Chapter 2.3

Relation between subcortical gray matter atrophy and conversion from mild cognitive impairment to Alzheimer’s disease

Hyon-Ah Yi1,6, Christiane Möller1, Nikki Dieleman1–5, Femke H. Bouwman1, Frederik Barkhof3, Philip Scheltens1, Wiesje M van der Flier1,2, Hugo Vrenken3,4

1Alzheimer center & Department of Neurology, 2Department of Epidemiology & Biostatistics, 3Department of Radiology & Nuclear Medicine, 4Department of Physics & Medical Technology, Neuroscience Campus Amsterdam, VU University Medical Center, P.O. Box 7057, 1007MB Amsterdam, the Netherlands, 5Department of Radiology, University Medical Center Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. 6Department of Neurology, Keimyung University School of medicine, Daegu, South Korea.

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Abstract

Objective: To investigate whether subcortical gray matter atrophy predicts progression from mild cognitive impairment (MCI) to Alzheimer’s disease (AD), and to compare subcortical volumes between AD, MCI and controls. To assess the correlation between subcortical gray matter volumes and severity of cognitive impairment.

Methods: We included 773 participants with 3D T1-weighted MRI at 3-Tesla, who were 181 control, who had subjective memory complaints with normal cognition, 201 MCI and 391 AD. During follow-up (2.0±0.9 years), 35 MCIs converted to AD (progressive MCI) and 160 MCIs remained stable (stable MCI). We segmented volumes of six subcortical structures of amygdala, thalamus, caudate nucleus, putamen, globus pallidus and nucleus accumbens, and of hippocampus, using FIRST.

Results: ANOVAs, adjusted for sex and age, showed that all structures, except globus pallidus, were smaller in AD than in controls. In addition, amygdala, thalamus, putamen, nucleus accumbens, and hippocampus were smaller in MCI than controls. Across groups, all subcortical gray matter volumes, except globus pallidus, showed positive correlation with cognitive function, as measured by MMSE (0.16<r<0.28, all p<0.05). Cox proportional hazards analyses adjusted for age, sex, education, CAMCOG-R and MMSE showed that smaller volumes of hippocampus and nucleus accumbens were associated with increased risk of progression from MCI to AD (hazards ratio [95% CI] 1.60 [1.15-2.21]; 1.60 [1.09-2.35], p<0.05)

Conclusions: In addition to hippocampus, also nucleus accumbens volume loss was associated with increased risk of progression from MCI to AD. Furthermore, volume loss of subcortical gray matter structures was associated with severity of cognitive impairment.

Keywords: subcortical atrophy, mild cognitive impairment, Alzheimer’s disease, MRI
Introduction
Mild cognitive impairment (MCI) is a condition of cognitive decline without significant social or occupational impairment.[1] Patients with MCI have an increased risk of dementia, mostly due to Alzheimer’s disease (AD) and for many patients, MCI represents a predementia stage of AD.[1-3] Early identification of MCI patients who are at risk of progression to AD is important, especially in the context of treatment trials.

Prior neuroimaging studies have suggested that hippocampal atrophy, FDG-PET pattern and positive amyloid imaging predicted progression from MCI to AD.[2] These studies have focused on cortical changes, as the neuropathology underlying AD (i.e. senile plaques and neurofibrillary tangles) has a predominantly cortical distribution.[4,5] Senile plaques and neurofibrillary tangles, however, have also been observed to extend into the subcortical structures including thalamus, putamen and amygdala.[4,6,7] Pittsburgh compound B (PiB)-PET studies supported these findings by showing increased amyloid retention in the thalamus or basal ganglia in sporadic AD as well as in presenillin mutation carriers as preclinical AD group.[8,9] In line with these observations, recent in vivo imaging studies showed structural subcortical involvement in AD. Several studies demonstrated subcortical atrophy or shape differences between AD and control, of putamen and thalamus,[10] amygdala and thalamus,[11] and of the striatum including nucleus accumbens.[12] Also there were few studies of subcortical change between MCI and control. Liu et al found that the baseline volumes of hippocampus, amygdala and nucleus accumbens were reduced in MCI compared to controls.[13] In another cross-sectional study, there were no difference between subcortical volumes of MCI and controls, such as thalamus, caudate nucleus and amygdala.[14]

