The association between deep gray matter changes and neurocognitive function in mild cognitive impairment and Alzheimer's disease: a tensor-based morphometric MRI study

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1. Abstract

Background Atrophy of deep gray matter (DGM) has been associated with a risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) and the degree of cognitive impairment. However, specific knowledge of the associations between degenerative DGM changes and neurocognitive functions remains scarce.

Objectives To examine degenerative DGM changes and evaluate their association with neurocognitive functions.

Method We examined DGM volume changes with tensor-based morphometry (TBM) and analyzed the relationships between DGM changes and neurocognitive functions in the control (n =58), MCI (n = 38) and AD (n = 58) groups with multiple linear regression analyses.

Results In all DGM areas, the AD group had the largest TBM volume changes. The differences in TBM volume changes were larger between the control group and the AD group than between the other pairs of groups. In the AD group, volume changes of the right thalamus were significantly associated with episodic memory, learning and semantic processing. Significant or trend-level associations were identified between the bilateral caudate nucleus changes and episodic memory as well as semantic processing. In the control and MCI groups, very few significant associations emerged.

Conclusions Atrophy of the DGM structures, especially the thalamus and caudate nucleus is related to cognitive impairment in AD. DGM atrophy is associated with tests reflecting both subcortical and cortical cognitive functions.

2. Introduction

Degenerative changes in deep gray matter structures (DGM) have been found in patients with both MCI and AD [1, 2-5] and in normal elderly individuals [1, 3, 6]. Atrophy of the nucleus accumbens [5] and the right caudate nucleus [5] predicted conversion from MCI to AD, and volume losses in DGM were associated with the severity of AD [7]. In normal older subjects, atrophy of the putamen and nucleus accumbens has been shown to be related to the incidence of dementia, and the volume of the nucleus accumbens has predicted cognitive decline [8].

The results regarding associations between DGM structures and cognitive functions in normal controls and patients with MCI and/or AD have been somewhat contradictory: In pooled groups of controls and patients, smaller bilateral volumes of all DGM structures, except the globus pallidus, were associated with lower general measures of cognitive function Mini Mental State Examination (MMSE) and Cambridge Cognitive Examination (CAMCOG) [5]. In the study of Roh et al. [7], however, only volume reduction of putamen predicted poorer cognitive test performance (executive, language and general cognitive function). Nie et al. [9] found that bilateral nucleus accumbens atrophy was associated with lower general cognitive test scores [MMSE and Montreal Cognitive Assessment (MOCA)]. Furthermore, smaller bilateral volumes of the caudate nucleus and thalamus have been associated with lower cognitive composite scores (not domain-specific scores) in a community sample [10]. However, only two studies have examined the relationship between degenerative DGM changes and cognitive function in AD. De Jong et al. [3] reported that reduced left thalamus, left striatum and the putamen volumes were associated with lower CAMCOG total scores. Cho et al. [2] determined that atrophy of the bilateral caudate nucleus and putamen was associated with declines in a semantic fluency task, whereas atrophy in the right side of the caudate nucleus and putamen were correlated with declines in a phonemic fluency task.

Tensor-based morphometry (TBM) is a fully automated MRI analysis method that focuses on local volume differences in the brain [11]. In this work, we compared images from this study to

typical AD-type changes in anatomy [12]. TBM has been used to detect the early stages of dementia and the progression of MCI to AD, as well as the differentiation of neurodegenerative diseases from each other [13-17]. To date, TBM has not been used for the evaluation of AD-type DGM changes and their association with cognition.

The aims of this study were to examine AD-type DGM changes with TBM and evaluate the relationships between DGM changes and neurocognitive functions in the control, MCI and AD groups. Our hypothesis was that AD-type changes in both sides of the thalamus, putamen and caudate nucleus exist in the MCI and AD groups, and these changes, particularly in the AD group, would be associated with impairments in cognitive functions.

