Entorhinal cortex atrophy differentiates Parkinson's disease patients with and without dementia

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Abstract

Background—Volumetric measures of mesial temporal lobe structures on magnetic resonance imaging scans recently have been explored as potential biomarkers of dementia in patients with Parkinson's disease, with investigations primarily focused on hippocampal volume. Both in vivo magnetic resonance imaging and post-mortem tissue studies in Alzheimer's disease, however, demonstrate that the entorhinal cortex is involved earlier in disease-related pathology than the hippocampus. The entorhinal cortex, a region integral in declarative memory function, projects multimodal sensory information to the hippocampus via the perforant path. In Parkinson's disease, entorhinal cortex atrophy as measured on magnetic resonance imaging, however, has received less attention compared to hippocampal atrophy.

Methods—We compared entorhinal cortex and hippocampal atrophy in 12 subjects with Parkinson's disease dementia including memory impairment, 14 Parkinson's disease subjects with normal cognition, and 14 healthy controls with normal cognition, using manual segmentation methods on magnetic resonance imaging scans.

Results—While hippocampal volumes were similar in the two Parkinson's disease cognitive groups, entorhinal cortex volumes were substantially smaller in the demented Parkinson's disease subjects compared the cognitively normal Parkinson's disease subjects (p<0.05). In addition, normalized entorhinal cortex and hippocampal volumes for right and left hemispheres were significantly lower in the demented Parkinson's disease group compared to healthy controls.

Conclusions—Our findings suggest that entorhinal cortex atrophy differentiates demented and cognitively normal Parkinson's disease subjects, in contrast to hippocampal atrophy. Thus, entorhinal cortex atrophy on magnetic resonance imaging may be a potential biomarker for dementia in Parkinson's disease, particularly in the setting of memory impairment.
Keywords
Parkinson's disease; cognition; magnetic resonance imaging; mesial temporal lobe; Alzheimer's disease

Introduction
Dementia is a frequent and disabling outcome in the course of Parkinson's disease (PD) and greatly affects morbidity, mortality, and quality of life. Longitudinal studies demonstrate that about 80% of PD patients will develop dementia (PDD). Thus, it is critical to identify biomarkers associated with the development of PDD.

Structural magnetic resonance imaging (MRI) provides an in vivo method for the assessment of neuroanatomical substrates of dementia and associated neuropathological changes. For example, volumetric MRI has emerged as an important in vivo marker of Alzheimer's disease (AD) and amnestic mild cognitive impairment (MCI), with studies demonstrating hippocampal and entorhinal cortex atrophy on MRI in these patients. These mesial temporal lobe regions are important in declarative memory function and the entorhinal cortex, which projects to the hippocampus via the perforant pathway, is particularly vulnerable to early AD-associated neuropathology. Atrophy in these regions on MRI correlates with histological changes found in post-mortem AD cases. MRI-derived volume loss in specific brain regions may also serve as a marker of incipient dementia, and entorhinal cortex atrophy on baseline MRI may better predict conversion to AD in those with amnestic MCI or cognitive complaints. Furthermore, revised criteria for AD and MCI now incorporate MRI evidence of mesial temporal lobe atrophy into the diagnostic algorithms.

Hippocampal atrophy on MRI also occurs in PD dementia, though to a lesser degree than in AD. Non-demented PD patients also demonstrate hippocampal atrophy on MRI, though not in all studies. Variable results in studies of non-demented PD patients may occur because some of these patients have normal cognition but others have mild cognitive impairment (i.e., cognitively impaired but not meeting dementia criteria). Thus, “non-demented” is not necessarily synonymous with “cognitively normal.” Overall, the presence of hippocampal atrophy in demented and non-demented PD patients suggests that it is not a specific marker for PDD.