Only a few, small studies have evaluated the value of subcortical atrophy for predicting progression from MCI to AD. Tang et al[15] reported that atrophy in hippocampus and amygdala, and lateral ventricular expansion could discriminate MCI progressing to AD from stable MCI. On the contrary, Liu et al[13] found that the volume of caudate nucleus and amygdala rather than hippocampus were independent predictors of progression from MCI to AD.

In the current study, we used cross-sectional imaging and longitudinal clinical follow-up, aiming, first, to compare volumes of six subcortical structures cross-sectionally, namely thalamus, caudate nucleus, putamen, globus pallidus, amygdala and nucleus accumbens as well as hippocampus, between AD, MCI and controls. Second, we aimed to analyze correlation between subcortical volumes and severity of cognitive impairment. Finally, we aimed to investigate the predictive value of subcortical volumes for progression from MCI to AD with longitudinal clinical follow up. Based on the prior works[13,15] we hypothesized that the volumes of amygdala, caudate nucleus or hippocampus could predict progression from MCI to AD.

Methods
Participants
This was a retrospective study. From the Amsterdam Dementia Cohort,[16] consisting of all patients who visited the memory clinic for evaluation of their cognitive
complaints, we considered for inclusion all patients who visited between January 2008 and December 2011. Diagnostic work-up included clinical assessment of medical history, neurological examination, laboratory tests, neuropsychological tests and brain MRI. Diagnoses were made by consensus in a multidisciplinary meeting. The diagnosis of probable AD was based on the criteria of the National Institute of Neurological and Communicative Diseases and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA).[17] Patients with MCI fulfilled the criteria defined by Petersen.[1] When all clinical investigations were normal (i.e. criteria for MCI or any psychiatric disorder not met), patients were considered to have subjective complaints. Patients visited the clinic annually or according to clinical needs, and their diagnosis was re-evaluated with clinical course and neuropsychological tests including Mini Mental State Examination (MMSE)[18] and the Cambridge Cognitive Examination-Revised (CAMCOG-R).[19] The CAMCOG-R allows the assessment of eight cognitive domains, including orientation, comprehension, expression, memory, attention and calculation, praxis, abstract reasoning, and perception, with a maximum score of 104. We followed up all participants for 2.0±0.9 years and reviewed their clinical records. Patients were scheduled for a new visit annually or according to clinical needs, which explains the variability in follow-up times in our samples. Not all tests are always performed at every visit.

We classified MCI patients as progressive MCI (p-MCI) if they were diagnosed as having a form of dementia at a follow-up clinical examination, and as stable MCI (s-MCI) otherwise. Patients with subjective complaints who showed normal cognition through follow-up duration served as controls in this study. We excluded patients if any of the following criteria were met: age <55 or >90, other medical or neurological conditions to affect cognition such as vascular dementia or dementia with Lewy bodies, history of psychiatric episodes or substances abuse, history of being diagnosed as dementia, abnormal brain scans (details given below under “Imaging acquisition and analysis”), or failure of FIRST image analysis algorithm.[20]

This study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki. This study was approved by medical ethics committee of the VU university hospital, Amsterdam, and written informed consent for their clinical data was obtained from all patients for research purposes.