3. Materials and Methods

3.1 Subjects

The subjects with MCI (n = 38) and AD (n = 58) were consecutive patients at the Turku University Hospital (PET Centre and Division of Clinical Neurosciences), the controls (n = 58) were community dwelling healthy older adults. Subjects were recruited into the study between 2000 and 2008. The total number study subjects was n = 154. The MCI diagnosis was based on the criteria of Petersen et al. [18] (normal ADL-function, subjective memory impairment and an impairment of at least - 1.5 SD compared to age-appropriate norms in at least two tests of episodic memory). Patients with AD fulfilled the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria for dementia and the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association) criteria for probable AD [19]. The control subjects were healthy volunteers who had no history of neurological or psychiatric disease and who had scores within the age-adjusted Finnish norms in neurocognitive testing. The exclusion criteria included medications that could possibly affect cognitive functions (such as benzodiazepines, antipsychotics, anticholinergics), imaging findings suggesting an etiology of memory impairment other than AD-type degeneration, and severe medical conditions that could affect cognition.

The education level of the subjects, as shown in Table 1 was operationalized as follows: 1 = comprehensive school, 2 = vocational school, 3 = college degree and 4 = university degree.

3.2 Magnetic resonance imaging

MR imaging of the subjects' brains was performed with a 1.5 T Philips Intera (Best, the Netherlands) or 1.5 T MRI GE Signa Horizon LX EchoSpeed (General Electric Medical Systems, Milwaukee, Wisconsin, USA). In the Philips scanner, an axial three-dimensional (3D) T1/FFE (Fast Field Echo) sequence was used for analysis (voxel size 0.50 x 0.50 x 1.00 mm). In the GE scanner, an axial 3D FSPGR (Fast SPoiled GRadient-echo) (voxel size 1.1 x 1.1 x 1.5 mm) was used.

More specific details regarding the MR scans have been previously described by Tuokkola et al. [16, 17].

3.3. Measures of cognitive function

The neurocognitive tests used in the present study are validated and well-established neuropsychological measures of episodic memory (Wechsler Memory Scale-Revised: logical memory, immediate and delayed recall, [22]) and learning [CERAD (The Consortium to Establish a Registry for

Alzheimer's disease) word list learning [19]], language and semantic function (CERAD naming and animal fluency [19]), visuoconstructive (CERAD constructional praxis [19]) and visuomotor (Trail Making Test A [21]) functions.

3.4. Tensor-based morphometry

For the TBM analysis, the right and left sides of the thalamus, putamen and caudate nucleus were selected as the six DGM areas of interest.

The multitemplate TBM method was used to improve the robustness of the analysis [12]. Thirty template images from subjects with AD, subjects with MCI or control subjects (ten per group) were collected from the ADNI dataset [23], and a mean anatomical template (MAT) was constructed for a reference space of the analysis. The registration from the MAT to an image from this study was computed 30 times using each template image once. The determinant of the Jacobian matrix, the Jacobian, for each voxel was computed from these registrations to quantify the local volume change compared to the MAT. Finally, the average Jacobian was computed from the 30 Jacobians for each voxel. The final TBM index value (IV) for each DGM area of interest was computed by measuring the similarity of the Jacobian values within the area of interest to the typical AD-related pattern of Jacobians modeled from the ADNI dataset.

As described in our previous studies [16, 17], high index values (IVs) of TBM indicate similarity to Alzheimer's disease, which show a better fit to the AD-type changes on average. In contrast, low IVs indicate similarity to control subjects, which show a worse fit to the AD-type changes.

Additional technical details of the TBM are described in Koikkalainen et al. [12].

3.5 Statistical analysis

The group differences in age were analyzed by one-way analysis of variance (ANOVA) with pairwise comparisons with Tukey corrections, and MMSE differences were analyzed by the Kruskal-Wallis test continued with Mann-Whitney U test when significant. Sex and education differences between groups were tested with Chi-square test. The statistics of the TBM IVs and cognitive test results of the groups were analyzed with one-way ANOVAs with pairwise comparisons with Tukey's corrections for multiple comparisons. Cohen's d was analyzed to measure the effect sizes in the group comparisons of the cognitive function results.

Associations between cognitive functions and TBM IVs in DGM areas were analyzed separately for the three groups (MCI, AD, controls) by multiple linear regression analyses, one analysis for each cognitive test. All DGM areas were included in the model as predictors. To further illustrate the association between each cognitive test and one DGM area, Pearson correlation coefficient were used in Table 4 and Supplementary Table 1.