Entorhinal cortex atrophy on MRI may be a better marker for dementia in PD since this region, which projects to the hippocampus, may be pathologically affected earlier than the hippocampus. Indeed, post-mortem PDD cases exhibit neuropathological changes in this structure, though the relative contributions from Lewy bodies, Lewy neurites, amyloid plaques, and neurofibrillary tangles remain controversial. Entorhinal cortex atrophy on MRI may reflect these underlying neuropathological changes. Only one volumetric MRI study has investigated entorhinal cortex atrophy in PDD and non-demented PD subjects. Entorhinal cortex volumes were significantly smaller in the PDD group compared to healthy controls, while the PDD group had smaller mean entorhinal cortex volumes compared to the non-demented PD group, this difference was not significant on post-hoc comparisons. Since differences in methodologies and clinical groups may influence study results, entorhinal cortex atrophy on MRI warrants further investigation as an in vivo marker that can distinguish PDD patients, particularly those with memory impairment, from cognitively intact PD patients.

Our study aim was to examine entorhinal cortex and hippocampal atrophy using manual segmentation in two highly contrasting PD cognitive groups (i.e., subjects categorized as...
PDD and PD with normal cognition [PD-NC]), compared to healthy controls (HC) with normal cognition. Although several semi-automated MRI techniques to detect brain atrophy are available, small areas with individual variability such as entorhinal cortex are best studied using manual segmentation. We hypothesized that entorhinal cortex volumes would not only distinguish PDD from HC subjects, but also would differentiate PDD from PD-NC subjects, in contrast to hippocampal volumes.

**Methods**

**Subjects**

Forty subjects (12 PDD, 14 PD-NC, and 14 HC) were studied. PD subjects were recruited from the Rush University Movement Disorders clinic and examined by a movement disorders neurologist (JGG). The PD subjects met United Kingdom Parkinson's Disease Society Brain Bank criteria. Atypical or secondary forms of parkinsonism (e.g., multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, dementia with Lewy bodies [DLB] or parkinsonism due to neuroleptic exposure, cerebrovascular disease, or known structural causes) were excluded. PD subjects were matched by age (+/- 3 years), gender, and education (+/- 3 years) to controls. Controls were recruited from the community as part of an ongoing, longitudinal neuroimaging study of aging and AD. As part of this study, the controls underwent evaluations including medical history, neurological examination, neuropsychological testing, blood tests, and MRI scans; in addition, these controls have been followed with annual clinical evaluations and MRI scans for over 10 years. Controls had normal neurologic examinations, normal cognition, and Mini-mental State Examination (MMSE) scores ≥28. Controls were used solely as a reference for the neuroimaging comparisons across subject groups, not for comparisons of neuropsychological data. Exclusionary criteria for participants included: contraindications to MRI (e.g., cardiac pacemaker/defibrillator, surgical clips, foreign metallic implants); major depression; severe or unstable medical conditions; neurosurgery; seizures or other conditions that could cause cognitive impairment; or anticholinergic medications. Informed consent was obtained from all participants according to the Institutional Review Board rules of Rush University Medical Center, Chicago, IL.

**Clinical and neuropsychological evaluations of PD subjects**

The clinical evaluation of PD subjects included: assessments of demographic and disease-related variables, Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor scores, Hoehn and Yahr stage, and PD medications converted to levodopa equivalent doses (LED). The neuropsychological evaluation assessed 4 cognitive domains (attention/executive function, language, memory, and visuospatial function) and depression. Raw scores for the cognitive tests were transformed to z-scores based on normative data. Cognitive domain scores were calculated by averaging the z-scores for the neuropsychological tests within specific cognitive domains: 1) declarative memory - Consortium to Establish a Registry for Alzheimer's disease (CERAD) word list trials, delayed recall, 2) attention/executive function - Digit span, Symbol Digit Modalities Test, Category naming of animals, 3) language - 15-item Boston Naming Test, Similarieties, and 4) visuospatial function - 15-item Judgment of Line Orientation, intersecting pentagon drawing item from the MMSE using an ordinal 6-point scale. PDD or PD-NC diagnoses were determined in a consensus conference (neurologist [JGG], neuropsychologists [GTS, BB]) incorporating Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria for PD dementia to include memory impairment, neuropsychological test performance, semi-structured interview with the subject and/or caregiver, and clinical impression.
MRI protocol and processing

MR images were acquired on a 1.5 Tesla General Electric Signa scanner, using the manufacturer's 3D Fourier transform spoiled gradient recalled pulse (SPGR) sequence with the following acquisition parameters: 124 contiguous coronal images, 1.6 mm thick, matrix=256x192, field of view=22 cm, TR/TE=33.3/7 msec, flip angle=35°, signals averaged=1.