**Imaging acquisition and analysis**

Brain MRI was performed at the initial visit, using a 3.0 Tesla scanner (Signa, HDxt, GE Healthcare, Milwaukee, WI, USA) with an 8-channel head coil. For measurement of the subcortical volumes, a three-dimensional, T1-weighted-fast spoiled gradient echo sequence was obtained with acquisition parameters as follows: repetition time/echo time/inversion time 708/7/450 ms; flip angle, 12˚; matrix size, 256 × 256; field of view, 250mm; 180 sagittal slices; slice thickness, 1mm; voxel size, 0.98 ×0.98×1 mm. Routine T2-weighted, and fast fluid-attenuated inversion recovery (FLAIR) and susceptibility weighted images were also obtained to exclude structural lesions that may affect cognitive function such as mass or vascular lesions of large territorial or strategic infarcts, and severe white matter hyperintensities of Fazekas grade 3.[21]
All the images were processed and analyzed automatically with the tools of the FSL software package (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/fswiki/). Using the algorithm FIRST (FMRIB's integrated registration and segmentation tool),[20] we segmented bilateral amygdala, thalamus, hippocampus, globus pallidus, nucleus accumbens, caudate nucleus and putamen. Left and right volumes of the same structure were summed. Examples of subcortical segmentation using FIRST are presented in Figure 1. Total brain volume, automatically calculated using SIENAX (Structural Image Evaluation using Normalization of Atrophy Cross-sectional),[22,23] was normalized for head size via volumetric scaling factor (VSF), which was calculated by registering the brain image to MNI152 (Montreal Neurological Institute, Montreal, Canada) space. Similarly, all structural volumes obtained from FIRST were normalized for head size by multiplying by the VSF.

**Statistical analysis**
We performed statistical analysis using IBM SPSS statistics for Windows, version 20 (IBM Corp). We compared groups using χ² test, t-test and one-way analysis of variance (ANOVA) followed by Bonferroni’s post hoc test where appropriate. To evaluate the differences of volumes in each subcortical structure among diagnostic groups, we used ANOVA with post hoc Bonferroni t-test corrected for age and sex. A Pearson's bivariate correlation analysis and partial correlation corrected for age and sex were performed to examine the correlation of cognitive function and subcortical structural volume. To account for the fact that CAMCOG and MMSE measure similar concepts, we set the threshold for statistical significance of these correlations at p=0.025.

We performed Cox proportional hazards model to evaluate the predictive value of subcortical atrophy for progression from MCI to AD. Hazard ratios (HR) with 95% confidence interval (CI) are presented. We normalized volumes of all subcortical structures to z-scores and multiplied this by -1. The resulting HR’s can be interpreted as increased risk of progression to AD for every standard deviation smaller volume. In model 1, unadjusted hazard ratios are presented. In model 2, age, sex and education are corrected for and in model 3, CAMCOG-R, baseline MMSE are additionally included. In addition, to minimize the influence of global atrophy, we controlled for brain volume also. Finally, to assess the combined predictive value of the best combination of markers, we performed a forward stepwise Cox regression analysis including all baseline DGM volumes as possible predictors. Because the diagnosis (MCI or AD) at follow-up is a dichotomous variable and it may in some cases have been influenced by the baseline imaging, we also performed an exploratory analysis investigating the correlations between baseline volumes and follow-up MMSE scores. We assessed bivariate Pearson’s correlations, as well as partial correlations adjusted for age, sex, education level and follow-up duration.

**Results**

**Demographic characteristics of the participants**
Out of the initial 1,012 individuals included in the dataset, 239 patients were excluded for the following reasons: 72 patients had lacunes in the basal ganglia, in 72 patients...
the FIRST image analysis software failed, 5 patients among the patients who were initially diagnosed as AD were diagnosed with other types of dementia at follow-up visit, 76 controls were below age 55, and 14 controls had deteriorated cognition at follow up. Finally 773 subjects were analyzed; 181 controls (65±8 years; F/M 82/99), 201 MCI (70±9 years; F/M 82/119) and 391 AD (69±9 years; F/M 221/170). For the comparison between s-MCI and p-MCI, 6 MCI patients were additionally excluded, as they progressed to other types of dementia rather than AD. Of the remaining 195 MCI patients, 35 progressed to AD, while 160 remained stable. Demographic and clinical characteristics by group are presented in Table 1. There were significant differences of age, gender, education and cognitive scores between groups (p<0.05). Post hoc comparisons showed that AD and MCI were older and less educated, and had longer duration of follow-up than controls. There were no differences of age, gender, or follow-up duration between AD and MCI.

