the bottom (ventral surface). Baseline to follow-up changes for the subjects without dementia, treated subjects, and untreated subjects are shown in the left, middle, and right columns, respectively. Boundaries between the 3 zones of the hippocampal surface (ie, lateral, superior, and inferior medial) are drawn in black and all 3 zones are labeled (CA1=CA1, SUB=subiculum, REM=remainder, which comprises CA2-4 plus the dentate gyrus). Rates of change (slopes) of inward variation of the hippocampal surface are represented by cooler flame colors (ie, blue to purple), while slopes of outward variation are represented by warmer colors (ie, orange to red).

Figure 2. Comparison of the patterns of longitudinal change on the hippocampal surfaces in subjects with very mild dementia of the Alzheimer type treated with donepezil hydrochloride, untreated subjects with dementia of the Alzheimer type, and subjects without dementia. Top panels show the left and right hippocampi viewed from the top (dorsal surface), while bottom panels show the left and right hippocampi viewed from the bottom (ventral surface). Comparisons (difference in the mean, unadjusted for covariates) between treated subjects and subjects without dementia are shown in the left column. Comparisons between untreated subjects and subjects without dementia are shown in the middle column. Comparisons between untreated subjects and subjects without dementia are shown in the right column. Boundaries between the 3 zones of the hippocampal surface (ie, lateral, superior, and inferior medial) are drawn in black and all 3 zones are labeled (CA1=CA1, SUB=subiculum, REM=remainder, which comprises CA2-4 plus the dentate gyrus). Rates of change (slopes) of hippocampal surface variation are compared. Surface locations showing significant differences (P<.05, uncorrected for multiple comparisons) are visualized with blue to purple (for inward) and orange to red (for outward).
treatment of AD, such as donepezil, can alter hippocampal volume loss. Volumetric magnetic resonance imaging of the whole brain or medial temporal lobe structures is now being considered as a possible outcome measure in therapeutic trials for patients with AD and mild cognitive impairment.2,11 In patients with moderate stages of amnestic mild cognitive impairment, cognitive testing may provide more predictive accuracy for disease progression than measures of ventricular volume expansion or whole-brain, entorhinal cortex, or hippocampal volume loss.28 In this study, we compared rates of change in hippocampal volume as well as CA1 and subiculum subfield deformation in donepezil-treated and untreated subjects with very mild DAT with comparison subjects without dementia. The main finding of this study was that the donepezil-treated and untreated subjects with DAT did not differ in their rates of changes of these hippocampal measures. This finding suggests that whatever symptomatic benefits might have been experienced by treatment with donepezil in our subjects were not accompanied by a parallel effect on hippocampal structure. Because treatment (or no treatment) with donepezil was naturalistic in this study and not systematically evaluated using structured instruments, the degree of symptom amelioration experienced by the donepezil-treated patients is not known.

Our findings disagree with some previous reports.29,30 In a study of hippocampal volume loss over 1-year intervals in 54 patients with DAT treated with donepezil compared with historical controls, the mean annual rate of hippocampal atrophy in the donepezil-treated group (3.82%) was significantly lower than in the historical comparison group (5.04%).29 Another report described a significant effect of donepezil treatment in 67 patients with DAT in a prospective, double-blind, placebo-controlled 6-month trial.30 In our current study, changes in hippocampal volumes over time were not hypothesized but rather were assessed in an exploratory fashion. The reasons for the discrepancy of our findings with these previous findings may be the small samples in our study, which would have precluded detecting a volume difference in slopes (expressed as percentage of change per year) of less than 1.6% (the slope difference between the treated and untreated subjects in the current study was 0.64% on the left side and 0.46% on the right side of the hippocampus).

We found that the pattern of longitudinal change for the treated subjects was more similar with the pattern for the subjects without dementia than with the untreated subjects (Figure 1). Heterogeneity in the clinical populations included in the 3 studies may also be a likely explanation. Also, different methods were used to assess time-dependent changes in hippocampal structure. The methods used in the present study were developed for the specific purpose of assessing time-dependent changes in both the volume and surface variation of the hippocampus and were shown to be capable of detecting small degrees of volume loss and surface deformation.10,26

Our study has several limitations. Although a prospective randomized, placebo-controlled study is desirable, it is unattainable today because of ethical considerations. The donepezil-treated subjects with DAT were prospectively recruited into this longitudinal study of hippocampal structure along with age-matched controls, while the untreated subjects with DAT were drawn from a previously published longitudinal study of the natural course of AD. The potential confounding effect of these 2 naturalistic cohorts was dealt with by including it as a covariate in all statistical tests and examining the cohort effect in these tests. We also observed that for both baseline measures and their rates of change, the variances remained about the same whether the 2 cohorts of control subjects were combined or not. Nonetheless, clinical differences that may have influenced the capacity of the patients to respond to treatment cannot be completely excluded as confounds. Also, the numbers of subjects included in the treated and untreated DAT groups were relatively small. Larger numbers of subjects may have allowed us to detect more subtle effects of drug treatment on the measures of hippocampal structure selected as outcome measures for the study (trend observed in Figure 2). However, the measures we selected for study were adequate to detect disease progression in untreated subjects with DAT.9 Finally, we cannot exclude the possibility that measures of neuroanatomical progression other than the selected measures of hippocampal structure may have been able to detect an effect of treatment. While the amelioration of dementia symptoms in patients with DAT is a critical measure of the utility of any treatment for AD, it is also important to assess the effects of treatment on some measure that reflects the underlying disease process. This will become especially important as putative “disease-altering” treatments are developed and tested in clinical trials. Changes in neuroanatomical structures are likely to be important indicators in such studies.

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Author Contributions: Dr Csernansky takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wang, Morris, and Csernansky. Acquisition of data: Wang, Morris, and Galvin. Analysis and interpretation of data: Wang, Harms, Staggs, Xiong, Morris, Csernansky, and Galvin. Drafting of the manuscript: Wang and Galvin. Critical revision of the manuscript for important intellectual content: Wang, Harms, Staggs, Xiong, Morris, Csernansky, and Galvin. Statistical analysis: Wang, Harms, Staggs, and Xiong. Obtained funding: Morris and Csernansky. Administrative, technical, and material support: Staggs, Morris, and Csernansky. Study supervision: Wang and Galvin.

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REFERENCES


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