Entorhinal cortex and hippocampal volumes were manually segmented using Analyze software (Mayo Clinic Foundation, Rochester, MN) with each hemisphere computed separately from coronal slices oriented perpendicularly to the long axis of the hippocampal formation (Figure 1). Entorhinal cortex tracings began with the first section in which the gyrus ambiens, amygdala, and white matter of the parahippocampal gyrus were visible and ended two slices prior to where the lateral geniculate nucleus first appeared. The superomedial border rostrally was the sulcus semiamnularis and caudally, the subiculum; the shoulder of the collateral sulcus was used as the ventrolateral border. Hippocampal volume included the fimbria, dentate gyrus, hippocampus proper, and subiculum, starting with the slice where the hippocampus could be clearly differentiated from the amygdala by the alveus and ending immediately rostral to the full appearance of the fornix.

To correct for individual differences in brain size, volumes for each region of interest were divided by total intracranial volume (i.e., normalized). Intracranial volume was computed by tracing the inner table of the cranium in consecutive, sagittally-formatted, 5-mm sections spanning the entire brain with a straight line drawn from the inner surface of the clivus to the occipital bone, at the level of the foramen magnum. Normalized volumes were determined using the following formula: absolute volume (mm$^3$/intracranial volume (mm$^3$) × 1000.

Raters (JGG and TRS) were trained to be within 95% of each other and of LdeT-M; intra-rater correlation coefficients for entorhinal cortex and hippocampal volumes were high for TRS and for JGG (0.98 and 0.99, respectively). Tracings were checked, slice-by-slice, by LdeT-M. Raters were blinded to participant identity and diagnosis.

Statistical analyses

Statistical analyses were performed using SPSS 18.0 (PASW 18, Chicago, IL). Demographic variables were compared across the 3 groups using one-way analysis of variance (ANOVA) and post-hoc comparisons with Scheffe tests. Gender differences were compared using Chi-square tests. Disease-related characteristics were compared using independent t-tests for continuous variables or non-parametric tests for ordinal variables. To assess group and hemispheric differences in entorhinal cortex and hippocampal volumes in the 3 groups, repeated measure ANOVAs were done separately for each region of interest, with groups as the between-subject factor and hemispheres as the within-subject factor, followed by post-hoc comparisons with Scheffe tests. Relationships between entorhinal cortex or hippocampal volumes and cognitive domain scores were examined using linear regressions, with region of interest as the dependent variable and cognitive domain z-scores as predictor variables. Statistical significance was set at p<0.05.

Results

Clinical features (Table 1)

There were no significant differences among the PDD, PD-NC or HC groups in age (p=0.129), gender (p=0.206), or education (p=0.444). There was a significant group effect for MMSE scores (F [2, 37] = 38.8, p<0.0001) with lower scores in the PDD group. Post-hoc comparisons for MMSE scores revealed that both the PD-NC and HC groups differed significantly from the PDD group (p<0.0001), but not from each other. PDD subjects had
slightly longer disease durations than PD-NC subjects (9.0 +/- 3.3 vs. 12.5 +/- 5.3 years, p=0.051). Demented PD subjects had worse motor severity as measured by Hoehn and Yahr stage (p=0.012), but differences between PDD and PD-NC for UPDRS Part III total motor scores and LEDDs were not significant; neither were Hamilton depression rating scores which were low overall, reflecting a non-depressed PD cohort.

**Neuropsychological features of the PD subjects (Table 2)**

There were significant differences on raw neuropsychological test scores with worse cognitive performance in PDD subjects, compared to the PD-NC subjects. As often found in PD, performance was better on recognition tasks than on free recall; however, the PDD subjects performed significantly worse on both tasks compared to PD-NC subjects. Cognitive domain z-scores for memory as well as attention/executive function, language, and visuospatial function were significantly worse in PDD subjects compared to PD-NC subjects.