Subcortical volume
Volumes of all structures in each clinical group are presented by group in Table 1 and Figure 2. ANOVAs, adjusted for age, sex and education, showed that all subcortical gray matter volumes except globus pallidus differed between groups (p<0.05) and showed a tendency to decrease from controls to MCI and further to AD. Post hoc tests showed that all structures were smaller in AD than in controls, except globus pallidus, and were smaller in MCI than controls except globus pallidus and caudate nucleus. The volumes of hippocampus, thalamus and caudate nucleus were smaller in AD compared to MCI.

Correlation between cognitive function and subcortical volumes
Pearson’s correlation across groups showed positive correlations of all subcortical structural volumes besides globus pallidus with cognitive function, measured by MMSE (0.13 <r<0.26, all p<0.000) and CAMCOG (0.12<r<0.30, all p<0.025) (Figure 3). Results remained essentially unchanged when we used partial correlations corrected for age, sex and education. In analyses within MCI, thalamus and amygdala volumes were positively correlated with MMSE (respectively r=0.19 and 0.23, p=0.008 and 0.001), and amygdala volume was positively correlated with CAMCOG (r=0.178, p=0.014) although the correlation coefficients were low. On controlling for age, sex and education, there were correlations between amygdala volume and MMSE (r=0.18, p=0.008), and between caudate nucleus volume and CAMCOG (respectively r=0.17, p=0.024)

Prediction of progression from MCI to AD
The comparison between 160 s-MCI (70±9 years; F/M 64/96) and 35 p-MCI (70±10 years, F/M 18/17) did not show any difference in age, gender, education, baseline cognitive scores, and follow-up duration (Table 2). Adjusted for age, sex and education, atrophy of hippocampus and amygdala was more extensive in p-MCI than in s-MCI (hippocampus p<0.001; amygdala p=0.045), and most of the structures were smaller in p-MCI than in s-MCI. Finally we used Cox proportional hazards analysis to evaluate the predictive value of baseline volume of each subcortical structure for progression to AD in MCI patients. Table 3 shows crude and adjusted progression risk
of baseline subcortical volume. In the crude model, smaller volume of hippocampus and nucleus accumbens conferred a higher risk of progression from MCI to AD (HR [95% CI]: hippocampus 1.56 (1.16-2.11), nucleus accumbens 1.59 (1.16-2.18), for both p<0.05). Upon adjustment for age, sex, education, CAMCOG-R and MMSE, these results remained significant (p<0.05). Controlling for normalized brain volume showed similar results (HR [95% CI] 1.55 (1.11-2.16); 1.54 (1.03-2.30) p<0.05, for hippocampus and nucleus accumbens). When using a forward stepwise model to select the best predictors, only hippocampus remained significant (HR (95% CI) 1.59 (1.15-2.21)).

**Correlation of follow-up MMSE scores and baseline volumes**

MMSE scores at the follow-up visit were available for 116 of these MCI patients. The bivariate Pearson’s correlations between baseline volumes and follow-up MMSE scores revealed no significant correlations. When adjusting for age, sex and educational level, there was a trend for a weak correlation between MMSE score at follow-up and hippocampus volume at baseline (r=0.182, p=0.054), and no significant correlations.

**Discussion**

The main finding of this study is that in addition to baseline hippocampal volume, also baseline nucleus accumbens volume predicted progression from MCI to AD during 2 years of clinical follow-up. However, when including all baseline volumes as candidate predictors, forward stepwise Cox regression revealed that nucleus accumbens volume had no added independent predictive value over and above that of hippocampal volume. Baseline volumes of other subcortical structures were not predictive of progression to AD, despite the observation of decreasing volumes from controls to MCI to AD, and significant associations with cognitions for all structures except globus pallidus.

