Brain atrophy associated with baseline and longitudinal measures of cognition

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Abstract

The overall goal was to identify patterns of brain atrophy associated with cognitive impairment and future cognitive decline in non-demented elders. Seventy-one participants were studied with structural MRI and neuropsychological testing at baseline and 1 year follow-up. Deformation-based morphometry was used to examine the relationship between regional baseline brain tissue volume with baseline and longitudinal measures of delayed verbal memory, semantic memory, and executive function. Smaller right hippocampal and entorhinal cortex (ERC) volumes at baseline were associated with worse delayed verbal memory performance at baseline while smaller left ERC volume was associated with greater longitudinal decline. Smaller left superior temporal cortex at baseline was associated with worse semantic memory at baseline, while smaller left temporal white and gray matter volumes were associated with greater semantic memory decline. Increased CSF and smaller frontal lobe volumes were associated with impaired executive function at baseline and greater longitudinal executive decline. These findings suggest that baseline volumes of prefrontal and temporal regions may underlie continuing cognitive decline due to aging, pathology, or both in non-demented elderly individuals.

Keywords

deformation morphometry; longitudinal; brain; MRI; cognition; memory; executive function

1. Introduction

Progressive loss of cognitive abilities in the elderly due to normal aging, Alzheimer’s disease (AD) and other neurodegenerative diseases cause huge personal, social, and health
burdens. Most imaging research on the transitional state between normal aging and AD has focused on deficits in episodic memory. Deficits in other cognitive domains, such as executive function (Perry and Hodges, 1999) and semantic memory (Lambon Ralph, et al., 1997), have also been noted in patients with early AD. This suggests that executive (Houston, et al., 2005) and semantic memory (Adlam, et al., 2006) dysfunction might also be useful markers of incipient AD, and one can speculate that AD may cause brain tissue loss in the areas underlying these functions. Furthermore, it would appear reasonable to speculate that the impairments of memory, language, and executive function are either additive or more than additive in leading to overall functional decline and dementia. Therefore, it is important to examine the relationship between brain tissue volume and executive and memory within an aging but non-demented population.

Several studies using magnetic resonance imaging (MRI) have shown that the presence of brain atrophy in healthy elderly and non-demented impaired subjects at baseline can predict future conversion to dementia (de Leon, et al., 1993; Jack, et al., 1999; Killiany, et al., 2000). However, most studies focused on memory and employed region of interest (ROI) approaches, which limits the number of brain regions that can realistically be studied. Furthermore, these ROI volume analyses are sensitive at poorly defined anatomic boundaries to delineation errors, which can be of greater magnitude than group regional volume differences. These limitations can potentially be overcome by using automated whole-brain analysis methods such as voxel-based morphometry (VBM) (Ashburner and Friston, 2000) and deformation based morphometry (DBM) (Studholme, et al., 2004), which can potentially characterize the spatial pattern of brain atrophy associated with future cognitive decline. Longitudinal studies have used VBM to compare baseline brain atrophy between groups of subjects with different rates of disease progression, for example AD converters vs. non-converters (Hamalainen, et al., 2007; Whitwell, et al., 2007). However, there has not been a focus on the spatial pattern of brain atrophy that can “predict” future decline in specific cognitive domains.

It is generally accepted that neurodegeneration progresses in the brain for years prior to the development of symptoms. As treatments that may slow the neurodegenerative process due to AD or other causes are developed, it becomes increasingly important to develop diagnostic techniques that identify non-demented subjects who are at future risk for cognitive decline and ultimate conversion to dementia. Cognitive decline among non-demented elders can be due to aging, pathology, or both. Numerous classifications of mild cognitive impairment (MCI) have been developed with the aim of identifying elders at greatest risk of cognitive decline. Some systems attempt to measure age-related decline (e.g., ARCD: age related cognitive decline), while others attempt to measure pathological decline (e.g., AAMI: age associated memory impairment, A-MCI: Mayo amnestic mild cognitive impairment) (American Psychiatric Association, 2000; Crook, et al., 1986; Ebly, et al., 1995; Petersen, et al., 1999). Previous large-scale studies have found that current classifications of MCI fail to identify many patients at high risk of progressing to dementia, such as those with global cognitive deficits (Matthews, et al., 2008; Palmer, et al., 2008).