The analyses were performed using SPSS 23 (SPSS Inc., Chicago, Illinois, USA), with the exception of Cohen's d results, which were analyzed using the Social Science Statistics website [24].

4. Results

4.1 Demographic characteristics

Demographic characteristics and results of statistical analyzes are shown in Table 1.

The AD subjects had significantly lower education levels than the subjects with MCI and the controls. All groups significantly differed from each other in terms of mean MMSE scores. There were no significant differences in age or sex distribution between the groups.

4.2 Tensor-based morphometry

The descriptive TBM IV statistics, the group comparisons and results of statistical analyzes are shown in Table 2.

In all brain areas, the highest mean and median IVs were identified in the AD group. In the MCI and control groups, the highest and lowest mean and median IVs varied between the groups. The difference between the control and AD groups was significant in all brain areas, except in the left thalamus and right putamen. The difference between the control and MCI groups was significant only on the right side of the putamen, and the differences between the MCI and AD groups were in the left thalamus and both sides of the putamen. The group results of the structural analyses are presented in visual form in Figure 1.

4.3. Cognitive differences between groups

Descriptive statistics on the neurocognitive test performances, the group comparisons and results of statistical analyzes are shown in Table 3.

As expected, the AD group performed significantly worse in all cognitive tests than the control group. The MCI group performed significantly worse than the control group on measures of memory (immediate free recall and consolidation in the logical memory test). In particular, the MCI patients were most impaired in tests of episodic memory (medium to large effect sizes in the control vs MCI comparison). The MCI group performed significantly better than the AD group on all tests of memory and learning, as well as in the naming and visuomotor function tasks.

4.5. Association analysis of tensor-based morphometry and cognitive functions

Multiple linear regression analyses between the TBM IVs and cognitive test results were conducted within each group. To minimize the risk of type 1 errors in the multiple linear regression model, we adopted an α level of $p < 0.01$ for statistical significance. We focused on the AD group, as very few significant associations were identified in the control group and the MCI group, and no clear clusters emerged (AD group results of statistical analyzes are in Table 4, and all group results are in Supplementary Table 1).

In the AD group, the cluster with the highest number of significant associations was observed for measures of episodic memory, learning and verbal function, and the TBM IV of the right thalamus. Significant associations were also identified between semantic processing and the bilateral caudate nucleus TBM IVs. The unilateral right caudate nucleus TBM IV was associated with free recall (a trend-level association was also identified in the MCI group), whereas the left caudate nucleus TBM IV was associated with visuomotor scanning. A trend-level association between visuomotor scanning was also identified in the right caudate nucleus in the AD group, and this association reached statistical significance in the MCI group. The association between both sides of the caudate nucleus and cognitive function in AD was supported by the finding that trend-level associations were bilaterally identified for learning and unilaterally for memory consolidation (left) and free recall (right). In the control group, limited significant associations were identified between the left thalamus and visuomotor scanning and the right putamen and memory consolidation.

5. Discussion

The aims of the study were to examine degenerative deep gray matter (DGM) changes with tensor-based morphometry (TBM) and evaluate their association with cognitive function in the three study groups. To the best of our knowledge, this investigation was the first study in which TBM was used for association analyses with cognitive performance. The main finding of the study was that reduced volumes of the right thalamus and bilateral caudate nucleus were associated with cognitive impairment in AD.

Our findings of DGM volume changes are in agreement with previous findings of decreased putamen [3] and thalamus [2] volumes in patients with AD, but extend the finding showing volume change also in the caudate nucleus. In addition our study also including subjects with MCI and used a fully automated TBM analysis. TBM was found to be a feasible tool to evaluate structural changes in DGM by showing that it is possible to detect visually invisible AD type volume changes between the groups of AD and MCI patients and healthy controls.

In the AD group, a cluster in the right thalamus and bilateral caudate nucleus with associations to changes in cognition was identified. The reason for the associations between decreased volume of the right thalamus with poorer verbal tasks may be due to i) the finding that the reduced index values were observed only in the right thalamus of the AD subjects; ii) the less robust functional asymmetry at the thalamic level than at the cortical level; or iii) the supporting role of the thalamus in episodic and semantic memory processes. Because our set of neuropsychological tests did not include visual memory or more demanding visuospatial tasks, it is unclear whether these measures would have also been associated with thalamic changes. Cho et al. [2] did not identify associations between thalamic volume changes and cognitive decline in AD. The potential explanations may be in the different group sizes or in the longitudinal design of their study compared to our cross-sectional design.

In the AD group, significant or trend-level associations between decreased bilateral caudate index values and measures of learning, free recall, semantic processing and visuomotor scanning are in line with Cho et al. [2], who identified an association between atrophy of the bilateral caudate volumes and decreases in semantic fluency in AD patients. The semantic fluency task requires the ability to quickly retrieve and produce as many animal names as possible for one minute; thus, it has been shown to require more semantic processing than phonemic fluency (producing words beginning with a specific letter) as it also taps into speed and flexibility. The association between atrophy of the left caudate and slower visuomotor speed could support the notion that the caudate nucleus is involved in the speed aspect of the semantic fluency task. In contrast to our results, Cho et al. [2] did not identify associations between a decline in verbal learning and DGM structures.

In our study, no systematic clusters of significant brain-cognition associations appeared in the healthy controls or the subjects with MCI, which is in line with previous studies [10, 25]. The only statistically significant or trend-level brain-cognition association in all three groups was between slower visuomotor scanning and smaller index value of the left thalamus. One potential explanation for this finding may be related to basic motor coordination, as most subjects were right-handed.

There are several limitations in this study. In the MR scanning, the voxel sizes of the scanners varied, which may have reduced contrast in the small DGM structures. Specific DGM sequences would have also improved the accuracy of the TBM registrations. In addition to the relatively small sample size of the MCI group, the early disease stage among subjects in the MCI group may also explain why the MCI group did not differ from the control group. A possible risk of type 1 error in the

statistical analysis may have caused incorrect associations. In addition, our set of cognitive tests did not measure a specific DGM dysfunction, which makes it difficult to interpret the association results. One should also bear in mind that associations do not imply causal directions.

The strengths of our study are that, compared to visually based analysis methods, machine learning TBM provides an automatic, objective and detailed analysis method with more homogenous quality of the brain structures. The method also provides a quantitative estimate of the changes, and the results can be presented in visual form (Figure 1). In addition, multitemplate TBM was found to be a feasible tool to evaluate DGM structural changes and is usable for association analyses with cognitive performances of patients with dementia.

In conclusion, our study shows that TBM is a feasible method to evaluate DGM structural changes in patients with MCI and AD and the relation to cognition. Our results indicate that atrophy of DGM structures is related to cognitive impairment in AD, and DGM atrophy seems to affect tests that involve a "subcortical" or speed element, such as semantic fluency and visuomotor scanning, as well as more "cortical" cognitive functions, such as episodic memory. From a structural point of view, the thalamus and caudate nucleus seem to be the most important DGM structures for cognitive function in AD. In the future, it would be interesting to define when the DGM changes begin to appear during the degenerative process of the brain and to investigate whether the earliest changes are possible to detect with specific cognitive indicators. In addition, it would be interesting to study possible volume changes in subcomponents of the DGM structures. These studies would need larger study groups, a longitudinal study design and a specific TBM validation set for the DGM areas.

8. Statements

8.1. Statement of Ethics

The study was approved by the Joint Ethical Committee of the University of Turku and Turku University City Hospital and was performed in accordance with the 1964 Declaration of Helsinki and its subsequent amendments. The subjects received oral and written information regarding the study and provided informed consent prior to their inclusion in this study.

8.2. Disclosure Statement

J Koikkalainen and J Lötjönen are shareholders in Combinostics Ltd. The other authors have no conflict of interest to declare.

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8.4. Author Contributions

T.T. collected the MR data, performed the statistical analysis and wrote the manuscript. M.K. interpreted the statistical data and wrote the manuscript. J.K. performed the TBM data analysis and wrote the manuscript. R.P. collected the MR data. J.L. conducted the TBM study and supervised the

TBM data analysis. E.L. and S.H. were supervisors of the statistical analysis. J.O.R. conducted the study, supervised the MRI data collection and interpreted the statistical data.

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Table 1. Demographic details of the study groups.

Demographic		control	MCI	AD	Chi-square (df) * / Test statistics F (df) ¥	Overall p-value between the groups	Pairwise comparisons Groups	p-values
Number of subjects	total (154)	58	38	58				
Sex	male (77) / female (77)	28/30	17/21	32/26	1.10 (2) *	0.57		
Education	total (151)/ 1 (80)/ 2 (54)/ 3 (2)/ 4 (15)	total (56)/ 1 (25)/ 2 (23)/ 3 (2)/ 4 (6)	total (37)/ 1 (17)/ 2 (12)/ 3 (0)/ 4 (8)	total (58)/ 1 (38)/ 2 (19)/ 3 (0)/ 4 (1)	8.54 (2) *	*0.014	C vs. AD C vs. MCI MCI vs. AD	**0.01 0.74 *0.02
Age (y)	mean (SD)	71.8 (5.5)	73.7 (5.8)	74.0 (4.9)				
	median	71.3	73.5	72.6	2.76 (2) ¥	*0.07		
	min/max	57.7/87.8	61.1/85.5	57.7/85.5				
MMSE	mean (SD)	27.6 (1.3)	26.4 (2.0)	21.5 (4.2)			C vs. AD	****<0,0001
	median	28	26	22	94,90 (2) ¥	****<0.0001	C vs. MCI	*0.029
	min/max	25/30	25/30	6/29			MCI vs. AD	****<0.0001
Handedness	right (143) / left (4) / both (7)	53/2/3	36/0/2	54/2/2				

Stastitical analysis: to test differences between groups, ANOVA continued with pairwise comparisons with Tukey's corrections, Kruskal-Wallis test continued with Mann-Whitney U test and Chi-square test were used. * $\alpha < 0.05$, ** $\alpha < 0.01$, *** $\alpha < 0.001$ and **** $\alpha < 0.0001$. MCI, mild cognitive impairment, AD, Alzheimer's disease, df, degree of freedom, SD, standard deviation, MMSE, Mini-Mental State Examination.

Table 2. Statistical results of the tensor-based morphometry analysis.

Brain areas	Group	TBM results (IVs)			Test statistics F (df)	Overall p-value between the groups	Pairwise comparisons	
		Mean	Median	SD			Groups	p-value
Thalamus right	control	-0.208	-0.247	0.19	4.61 (2)	*0.011	control vs. MCI	0.914
	MCI	-0.190	-0.230	0.20			control vs. AD	*0.013
	AD	-0.094	-0.140	0.24			MCI vs. AD	0.082
Thalamus left	control	-0.282	-0.316	0.20	4.49 (2)	*0.013	control vs. MCI	0.659
	MCI	-0.319	-0.354	0.21			control vs. AD	0.078
	AD	-0.199	-0.245	0.21			MCI vs. AD	*0.015
Putamen right	control	-0.103	-0.106	0.17	8.44 (2)	****<0.0001	control vs. MCI	*0.022
	MCI	-0.195	-0.233	0.17			control vs. AD	0.251
	AD	-0.054	-0.067	0.16			MCI vs. AD	****<0.0001
Putamen left	control	-0.131	-0.111	0.15	9.81 (2)	****<0.0001	control vs. MCI	0.146
	MCI	-0.195	-0.203	0.18			control vs. AD	*0.018
	AD	-0.049	-0.055	0.15			MCI vs. AD	****<0.0001
Caudate nucleus right	control	0.011	0.001	0.23	4.75 (2)	*0.010	control vs. MCI	0.671
	MCI	0.057	0.091	0.27			control vs. AD	***0.008
	AD	0.158	0.155	0.29			MCI vs. AD	0.159
Caudate nucleus left	control	-0.154	-0.154	0.24	6.75 (2)	**0.002	control vs. MCI	0.380
	MCI	-0.079	-0.058	0.23			control vs. AD	***0.001
	AD	0.030	0.024	0.32			MCI vs. AD	0.135

Statistical analysis: to test TBM differences between the groups, one-way ANOVA continued with pairwise comparisons with Tukey's corrections were used. * $\alpha < 0.05$, ** $\alpha < 0.01$, *** $\alpha < 0.001$, and **** $\alpha < 0.0001$. TBM, tensor-based morphometry, IVs, index values, SD, standard deviation, df, degree of freedom, MCI, mild cognitive impairment, AD, Alzheimer's disease

Table 3. Statistical results of cognitive function analysis.

Cognitive function (test)	Group	Neurocognitive results			Test statistics F (df)	Overall p-value between the groups	Pairwise comparisons		Cohen's d
		Mean	Median	SD			Group	p-value	
Free recall (WMS-R Logical memory immediate recall)	control	20.6	20.0	7.0	30.02 (2)	****<0.0001	control vs. MCI	**0.005	0.66
	MCI	16.2	15.0	6.3			control vs. AD	****<0.0001	1.43
	AD	11.0	11.0	6.4			MCI vs. AD	***<0.001	0.82
Memory consolidation (WMS-R Logical memory delayed recall)	control	16.8	17.0	6.5	32.19 (2)	****<0.0001	control vs. MCI	**0.001	0.81
	MCI	11.1	8.0	7.6			control vs. AD	****<0.0001	1.57
	AD	6.3	3.0	6.9			MCI vs. AD	**0.004	0.66
Learning (CERAD wordlist learning)	control	19.8	20.0	4.4	19.56 (2)	****<0.0001	control vs. MCI	0.528	0.21
	MCI	18.9	20.0	4.2			control vs. AD	****<0.0001	1.11
	AD	14.2	14.0	5.6			MCI vs. AD	****<0.0001	0.95
Naming (CERAD naming)	control	13.0	13.0	1.7	21.63 (2)	****<0.0001	control vs. MCI	0.209	0.37
	MCI	12.3	13.0	2.1			control vs. AD	****<0.0001	1.24
	AD	9.9	10.0	3.1			MCI vs. AD	****<0.0001	0.91
Semantic processing (CERAD animal fluency)	control	21.8	21.5	5.3	5.65 (2)	**0.004	control vs. MCI	0.209	0.44
	MCI	19.6	19.0	4.6			control vs. AD	**0.003	0.58
	AD	17.8	17.5	8.1			MCI vs. AD	0.406	0.27
Visuoconstructive function (CERAD Constructional praxis)	control	9.6	10.0	1.9	3.94 (2)	*0.022	control vs. MCI	1.000	0.06
	MCI	9.7	10.0	1.6			control vs. AD	*0.035	0.41
	AD	8.8	9.0	2.0			MCI vs. AD	0.068	0.50
Visuomotor function (TMT-A)	control	71.1	64.0	36.1	11.74 (2)	****<0.0001	control vs. MCI	0.125	0.40
	MCI	86.8	83.5	41.9			control vs. AD	****<0.0001	0.82
	AD	108.9	95.0	54.3			MCI vs. AD	*0.046	0.46

Statistical analysis: to test cognitive function differences between the groups, ANOVA continued with pairwise comparisons with Tukey's corrections were used. To test effect sizes in the group comparisons, Cohen's d were used. * $\alpha < 0.05$, ** $\alpha < 0.01$, *** $\alpha < 0.001$, and **** $\alpha < 0.0001$. SD, standard deviation, df, degree of freedom, WMS-R, Wechsler Memory Scale – Revised, CERAD, The Consortium to Establish a Registry for Alzheimer's disease, TMT-A, Trail Making Test A, MCI, mild cognitive impairment, AD, Alzheimer's disease

Table 4. Statistical results of the multiple linear regression analysis and Pearson correlation coefficient in the AD group

AD group	Right thalamus		Left thalamus		Right putamen		Left putamen		Right caudate nucleus		Left caudate nucleus	
	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson
Free recall	***0.001	-0.383	0.128	-0.193	0.112	-0.201	*0.032	-0.289	***0.004	-0.343	*0.011	-0.301
Memory consolidation	***0.001	-0.375	0.105	-0.204	0.213	-0.150	0.138	-0.201	*0.026	-0.266	0.065	-0.229
Semantic processing	***0.004	-0.313	0.300	-0.134	0.273	-0.150	0.077	-0.245	**0.007	-0.301	***0.001	-0.350
Naming (b)	0.653	-0.093	0.303	0.115	0.351	0.101	0.570	-0.092	0.401	-0.133	0.502	-0.124
Learning (c)	**0.005	-0.353	0.434	-0.210	0.167	-0.211	*0.014	-0.359	*0.024	0.023	*0.025	-0.286
Visuoconstructive function (b)	0.522	-0.038	0.395	-0.046	0.614	0.035	0.256	-0.085	0.371	-0.044	0.248	-0.111
Visuomotor scanning (d)	*0.013	0.345	*0.015	0.323	0.214	0.179	0.263	0.172	*0.012	0.347	***0.001	0.420

Statistical analysis: to test associations and their directions between the DGM areas and cognitive test results, multiple linear regression analyses and Pearson correlations were used. p-values stem from the multiple linear regression analyses. (b), cube of x (x^3), (c), square of x (x^2), (d), natural logarithmic conversion (Ln). * $\alpha < 0.05$, ** $\alpha < 0.01$, and *** $\alpha < 0.005$. AD, Alzheimer's disease.

Supplementary Table 1. Statistical results of the multiple linear regression analyses and Pearson correlation coefficients for the control, MCI and AD groups.

Control group	Right thalamus		Left thalamus		Right putamen		Left putamen		Right caudate nucleus		Left caudate nucleus	
	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson
Free recall	0.192	0.230	0.109	-0.129	*0.013	-0.306	0.191	-0.162	0.822	0.047	0.406	0.171
Memory consolidation	0.265	0.206	0.172	-0.111	**0.007	-0.339	0.277	-0.144	0.950	0.007	0.459	0.160
Semantic processing	0.712	0.035	0.763	0.025	0.875	-0.144	0.492	0.017	0.594	-0.132	0.837	0.033
Naming (b)	0.245	0.134	0.781	0.041	0.923	-0.069	0.962	-0.046	0.702	-0.014	0.309	0.116
Learning (c)	0.591	0.156	0.144	-0.036	0.402	-0.119	0.708	-0.042	0.938	0.047	0.915	0.108
Visuoconstructive function (b)	0.385	-0.063	0.071	-0.177	0.137	-0.174	0.775	-0.021	*0.037	-0.257	0.249	-0.098
Visuomotor scanning (d)	0.274	0.213	**0.005	0.302	*0.038	0.238	0.098	0.206	0.210	0.240	0.323	0.220

MCI group	Right thalamus		Left thalamus		Right putamen		Left putamen		Right caudate nucleus		Left caudate nucleus	
	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson
Free recall	0.116	-0.196	*0.033	-0.360	0.818	-0.069	0.306	-0.173	*0.049	-0.328	0.452	-0.162
Memory consolidation	0.210	-0.196	*0.040	-0.319	0.999	0.027	0.595	-0.065	0.064	-0.287	0.755	-0.074
Semantic processing	0.920	0.051	0.979	-0.001	0.456	0.056	0.648	-0.085	0.860	0.073	0.663	0.012
Naming (b)	0.222	-0.292	0.114	-0.340	0.283	-0.348	0.062	-0.376	0.397	-0.249	0.843	-0.173
Learning (c)	0.617	-0.029	0.384	-0.144	0.143	0.135	0.907	-0.017	0.538	0.106	0.775	0.014
Visuoconstructive function (b)	0.073	-0.249	0.360	-0.121	0.074	-0.328	0.061	-0.295	0.165	-0.192	0.363	-0.155
Visuomotor scanning (d)	*0.033	0.388	*0.028	0.348	0.197	0.275	0.085	0.288	***0.003	0.513	0.167	0.354

AD group	Right thalamus		Left thalamus		Right putamen		Left putamen		Right caudate nucleus		Left caudate nucleus	
	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson	p value	Pearson
Free recall	***0.001	-0.383	0.128	-0.193	0.112	-0.201	*0.032	-0.289	***0.004	-0.343	*0.011	-0.301
Memory consolidation	***0.001	-0.375	0.105	-0.204	0.213	-0.150	0.138	-0.201	*0.026	-0.266	0.065	-0.229
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Figure 1. Visualization of TBM results of DGM areas for control, MCI and AD groups.