As early identification of MCI patients at risk for progression to probable AD continues to be an important goal both for clinical treatment trials and ultimately for individual clinical treatment, it is important to identify in vivo imaging measures that can aid this identification. Specifically, baseline subcortical volumes would be easily accessible and suitable measures, because they require just a single MRI and can be determined with acceptable reliability using automated methods.[20,24] We hypothesized that subcortical atrophy contributes to AD pathogenesis as in the previous pathologic and neuroimaging reports[4,10,25] and that it could predict progression of MCI to AD. As expected, we observed that hippocampal volume in MCI predicted subsequent progression to AD. In addition, we observed that nucleus accumbens volume also predicted subsequent progression to AD. Despite the volume difference between AD, MCI and controls, other subcortical gray matter volumes did not predict progression from MCI to AD. There have been few former reports to evaluate subcortical structural volume differences as predictors of progression from MCI to AD. Liu et al demonstrated that baseline amygdala and caudate volume had 69% accuracy in predicting AD in MCI during 1 year follow-up.[13] Although there was a report that emphasized the unique role of hippocampal atrophy as a marker of progression to AD from MCI, they adopted hippocampus and amygdala only using region of interest
volumetry and this could not present supportive evidence of subcortical role in progression to AD.[26] Some prior studies showed that subcortical volume decreased as cognitive function became worse in AD [11,27], but they did not investigate the relation with progression of MCI.

In the current study, we investigated the role of baseline subcortical volume in progression of MCI during an average of 2-year follow up. We observed significant difference in baseline hippocampus and amygdala volume between s-MCI and p-MCI, but Cox proportional hazard analysis showed that only hippocampus and nucleus accumbens volume predicted clinical progression. Since MMSE scores may be more sensitive to change, and imaging can be used in the diagnostic process, MMSE is a potentially more objective and sensitive outcome measure than diagnostic status. However, our exploratory additional analysis revealed no correlations of follow-up MMSE scores with baseline volumes, except for a trend for hippocampal volume. In comparison between AD and MCI, the volumes of a part of basal ganglia and thalamus were significantly lower in AD than in MCI, but none of these predicted progression from MCI to AD. A previous study also found pathologic striatal involvement in AD[7] and that the nucleus accumbens as a part of ventral striatum as well as hippocampal atrophy is a significant indicator for cognitive decline.[28]

The lack of clinical predictive value in MCI patients appears not to be due to any lack of sensitivity of our method, or any absence of atrophy in these structures in our patients. In fact, there were significant subcortical volume differences between controls, MCI and AD. Most of the prior imaging analyses in AD or MCI have paid attention to cortical change rather than subcortical structures and more vulnerable regions in AD such as hippocampus or entorhinal cortex.[29-31] The hypothesis of the subcortical involvement in AD has been based on pathological studies in AD in addition to recent imaging studies. Braak and Braak[4] documented that there were subcortical depositions of neurofibrillary tangles in thalamus and amygdala, in the transentorhinal stages of AD. The subcortical involvement could be a late phenomenon of AD as multiple studies have reported that the symptoms related to frontal-subcortical circuit disruption generally appear in the later stages.[32-34] However, a few studies showed functional and structural involvement of the subcortical regions already in the early stages of AD.[10,11,15] These studies have shown inconsistent results, in which some studies found atrophy of all the subcortical structures, while some observed decreased volumes of specific regions only besides hippocampus, for example, thalamus and caudate nucleus involvement, or putamen and globus pallidus.[11, 15] Most studies focused on the volume difference between AD and healthy control and a few studies included MCI in the comparisons. One of them showed no significant baseline volume difference between AD and MCI.[26] In our large study, however, all the baseline subcortical structures except globus pallidus were significantly atrophied in AD compared to MCI and controls, and also smaller in MCI than controls, which is compatible with some previous studies including a report of pathological topographic distribution in AD.[26] This confirmed subcortical involvement even in an early stage of AD-like disease.