Therefore, we undertook a prospective study of non-demented elders. Non-demented elders are a heterogeneous group, comprised of normal people undergoing healthy aging, normal people with asymptomatic pathology (such as Alzheimer’s Disease), people with cognitive impairment due to age, and those with cognitive impairment due to pathology. Some non-demented elders will be cognitively stable (i.e., no change in cognition over time), while cognition in others will get better or worse over time (Palmer, et al., 2002). We enrolled both cognitively normal and cognitively impaired elders, since we cannot identify pathology in-vivo or identify stable vs. declining elders in either group at baseline. Although some of our patients could be classified as some version of MCI, we did not group our subjects since
previous work showed that MCI diagnostic criteria failed to predict decline in many cases (Matthews, et al., 2008; Palmer, et al., 2008). Our aim was to characterize the spatial pattern of baseline brain tissue volume associated with baseline cognition and longitudinal cognitive decline. Spatial patterns of brain tissue volume associated with longitudinal cognitive decline may prove useful for early identification of both cognitively normal and cognitively impaired elders that are cognitively unstable, regardless of etiology. We examined the cognitive domains of verbal memory, semantic memory (i.e., object naming ability), and executive function. There are well established relationships between brain integrity and cognition; medial temporal lobe with delayed memory, temporal lobe with semantic memory, and frontal lobe with executive function, and we hypothesized that baseline atrophy in these regions would be associated with worse baseline cognition and greater continuing cognitive decline.

2. Methods

2.1 Participants

Seventy-one participants, recruited by advertisements in the community or referred by one of several memory clinics in the San Francisco Bay Area, including the Memory Disorders Clinic at the San Francisco Veterans Affairs Medical Center, the Memory and Aging Center at the University of California, San Francisco, and the Memory Disorders Clinic at the California Pacific Medical Center, were examined. Study procedures include a neurological exam and structural MRI at baseline, and comprehensive neuropsychological testing at baseline and 1 year followup. All participants gave written informed consent, approved by review boards of the University of California San Francisco and the San Francisco VA Medical Center.

The mean subject age was 73 ± 8 years (range 50–92), with education of 17 ± 3 years, and MMSE of 28.5 ± 1.8 (range 23–30). Twenty-five subjects had a clinical dementia rating (CDR, (Morris, 1993) of 0.0 (12/25 male, 24 Caucasian, 1 Polynesian, age 60–87 yrs, MMSE 24–30), and the remaining forty-six subjects had a CDR of 0.5 (27/46 male, 44 Caucasian, 2 Asian, age 50–92 yrs, MMSE 23–30). We deliberately included participants who ranged along the continuum from healthy aging to impaired but not demented, in order to capture stable, slow, and rapid declines in cognition for regression analyses. Cognitive decline in these participants can be due to aging, pathology, or both. Moreover, since we cannot identify pathology in-vivo in either the CDR 0.0 or 0.5 group, we included all participants in the analysis.

2.2 Neuropsychological evaluation

Participants underwent comprehensive neuropsychological testing at entry to the study (baseline) and again after an average of 1.1 ± 0.2 years. We created a composite delayed verbal memory score from the following California Verbal Learning Test (Delis, et al., 2000) measures: immediate learning trial 5, short- and long-delayed free recall. To examine the participants’ semantic memory, we used the object-naming test from the Spanish and English Neuropsychological Assessment Scales (Mungas, et al., 2004). We created a composite executive function score from the verbal fluency, Stroop, and Trail-making tests of the Delis-Kaplan Executive Function System (D-KEFS) (Delis, et al., 2001). Category fluency was not included in the verbal fluency measures, since it is a better measure of semantic memory than executive function. The composite and object naming scores were scaled to have a mean of 100 and a standard deviation of 15 within a cognitively normal sample (Mungas, et al., 2003), with lower scores indexing greater impairment. Annualized change scores were computed as (Score_{follow-up} − Score_{baseline})/inter-test interval in years, where negative annualized change scores denote cognitive decline.
Nine of the 25 CDR 0 participants scored below the 100 on the cognitive composite measures; 2 on the composite memory measure, 3 on the composite executive measure, and an additional 4 on both memory and executive function. These participants may have pathology, but lack insight into their problems, or may not have knowledgeable informants, leading to a CDR=0 despite poor cognitive testing. Only thirty-six of the 46 CDR 0.5 participants scored below 100 on the cognitive composite measures; 14 on memory, 5 on executive function, and 17 on both. The remaining 10 CDR 0.5 participants scored highly on the cognitive composite measures.