**Entorhinal cortex and hippocampal volume measurements (Figure 2, Supplemental Table)**

Two factor repeated measures ANOVA revealed a significant effect for group (F [2, 37] = 13.11, p<0.0001) for the normalized entorhinal cortex volumes. On post-hoc comparisons, the PDD group had the smallest entorhinal cortex volumes and differed significantly from not only the HCs (p<0.0001), but also the PD-NCs (p=0.04). PD-NCs differed slightly, but significantly, from the HCs (p=0.049). There was also a significant effect for hemisphere (F [1, 37] = 6.73, p=0.014) due to larger right hemisphere volumes in all groups. However, there was no significant interaction between group and hemisphere (F [2, 37] = 0.764).

For the normalized hippocampal volumes, there were also significant group (F [2, 37] = 9.57, p<0.0001) effects, but in contrast to the entorhinal cortex volumes, post-hoc comparisons did not reveal significant differences between PDD and PD-NC subjects (p=0.173). However, there were significant differences between PDD and HCs (p<0.0001). Differences between PD-NC and HC groups were of borderline significance (p=0.053). Similar to the entorhinal cortex volumes, there were significant hemisphere effects due to larger right hemispheric volumes (F [1, 37] = 10.90, p=0.002), but no significant interaction between group and hemisphere (F [2, 37] = 2.47, p=0.098).

We also performed separate analyses of these two regions using age as a co-variate. Age was not significant in the model (entorhinal cortex, F [1, 36]=1.38, p=0.247 and hippocampus F [1, 36]=0.035, p=0.852). Controlling for age, volumetric results were similar to our original observations, such that the PDD group had significantly smaller entorhinal cortex volumes than the PD-NCs (p=0.04) and HCs (p<0.0001) and significantly smaller hippocampal volumes than the HCs (p<0.0001) but not the PD-NC group (p=0.09).

**Relationship of volumes to cognitive domain z-scores in PD subjects**

We performed linear regression analyses with normalized total entorhinal cortex and hippocampal volumes as dependent variables and cognitive domain z-scores (i.e., memory, attention/executive function, language, and visuospatial) as predictors. Models were run separately for entorhinal cortex and hippocampal volumes. Since we did not find any group by hemisphere effects on the repeated measure ANOVA analyses, normalized total volumes for the regions of interest were used in the linear regression analyses. Of the 4 cognitive domain z-scores entered in the models, only the memory domain z-score was a significant predictor of the volume. Memory domain z-scores accounted for 21% of the variance in normalized total entorhinal cortex volume (R²=0.21, F [1, 23] = 6.06, β = 0.457, p=0.02)
and 18% of the variance in normalized total hippocampal volume (R² = 0.18, F [1, 23] = 5.41, β = 0.427, p = 0.03).

**Discussion**

The main finding of our study is that entorhinal cortex volumes on MRI are significantly smaller in PDD subjects compared to PD-NC subjects, whereas hippocampal volumes are not. These findings suggest that MRI-derived entorhinal cortex atrophy may provide an *in vivo* marker of dementia in PD. PDD subjects also had smaller entorhinal cortex and hippocampal volumes compared to HCs. We found larger right-side entorhinal cortex and hippocampal volumes in the PD-NC and HC groups; similar hemispheric asymmetry has been described before in volumetric MRI studies of the hippocampus. For PDD, however, hemispheric asymmetry (larger right side) was seen only in the entorhinal cortex, thereby suggesting that right-sided hippocampal dominance diminishes as dementia ensues. Furthermore, memory, but not non-memory, z-scores significantly predicted the regions of interest, thereby supporting a functional role for mesial temporal lobe structures.