Many researchers have tried to find predictive factors of progression of AD with increasing importance of the neuroimaging biomarker for early detection of condition with AD pathology. Most trials have adopted hippocampal volume or cortical
thickness as a structural biomarker.[35,36] In additional study to detect progression probability in MCI to AD, investigators suggested that hippocampal atrophy rate [29,30,37] and ventricular expansion rate[30] could be predictive factors for progression of MCI to AD. In presymptomatic familial AD (FAD), the amyloid retention in the thalamus and striatum rather than fronto-temporal cortex using amyloid imaging[8,9] prompted studies of volume reduction in the same regions. A few studies of presymptomatic FAD reported atrophy of thalamus, caudate nucleus or putamen.[38] Although FAD is a condition with genetic background, we speculated that subcortical involvement might happen in the presymptomatic period in sporadic AD and its progression according to the severity of the AD pathology might be worthy of evaluation.

Nucleus accumbens is a part of ventral striatum which is prone to cognitive dysfunction through the connections to limbic areas in AD or elderly.[28] In addition to classical pathologic report of striatal involvement in AD,[4,7] there were several attempts to clarify the role of striatum in AD pathogenesis. De Jong et al[28] found that volume of the nucleus accumbens was smaller even in preclinical stages of dementia than in a group with normal cognition, and they reported that nucleus accumbens can be a significant indicator for progression to dementia through the steeper slope of cognitive decline. However they included elderly persons instead of patients with MCI, and used conversion to either vascular dementia or AD as an end-point. Our study instead looked specifically in MCI patients at the value of baseline subcortical volumes in predicting subsequent conversion from MCI to AD. Our findings add to the findings of De Jong et al., a role of cross-sectional nucleus accumbens volume in predicting progression from MCI to AD. In spite of a clear trend towards lower volume in the p-MCI group, there was no baseline volume difference of nucleus accumbens between s-MCI & p-MCI. This absence of a significant difference could be explained by the short follow-up duration in this study and the resulting relatively small group size of p-MCI, or alternatively, by the specific vulnerability of the nucleus accumbens. As a part of limbic circuit, the nucleus accumbens may be vulnerable to neurodegenerative processes already in a pre-clinical stage or early stages of AD, which could lead to similar degree of atrophy in both MCI groups. This hypothesis could be investigated in future studies e.g. by studying patients with subjective memory complaints and comparing those who subsequently progressed to AD to those without progression, to confirm the predictive role and vulnerability of nucleus accumbens.

We assessed the correlation between cognitive dysfunction and subcortical structural volume. Basically we expected that subcortical volume reduction might reflect cognitive deterioration as prior studies showed the correlation between cognitive status and structural changes.[10,11,36] Our findings in a large sample, including controls, MCI and AD, also demonstrated a significant positive correlation between MMSE and subcortical volumes with low correlation coefficients, and the role of globus pallidus on the cognition were negligible as in the other reports.[1,10]. From this, we could suggest that positive correlation between structural atrophy and cognitive status does not always simply mean a relation to further progression. Interesting finding was larger volume of globus pallidus in p-MCI comparing with s-MCI although it did not have any significance. Some studies in presymptomatic FAD
reported similar findings[38] and they explained this increment might reflect reactive neuronal hypertrophy and inflammatory process in the early presymptomatic period. From these results, the lack of volume difference of globus pallidus between groups might not be negligible but structural change of globus pallidus might happen in much later stage in AD-like neurodegeneration.

Our study has a number of strengths and limitations. Few studies have compared the subcortical structures between MCI, AD and controls, especially evaluating the predictive role of the subcortical structures besides medial temporal lobe structures in a large cross-sectional cohort. Also to reduce possible variability in other multicenter researches as much as possible, we used imaging data from a single scanner and constant imaging protocol. Among the possible limitations, the first is the fact that we could not study volume changes over time as it was a cross-sectional study. Although our actual goal was to find the value of the point-based subcortical volume reduction, adding more information such as atrophy rate or ventricular enlargement rate measured by longitudinal evaluation of imaging would give more powerful explanations in prediction of progression to AD from MCI on this current cross-sectional study. Another potential limitation is the fact that we did not sub-classify MCI patients as being amnestic or non-amnestic, while the future course and relationship with subcortical structures could be affected by clinical subtypes.[39]