2.3 Magnetic resonance imaging (MRI)
Coronal T1-weighted images were acquired on a 1.5 Tesla MR scanner (Vision, Siemens Medical Systems, Iselin NJ) using Magnetization Prepared Rapid Acquisition Gradient Echo (TR/TI/TE = 9/300/4 ms, 1×1 mm² in-plane resolution, 1.5 mm slabs) orthogonal to the long axis of the hippocampus. Images were acquired within an average of 0±12 days of the baseline neuropsychological assessment (range 0–56 days).

2.4 Creation of maps of baseline tissue volume
A B-Spline Free Form deformation algorithm driven by normalized mutual information (Studholme, et al., 2001) was used to register individual scans to a 72-year old female reference atlas, chosen to retain the finest anatomical structures for accurate registration (Studholme, et al., 2004). The Jacobian determinant of this transformation was computed at each voxel (resolution 1×1×1.5mm), giving the pattern of volume change required to force the individual anatomy to conform to the reference. An intensity consistent filtering approach (Studholme, et al., 2003) was then applied to create baseline tissue volume maps, where the value at each voxel represents the tissue volume relative to the reference (e.g., a voxel value of 1.15 denotes a volume 15% greater than the reference voxel).

2.5 Statistical analysis
Statistical measures were applied to locate voxels within the maps where baseline volume was associated with longitudinal changes in cognition. Using all subjects, we performed multiple regression analyses with the following continuous independent variables: annualized change in cognitive domain score, baseline cognitive domain score, age, and head size (defined as the average Jacobian determinant within the intracranial vault delineated on the reference anatomy). Separate regressions were computed for the delayed verbal memory, object naming, and executive functioning domains. For all analyses, the baseline deformation maps were dependent variables. Permutation testing and nonstationary random field theory cluster analysis were used to correct the statistical maps for multiple comparisons. (Nichols and Holmes, 2002; Worsley, et al., 2002). Statistical maps were overlaid on the spatially normalized average MRI (N=71), and displayed using the Rview software (http://rview.colin-studholme.net). The underlying structure (e.g., hippocampus, inferior longitudinal fasciculus) and tissue composition (e.g., WM) of statistically significant regions was inferred from the spatially normalized average MRI, which is less influenced by noise than the individual images, thus increasing our confidence in identification of brain anatomy.

3. Results
3.1 Neuropsychological data
These results are summarized in Table 1. The delayed verbal memory and executive function scores significantly declined between baseline and followup. There was no significant difference in semantic memory functioning between baseline and followup,
although some subjects did show decline, as reflected in the ranges shown in Table 1. In comparison to “normal” composite scores (100 ± 15), the sample was not impaired on any measure at baseline (all \( p > 0.4 \)), and scored significantly higher than “normal” on composite tests of semantic memory \( (p < 0.001) \) and executive function \( (p = 0.03) \). The change scores passed tests for normality and were thus valid continuous variables of main interest in the regression analyses. During the interval between baseline and the 1-year follow-up, six participants declined from CDR 0.0 to 0.5; ten declined from CDR 0.5 to 1.0, one declined from CDR 0.5 to 2.0, while six subjects improved from CDR 0.5 to 0.0.