Entorhinal cortex atrophy in PD may be more specific for dementia-related pathology including possible dual AD and PD pathology, particularly in the setting of memory deficits. We classified PDD subjects by DSM-IV criteria, which require impaired memory along with deficits in at least one other cognitive domain, to specifically assess the relationship between mesial temporal lobe regions of interest and memory function in PD. Not all PDD subjects, however, have memory impairment, and PDD criteria proposed by the Movement Disorder Society (MDS) allow impairment in non-memory domains. If these criteria were applied to our PDD cohort, all of our PD subjects with dementia would remain classified as demented, with memory being one of the impaired cognitive domains. While the presence of memory impairment in our PDD subjects may potentially reflect dual PD and AD pathology in these cases, future clinico-pathological studies will be needed to evaluate the underlying neuropathological contributions to PDD and relationships between neuroimaging and neuropathology. Few studies have investigated neuropathological correlates of MRI-derived mesial temporal lobe atrophy in Lewy body disorders. At present, the neuropathology of PDD remains heterogeneous with contributions from cortical and limbic Lewy bodies and Lewy neurites, brainstem degeneration, and amyloid plaques and neurofibrillary tangles.

Our findings of smaller entorhinal cortex volumes in PDD compared to PD-NC differ from the previous study examining entorhinal cortex volumes in PD by Kenny et al. and may be due to several methodological differences. Our studies utilized different inclusion/exclusion criteria and definitions of PDD. We matched our subject groups for age, gender, and education, whereas the other study did not. Manual segmentation protocols for measuring entorhinal cortex also differed in the neuroanatomical boundaries used and number of imaging slices included.

In addition, there were several differences in clinical features of our PD cohorts. Mean MMSE scores for the cognitively intact PD subjects were higher in our cohort (28.9 +/- 1.1 vs. 26.7 +/- 1.8). Although the MMSE may not be a very sensitive test for PDD or PD-MCI, the higher MMSE scores in our non-demented PD cohort, along with their performance on detailed neuropsychological testing, support their diagnosis as cognitively normal PD and diminish the likelihood that they really have “mild cognitive impairment.” Furthermore, disease durations for the PD groups differed between the two studies. PD subjects in our cohort had long disease durations, ranging from 6-17 years, whereas Kenny et al reported durations as short as 1 year in demented and non-demented PD subjects. Our long PD duration solidifies our diagnostic confidence for PD. In addition, dementia was a
later-onset complication in our PDD subjects, occurring after a mean of 10.5 years (+/- 5.0). These points underscore often subtle, clinical differences between non-demented PD groups (cognitively normal vs. mild cognitive impairment but not demented) and between PDD and DLB subjects that may be associated with heterogeneous neuroimaging and neuropathology findings.

The presence of hippocampal atrophy across the cognitive spectrum in PD is supported by other MRI studies, and our study. Thus, hippocampal atrophy in PD may be the consequence of factors other than dementia-specific pathology including nigrostriatal dopaminergic depletion, disruption of noradrenergic or serotonergic projections to limbic structures, or concomitant, subsyndromal mood deficits. For example, infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into rodent substantia nigra pars compacta (SNPC) led not only to degeneration of nigrostriatal dopaminergic neurons, but also to cell loss in the hippocampal CA1 region; neuroinflammation with microglial activation was detected in the SNPC, hippocampus, and amygdala. Also, degeneration of the locus ceruleus and raphe nuclei occurs in PD and may disrupt noradrenergic and serotonergic projections to limbic structures; clinically, this may manifest as anxiety and depression, which often present as subsyndromal disorders and predate PD-related motor symptoms. While our PD subjects were not depressed and did not have a history of major depressive episodes, we cannot fully exclude the occurrence of minor or subclinical depressive symptoms at some point in their lives. Hippocampal atrophy on MRI in depressed patients (without PD) has been attributed to hypothalamic-pituitary-adrenal axis dysfunction. Indeed, hippocampal atrophy may be a downstream consequence of PD itself.

Our study’s strengths include a well-defined PD cohort with detailed motor and cognitive characterizations, clinical diagnoses by Movement Disorders specialists, and cognitive diagnoses by consensus conference with clinicians and neuropsychologists. PDD and PD-NC subjects had similar disease durations and LEDDs and were carefully matched by age, education, and gender to healthy controls. Furthermore, volumetric analyses were performed in a blinded fashion, demonstrated good reliability, and utilized region of interest protocols developed at our center. Limitations include the small sample size, tertiary clinic referral pattern, and lack of clinico-pathological correlations to date. Manual segmentation techniques may be time consuming and operator dependent; while these features may limit its use in large scale, longitudinal studies, manual segmentation is well-suited for studying small brain regions such as the entorhinal cortex and for smaller-scale, hypothesis-generating studies.