However, there was a report of longitudinal comparison between MCI subtypes, which showed no difference between the chance of reversion or the risk of conversion to AD, suggesting MCI subtypes were diagnostically unstable.[40] In addition, due to the relatively short follow-up duration, it should be expected that a substantial proportion of the s-MCI patients will later progress to AD. As this was a retrospective study, we accepted variability in follow-up times. Patients were scheduled for a new visit annually or according to clinical needs, leading to variability in follow-up times in our samples. To maximize discriminative power, we considered the last clinical follow-up time point available, leading to additional variability in follow-up duration, and 8 patients with follow-up duration under 1 year. Longer follow-up is needed to further confirm these results. Lastly, we did not include the information of disease duration and APOE genotypes in each patient. As long duration of disease could mean exhausted functional reservoir, information about disease duration would be important regardless of MMSE score. Since APOE genotype was inconsistently available in this patient group, we have decided not to include it in the analyses in order to maintain the maximum number of patients.

In conclusion, we confirmed the subcortical volume reduction in the MCI and AD, and found association with cognitive impairment. Nonetheless, besides nucleus accumbens, subcortical volume did not predict progression of MCI to AD, suggesting these structures have limited value as cross-sectional predictors of future disease course. Further study with larger sized sample would reveal more value of the subcortical volume on the given-time point as an imaging biomarker and it would benefit from therapeutic intervention.
Acknowledgements
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### Table 1. Demographics and normalized brain volume in each group at baseline

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Controls (n=181)</th>
<th>MCI (n=201)</th>
<th>AD (n=391)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65±8</td>
<td>70±9†</td>
<td>69±9†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, women/men (♀ %)</td>
<td>82/99, (45.3%)</td>
<td>82/119, (40.8%)</td>
<td>221/170, (56.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, years</td>
<td>5.01 ± 1.81</td>
<td>4.72 ± 1.79</td>
<td>4.66 ± 1.58†</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.07 ± 1.78</td>
<td>26.02± 2.60†</td>
<td>19.96 ± 5.07‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>92.34 ± 6.31</td>
<td>84.99 ± 8.06†</td>
<td>66.49 ± 15.43‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDR</td>
<td>0.07±0.29</td>
<td>0.39±0.24†</td>
<td>1.08±0.51‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Follow up, years</td>
<td>1.80±0.75</td>
<td>2.11±0.96</td>
<td>2.17±0.79</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Normalized volume(cm³)

| Thalamus      | 19.7±1.7       | 18.9±1.7†   | 18.6±1.7‡  | <0.001   |
| Caudate       | 9.0±1.0        | 8.8±1.0     | 8.6±1.0†,‡ | <0.001   |
| Putamen       | 12.3±1.2       | 11.7±1.3†   | 11.5±1.2‡  | <0.001   |
| Globus pallidus | 4.6±0.6     | 4.5±0.6     | 4.6±0.6    | NS       |
| Hippocampus   | 9.8±1.2        | 8.9±1.3†    | 8.4±1.3‡,† | <0.001   |
| Amygdala      | 3.9±0.6        | 3.6±0.5†    | 3.5±0.6†   | <0.001   |
| Nucleus accumbens | 1.1±0.3    | 0.9±0.3†    | 0.9±0.3†   | <0.001   |

All data are represented as (m±sd) unless indicated otherwise.

* chi-square test; ** Kruskal-Wallis test followed by Bonferroni’s post hoc test
For the normalized brain volume, ANOVA with Bonferroni’s post hoc test were performed with correcting for age, sex and education
† p<0.05 difference between subjects with controls and other groups; ‡ p<0.05 difference between subjects with MCI and AD; NS : non-significant

### Table 2. Comparison between s-MCI and p-MCI

<table>
<thead>
<tr>
<th>Demographics</th>
<th>s-MCI (n=160)</th>
<th>p-MCI (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70±8.8</td>
<td>70±9.6</td>
</tr>
<tr>
<td>Gender, women/men (♀ %)</td>
<td>64/96 (40.0%)</td>
<td>18/17 (51.4%)</td>
</tr>
<tr>
<td>Education, years</td>
<td>4.65±1.82</td>
<td>5.00±1.75</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.1±2.6</td>
<td>25.7 ±2.7</td>
</tr>
<tr>
<td>CAMCOG</td>
<td>85.0±8.4</td>
<td>84.5 ± 6.6</td>
</tr>
<tr>
<td>Follow up, years</td>
<td>2.1±1.0</td>
<td>2.2±1.0</td>
</tr>
</tbody>
</table>

Normalized volume(cm³)

| Thalamus      | 18.9±1.8      | 18.6±1.4     |
| Caudate       | 8.8±1.0       | 8.8±0.9      |
| Putamen       | 11.7±1.4      | 11.6±1.3     |
| Globus Pallidus | 4.5±0.6     | 4.6±0.7      |
| Hippocampus† | 9.1±1.3       | 8.3±1.2      |
| Amygdala‡    | 3.6±0.6       | 3.4±0.5‡     |
| Nucleus accumbens | 1.0±0.3    | 0.9±0.3‡     |

All data are represented as (m±sd) unless indicated otherwise.

* chi-square test; ** Kruskal-Wallis test followed by Bonferroni’s post hoc test.
For normalized brain volumes analyses, ANOVA with correction for age, sex and education was performed.
† p< 0.05; ‡ p <0.001
Table 3. Hazard ratios and 95% confidence intervals for progression to Alzheimer’s disease within MCI groups

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>1.26 (0.91-1.75)</td>
<td>1.09 (0.77-1.55)</td>
<td>1.10 (0.77-1.58)</td>
</tr>
<tr>
<td>Caudate</td>
<td>1.10 (0.80-1.51)</td>
<td>1.18 (0.87-1.61)</td>
<td>1.26 (0.88-1.80)</td>
</tr>
<tr>
<td>Putamen</td>
<td>1.13 (0.85-1.51)</td>
<td>1.02 (0.76-1.36)</td>
<td>1.10 (0.80-1.51)</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>0.88 (0.65-1.18)</td>
<td>0.84 (0.62-1.14)</td>
<td>0.88 (0.64-1.20)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>1.56 (1.16-2.11)</td>
<td>1.45 (1.07-2.00)</td>
<td>1.60 (1.15-2.21)</td>
</tr>
<tr>
<td>Amygdala</td>
<td>1.33 (0.98-1.81)</td>
<td>1.14 (0.80-1.61)</td>
<td>1.11 (0.77-1.60)</td>
</tr>
<tr>
<td>N. accumbens</td>
<td>1.59 (1.16-2.18)</td>
<td>1.47 (1.03-2.09)</td>
<td>1.60 (1.09-2.35)</td>
</tr>
</tbody>
</table>

†: p<0.05

Model 1: crude model, model 2: adjusted for age, sex & education, model 3: age, sex, education, CAMCOG-R & MMSE
Figure 1. Example of automated segmentation of subcortical gray matter structure using FIRST in MCI patient. Segmentations are shown overlaid on the 3D T1-weighted images in three orthogonal orientations, corresponding to the axial (left column), coronal (middle column) and sagittal (right column) planes. Colored structures: Yellow: Hippocampus, Light orange: Amygdala, Green: Thalamus, Light blue: Caudate nucleus, Pink: Putamen, Dark blue: Globus pallidus, Orange: Nucleus accumbens.

Figure 2. Normalized volume (cm$^3$) of six subcortical structures and hippocampus in control, MCI and AD. ANOVAs, adjusted for sex and age, showed that all subcortical gray matter volumes except globus pallidus differed between groups ($p<0.05$) and showed a tendency to decrease from controls to MCI and further to AD. Post hoc tests showed that all structures were smaller in AD than in controls, except globus pallidus, and were smaller in MCI than controls except globus pallidus and caudate nucleus, the volumes of hippocampus, thalamus and caudate nucleus were smaller in AD compared to MCI.
Figure 3. Scatter plots and trend lines show the association between normalized subcortical volumes and MMSE scores at baseline. X-axis represents MMSE score and Y-axis represents volume (cm³).
References