3.2 Deformation morphometry, baseline cognition, and continuing cognitive decline

Figure 1 shows T-statistic maps thresholded at \(|T| > 2.0\) overlaid on the spatially normalized average MRI. On the left, voxels shaded red and yellow show regions where lower baseline cognitive scores are associated with smaller baseline tissue volumes, and blue with larger baseline tissue volumes. On the right, voxels shaded red and yellow show regions where greater rates of cognitive decline are associated with smaller baseline tissue volumes, and blue with larger baseline tissue volumes. Cluster statistics are shown in Table 2, and major findings are described below.

3.2.1 Delayed verbal memory—Multiple comparison corrected cluster analysis revealed a cluster composed of voxels with strongly positive associations (i.e., smaller volumes associated with lower/worse cognitive scores) between baseline right hippocampal and entorhinal cortex (ERC) volume and baseline delayed verbal memory (Figure 1, left top panel, green contour). Smaller left hippocampus and ERC were also associated with decreased delayed verbal memory scores, but did not survive correction for multiple comparisons. The blue contour in the top right panel of Figure 1 shows a cluster composed of voxels where smaller baseline left ERC was associated with greater decline in delayed verbal memory over 1 year. There were also two significant clusters composed of voxels with positive associations located in the cerebellum. Using the nomenclature of Pierson et al., these clusters were located in the right superior posterior lobe lateral to the midline and left lateral superior posterior lobe (Pierson, et al., 2002).

3.2.2 Semantic memory (object naming)—Multiple comparison corrected cluster analysis revealed a cluster composed of voxels with strongly positive associations between baseline left superior temporal cortex and baseline object naming (Figure 1, left middle panel, green contour). The green contour in the right middle panel of Figure 1 shows a cluster composed of voxels where smaller left temporal white and gray matter was associated with greater decline in object naming over 1 year. A cluster of voxels associating smaller right inferior posterior cerebellar volumes with greater object naming decline was also observed, as well as two clusters associating greater declines in object naming with larger CSF volumes proximal to the cerebellum (not shown).

3.2.3 Executive function—Multiple comparison corrected cluster analysis revealed several significant clusters of voxels within the frontal lobe. The red, pink, and yellow contours in the left bottom panel of Figure 1 encompass regions where worse baseline executive function scores were associated with larger volumes of sulcal CSF adjacent to the posterior frontal and temporal lobes and larger lateral ventricular CSF volumes posteriorly. The green contour highlights a significant cluster extending superiorly (not shown in this axial view) associating smaller lateral posterior frontal gray and white matter with worse executive function; an additional cluster located deep in the left anterior frontal lobe encompassing white matter of the anterior region of the corona radiata was also observed (blue contour). The blue and green contours in the right bottom panel of Figure 1 encompass...
regions where smaller baseline dorsolateral prefrontal white matter volumes were associated with greater declines in executive function.

3.2.4 Associations with Age—Because associations with age were similar in all models, only age associations from the model with delayed memory are reported. Greater age at baseline was related to smaller tissue volumes in a large connected region that included bilateral anterior frontal lobe (primarily white matter, although gray matter was also affected), subcortical structures (especially thalamus), and bilateral anterior temporal lobes. Smaller tissue volumes in a region of right frontal/parietal white and gray matter (adjacent to the central sulcus) were also related to greater age at baseline. Both clusters were significant ($p<0.0002$), and within these regions tissue volumes were decreased an average of 1.5%/year of additional age (average of regression coefficients within the significant region). These regions are outlined by the red and pink contours in Figure 2. Greater age at baseline was also related to larger CSF volumes in several regions, also shown in Figure 2, outlined in green. These clusters were significant (all $p<0.03$), and within these regions CSF volumes were increased an average of 1.3%/year of additional age.

4. Discussion

The major findings of this study are: (1) Hippocampus and ERC volumes were associated with memory function at baseline and predicted memory decline. Smaller right hippocampal and ERC volumes were associated with worse delayed verbal memory performance at baseline; furthermore, smaller left ERC volume was associated with greater longitudinal decline in delayed verbal memory. (2) Left temporal cortex volumes were associated with semantic memory. Smaller temporal cortex volumes were associated with worse object naming at baseline; in addition smaller left temporal white and gray matter volumes were associated with greater longitudinal decline in object naming. (3) Frontal lobe volumes were associated with executive function. Smaller frontal lobe volumes and concomitant CSF increases were associated with worse executive functioning at baseline; additionally smaller frontal lobe volumes, particularly white matter, were associated with greater longitudinal decline in executive functioning.

4.1 Brain volume changes associated with delayed memory function

Not surprisingly, we observed an association between smaller hippocampal and ERC volumes and worse delayed verbal memory performance at baseline. This finding is consistent with reports of the importance of these brain regions for this type of memory (Squire and Zola-Morgan, 1991; Zola-Morgan, et al., 1986). Although our maps show effects bilaterally (see top left panel, Figure 1), only the cluster on the right survived corrections for multiple comparisons in this mixed sample of normal and cognitively impaired elderly participants. A larger or even more diverse sample may be needed to definitively determine whether this effect is truly lateralized. Alternatively, left and right medial temporal volumes could be delineated manually on each subject, or computed from each subject’s tissue volume map as the average Jacobian determinant within left and right medial temporal masks delineated on the reference. These volumes could be used in a statistical analysis to determine if the relationship between volume and verbal memory differed between hemispheres. A new finding, to our knowledge, was the observation that smaller left ERC volumes at baseline were associated with greater declines in delayed memory performance over 1 year. This is consistent with studies that have shown ERC volumes to be predictive of conversion to dementia (Devanand, et al., 2007), but it is noteworthy that we observed the association in a mixed sample of subjects, only some of whom converted to dementia during the study (as indexed by a CDR score $\geq 1.0$). This
suggests that smaller baseline ERC volumes may help to identify elderly patients at greater risk for declining memory.

4.2 Brain volume changes associated with semantic memory (object naming)

We also observed that smaller baseline left lateral temporal volumes were associated with worse performance on object naming tasks at baseline, even though the sample as a whole did not show impaired semantic memory. This result is consistent with previous reports linking left temporal lobe atrophy to deficits in semantic memory (Hodges, et al., 1992), a VBM study of AD patients that found a significant relationship between left lateral temporal cortical atrophy and naming accuracy (Grossman, et al., 2004) and neuroimaging studies of object naming that have reported functional activity in the left lateral temporal lobe (Price, et al., 1996). In addition, we observed that smaller baseline left temporal volumes were associated with greater declines in object naming over 1 year, which to our knowledge has not been previously reported. The major white matter tract encompassed in the region shown in the middle right panel of Figure 1 is the inferior longitudinal fasciculus, which connects the occipital and temporal lobes. Since function of both visual occipital regions and semantic temporal regions are required for object naming, it is plausible that greater atrophy of the white matter tract connecting these regions would be associated with greater object naming decline. Taken together, these results suggest that our participants with smaller left temporal volume at baseline are at greater risk for developing semantic memory problems over time.

4.3 Brain volume changes associated with Executive Function

The integrity of the frontal lobes have long been associated with measures of executive functions (Alvarez and Emory, 2006). Consistent with this, we observed smaller frontal gray and white matter volumes and greatly increased ventricular CSF volumes associated with worse performance on executive functioning tasks at baseline. The white matter atrophy has two loci: short fibers connecting adjacent frontal lobe regions, perhaps reflecting impaired communication within the frontal lobe; and regions of the anterior corona radiata, perhaps reflecting impaired connectivity of the frontal lobe. A new finding, to our knowledge, of this study is that smaller baseline bilateral dorsolateral prefrontal volume, particularly white matter, predicted future executive function decline. The white matter regions encompassed by the contours in the bottom right panel of Figure 1 include the superior region of the corona radiata and the superior longitudinal fasciculus. These long white matter tracts connect the frontal lobe with the rest of the brain, and suggests that reduced cortico-cortical connectivity is associated with future executive functioning decline. A previous study using VBM showed less GM density in the prefrontal and medial temporal lobes of elderly subjects who declined cognitively in the previous 3 years compared to those who did not (Tisserand, et al., 2004), i.e. cognitive decline predicted brain atrophy. Our new (to our knowledge) finding, using DBM, was that baseline brain volumes in the same brain regions were associated with continuing cognitive decline. Taken together, these results add to the body of evidence that frontal regions are of particular relevance in continuing cognitive decline in non-demented elderly individuals. These results also underscore the advantage of employing a whole brain voxel based approach, which indicates that multiple brain regions help predict future decline of multiple cognitive domains.

4.4 Exploratory cerebellar findings

It is noteworthy that we also found several associations between baseline cerebellar volume and cognitive function at both baseline and longitudinally. These findings are consistent with converging evidence from neuroimaging, neuropsychology, and neuroanatomical studies that suggest the cerebellum contributes to several areas of cognitive processing, including language, learning, and memory (Desmond and Fiez, 1998; Ivry and Fiez, 2000).
Although we have validated our deformation morphometry measures in the temporal and frontal lobes (Iordanova, et al., 2006; Studholme, et al., 2004), we have not validated our deformation morphometry measures in the cerebellum. Cerebellar region of interest analyses are difficult (Deshmukh, et al., 1997; Pierson, et al., 2002; Sowell, et al., 1996), but may be necessary in order to confirm our cerebellar deformation morphometry findings.

4.5 Associations with Age

Several regions of the brain were associated with age at baseline. We found smaller brain volumes bilaterally in the frontal and temporal lobes, subcortical nuclei (particularly thalamus), and right frontal/parietal regions adjacent to the lateral central sulcus associated with greater age at baseline. We also observed concomitant CSF volume increases associated with greater age at baseline. Although regions of the occipital lobe did not show tissue volume decreases with increasing age, there were CSF increases in the interhemispheric fissure in the occipital region. Our results are consistent with the previous reports of the effects of age on regional brain volumes that showed effects of age in orbital frontal regions, temporal regions, somatosensory and motor regions, and subcortical structures (Kennedy, et al., 2008; Raz, et al., 2005; Walhovd, et al., 2005). Because we used deformation morphometry of the whole brain and surrounding CSF, we were also able to observe CSF volume increases. Although curvilinear effects of age were previously reported in some of these regions, within the restricted age range of our participants, the effect of age is probably well modeled by a linear function.

4.6 Limitations and Conclusion

Our statistical models associating baseline brain volume with longitudinal cognition included independent variables for both baseline cognition and cognitive decline. We did not observe any significant associations between baseline brain volume and cognitive change when baseline cognitive scores were not included in the model. Since our sample included cognitively normal and impaired participants, the inclusion of baseline cognitive scores helped to explain variability due to baseline cognitive status, and suggests that the rate of cognitive change and its underlying anatomical substrate vary with respect to the stage of cognition.

As in any imaging study, there is the potential for scanner drift to bias results. However, in this study there were no circumstances where scanner drift would have presented a problem, such as longitudinal imaging or group comparisons where patients were not randomly studied over time. Even so, the Siemens MRI scanner underwent monthly maintenance, with recalibration of the gradients and coils, in order to minimize drift. Therefore, we do not believe our results can be attributed to scanner drift.

It should be emphasized that deformation morphometry is a method for quantifying the relationship between brain anatomy and disease or function, typically by computing statistics over groups of subjects. Therefore it does not provide any substantial diagnostic and prognostic support for individual cases. Despite a relatively small number of participants, the relationships between smaller baseline brain volumes and baseline or longitudinal cognition survived corrections for multiple comparisons. Therefore, they represent robust results and contribute to our understanding of the pattern of brain atrophy associated with future decline of delayed verbal memory, object naming, and executive function, and identify regions of the brain that underlie cognitive deficits observed in an aging population. Since we cannot identify pathology in-vivo in any of our participants, the etiology of the observed brain atrophy, baseline cognitive performance, and continuing cognitive decline cannot be identified as related to disease, developmental differences, genetics, or other factors. However, since we include age as a covariate in our models, the
linear effects of aging on brain volumes plays a small role in the reported relationships between brain volumes and cognition. Despite this ambiguity, we conclude that in non-demented elderly subjects, brain volume of multiple brain regions correlates with performance in multiple cognitive domains (memory, naming, and executive function), and that volume of different brain regions predicts continuing decline of multiple domains. These observations may facilitate the development of predictive or diagnostic techniques that could be used to identify both cognitively normal and cognitively impaired subjects at increased risk for continuing cognitive decline. Such methods may be used in prevention trials, and ultimately to guide preventative therapy.

Acknowledgments

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References


Figure 1.
The T-statistic map is overlaid on the spatially normalized average MRI. The contours delineate statistically significant clusters of association between baseline brain volume and either baseline (left panels) or change (right panels) in cognitive scores. The top panel shows results for delayed memory, the middle for object naming, and the bottom for executive function. Voxels shaded red/yellow indicate smaller baseline tissue volumes associated with either worse baseline or greater declines in cognition, and blue shaded voxels indicate larger baseline tissue volumes associated with worse baseline or greater declines in cognition.
Figure 2.
The T-statistic map is overlaid on the spatially normalized MRI. The contours delineate statistically significant clusters of association between baseline brain volume and age. Red and pink contours (encompassing blue shaded voxels) show regions where decreased tissue volume was associated with increasing age; green contours (encompassing red/yellow voxels) show regions of increased CSF volume with increasing age.
## Table 1

Neuropsychological test scores at baseline and 1 year follow-up

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 year follow-up</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Mean ± SD (min, max)</td>
<td>Mean ± SD (min, max)</td>
</tr>
<tr>
<td></td>
<td>99.1 ± 22.0 (62.1, 139.2)</td>
<td>93.6 ± 20.9* (62.1, 139.2)</td>
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<tr>
<td>Delayed Verbal Memory</td>
<td>108.7 ± 13.9 (72.6, 142.8)</td>
<td>107.1 ± 13.7 (64.8, 135.2)</td>
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<tr>
<td>Semantic Memory</td>
<td>104.3 ± 16.7 (67.8, 133.3)</td>
<td>102.7 ± 17.2** (61.7, 131.6)</td>
</tr>
<tr>
<td>Executive Function</td>
<td></td>
<td></td>
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</table>

* follow-up < baseline, p=0.0007
** follow-up < baseline, p=0.03
Table 2

Cluster statistics

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Location</th>
<th>Corrected p-value</th>
<th>Average Effect&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Contour&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Delayed memory</td>
<td>Right hippocampus/ERC</td>
<td>0.03</td>
<td>2.7</td>
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<td></td>
<td>Left ERC</td>
<td>0.004</td>
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<td></td>
<td>Mid superior posterior cerebellum</td>
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<td>5.5</td>
<td></td>
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<td></td>
<td>Left superior posterior cerebellum</td>
<td>&lt;0.001</td>
<td>4.6</td>
<td></td>
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<tr>
<td>Object naming</td>
<td>Left anterior temporal GM</td>
<td>0.05</td>
<td>6.8</td>
<td>Green</td>
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<td></td>
<td>Left anterior temporal WM</td>
<td>0.003</td>
<td>8.7</td>
<td>Green</td>
</tr>
<tr>
<td></td>
<td>Right inferior posterior cerebellum</td>
<td>&lt;0.001</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>Lateral posterior frontal WM/GM</td>
<td>0.002</td>
<td>7.3</td>
<td>Green</td>
</tr>
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<td></td>
<td>Frontal left deep WM</td>
<td>0.01</td>
<td>5.0</td>
<td>Blue</td>
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<td></td>
<td>Right ventricular CSF</td>
<td>&lt;0.001</td>
<td>-20.4</td>
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<td>-21.3</td>
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<td>Right posterior sulcal CSF</td>
<td>&lt;0.001</td>
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<td>0.3</td>
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<td>Longitudinal change</td>
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<td></td>
<td>Mid superior posterior cerebellum</td>
<td>0.05</td>
<td>1.8</td>
<td></td>
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</table>

<sup>a</sup>This is the average of the estimated regression coefficients over all voxels within the cluster, expressed as % volume change per each 10-point increase in the independent variable (either baseline or longitudinal change in cognitive score).

<sup>b</sup>The color of the contour encompassing each cluster, if shown in Figure 1.