We conclude that entorhinal cortex volumes on MRI are significantly smaller in PDD than PD-NC, whereas hippocampal volumes are not. Thus, entorhinal cortex atrophy on MRI may be a better in vivo marker for dementia in PD. These findings may shift our focus from the hippocampus to structures such as entorhinal cortex that are affected earlier in dementia and are more specific to memory deficits, possibly representing dual PD and AD pathologies. Studies with larger patient cohorts, detailed cognitive evaluations, cerebrospinal fluid biomarkers of beta-amyloid and tau proteins, and ultimately, post-mortem tissue will further our understanding of role of the entorhinal cortex in PD dementia and contributions from different pathologies. Prospective longitudinal studies that correlate clinical status and entorhinal cortex volumes for non-demented PD patients who convert to PDD will let us determine whether selective entorhinal cortex atrophy is a marker of incipient dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Leyla deToledo-Morrell, PhD:

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Other: none

References


Figure 1.
A coronal slice on a MRI scan illustrating the segmentation of the entorhinal cortex (outlined, right side) and Hippocampus (outlined, left side).
Figure 2.
Mean normalized volumes for A) entorhinal cortex and B) hippocampus. Abbreviations: HC, healthy controls; PD-NC, PD with normal cognition; PDD, PD dementia. Hemispheric volumes (absolute volume in mm$^3$/intracranial volume in mm$^3$ x 1000) are depicted (left, white; right, hatched). Vertical bars represent the standard error of the mean. Significant differences: + PD-NC vs. HC (p=0.049, entorhinal cortex; p=0.053, hippocampus); *PDD vs. HC (p<0.0001, entorhinal cortex; p<0.0001, hippocampus), § PDD vs. PD-NC (p=0.04, entorhinal cortex).
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Neuropsychological data for PD subjects

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</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.78 (1.11)</td>
<td>-2.33 (0.81)</td>
<td>0.000</td>
</tr>
<tr>
<td>Attention/Executive function</td>
<td>0.45 (0.79)</td>
<td>-1.09 (0.57)</td>
<td>0.000</td>
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<tr>
<td>Language</td>
<td>0.69 (0.63)</td>
<td>-1.6 (0.93)</td>
<td>0.000</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>0.02 (0.92)</td>
<td>-4.10 (3.30)</td>
<td>0.001</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Raw test scores</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD Word List trials</td>
<td>22.0 (4.1)</td>
<td>11.4 (2.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>CERAD Delayed Recall</td>
<td>7.5 (1.9)</td>
<td>1.9 (1.8)</td>
<td>0.000</td>
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<tr>
<td>CERAD Recognition</td>
<td>9.5 (0.9)</td>
<td>6.1 (2.3)</td>
<td>0.000</td>
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<tr>
<td>Digits forwards</td>
<td>10.1 (2.6)</td>
<td>9.3 (2.0)</td>
<td>0.391</td>
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<tr>
<td>Digits backwards</td>
<td>6.4 (1.9)</td>
<td>4.1 (1.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test</td>
<td>45.8 (10.3)</td>
<td>10.0 (6.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>Animal naming</td>
<td>20.1 (3.9)</td>
<td>10.2 (2.6)</td>
<td>0.000</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>14.6 (0.7)</td>
<td>11.8 (2.0)</td>
<td>0.001</td>
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<tr>
<td>Similarities</td>
<td>23.7 (5.4)</td>
<td>11.9 (6.5)</td>
<td>0.000</td>
</tr>
<tr>
<td>Judgment of Line Orientation</td>
<td>12.2 (2.6)</td>
<td>6.5 (3.6)</td>
<td>0.011</td>
</tr>
<tr>
<td>Pentagons, median (range)</td>
<td>6 (5-6)</td>
<td>4 (1-6)</td>
<td>0.000</td>
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</tbody>
</table>

Data presented as mean (SD) unless otherwise noted. Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease.