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Relationship between postural instability and subcortical volume loss in Alzheimer's disease

Young-Wook Lee, MD[a], Hyung Lee, MD, PhD[a,b], In-Sung Chung, MD, PhD[c], Hyon-Ah Yi, MD, PhD[a,b,*]

Abstract

The relationship between postural instability and subcortical structure in AD has received less attention. The aims of this study were to assess whether there are differences in the ability to control balance between Alzheimer's disease (AD) and controls, and to investigate the association between subcortical gray matter volumes and postural instability in AD.

We enrolled 107 consecutive AD patients and 37 controls. All participants underwent detailed neuropsychological evaluations, T1-weighted MRI at 3 T, and posture assessment using computerized dynamic posturography. We segmented the volumes of 6 subcortical structures of the amygdala, thalamus, caudate nucleus, putamen, globus pallidus and nucleus accumbens, and of hippocampus, using the FMRIBs integrated registration and segmentation tool.

All subcortical structures, except for the globus pallidus, were smaller in AD compared with controls on adjusting for age and gender. Falling frequencies in unilateral stance test (UST) and composite scores in sensory organization test (SOT) were worse in AD than in controls. The motor control test did not reveal any differences between groups. On subgroup analyses in AD, the groups with poor performance in UST or SOT exhibited significantly reduced nucleus accumbens and putamen volumes, and nucleus accumbens volume, respectively. The smaller volume of the nucleus accumbens was associated with postural instability in AD (OR [95% CI] 17.847 [2.59–122.80] for UST, 42.827[6.06–302.47] for SOT, all $P < .05$).

AD patients exhibited reduced ability to control balance compared with controls, and this postural instability was associated with nucleus accumbens volume loss. Furthermore, cognitive dysfunction was more prominent in the group with severe postural instability.

Abbreviations: AD = Alzheimer's disease, ANCOVA = analysis of covariance, CDP = computerized dynamic posturography, CI = confidence interval, COG = center of gravity, DA = dopamine, FIRST = FMRIBs integrated registration and segmentation tool, GP = globus pallidus, MCI = mild cognitive impairment, MCT = motor control test, MMSE = mini mental state examination, NAc = nucleus accumbens, OR = odds ratio, SCI = subjective cognitive impairment, SOT = sensory organization test, UST = unilateral stance test.

Keywords: Alzheimer's disease, postural instability, subcortical volume

1. Introduction

Postural instability in older adults and Alzheimer's disease (AD) is a common but serious problem as it may lead to severe injury with falling [1] and increases socioeconomic burden. However, the relationship between postural instability and cognitive function in AD has received little attention, given that several comorbidities are typically present in the elderly. In several cross-sectional studies, postural instability was associated with cognitive impairment and falling.[2–4] With the observation of disturbed balance and gait in the very early stages of AD,[5] patients with subjective cognitive impairment (SCI) or mild cognitive impairment (MCI) have also been found to have deficits in balance control with an increasing severity of cognitive impairment.[6,7]

The assessments of posture in most previous studies[5,8–10] were subjective and non-quantitative, as they were based on self-reported questionnaires or simple neurological examinations. It is generally accepted that computerized dynamic posturography (CDP) has the ability to evaluate balance quantitatively.[8,11,12] Thus, CDP has been widely used to diagnosis patients with postural instability and may predict the future risk of falling.

The neuropathology underlying AD has a predominantly cortical distribution,[13] but there have been a few evidences that showed subcortical involvement in AD.[13–15] In the aspects of regarding balance control as a part of spatial learning, the role of the hippocampus and the basal ganglia was suggested to be important.[16–17] The advances of neuroimaging enabled researchers to clarify brain areas responsible for clinical symptoms of AD. Regarding postural instabilities, a few structural factors such as ventricular size, white matter hyperintensities,[9,10,18] whole brain atrophy,[5] hippocampal volume,[19] and focal atrophy of fronto-parietal regions or sensorimotor regions [20] were suggested. However, subcortical structures have not been in the focus of previous studies despite evidences of the role of the subcortical structures on postural control. To the best of our knowledge, no study has focused on

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[a] Department of Neurology, [b] Brain Research Institute, [c] Department of Occupational and Environmental Medicine, Keimyung University School of Medicine, Daegu, South Korea.

[*] Correspondence: Hyon-Ah Yi, Department of Neurology, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu, South Korea (e-mails: geschwind@dsmc.or.kr, neurofree@gmail.com).

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the association between subcortical structural change and postural instability using CDP, a well-known quantitative balance control test, in AD.

In the current study, we used cross-sectional imaging data, first, to determine differences in the volumes of 6 subcortical structures, the thalamus, caudate nucleus, putamen, globus pallidus (GP), amygdala and nucleus accumbens (NAc), as well as the hippocampus between AD and controls. Second, we aimed to investigate differences in balance control between groups as assessed by CDP. Finally, we aimed to determine the role of the subcortical structures on posture in AD. We hypothesized that the ability to control balance might be different in AD and controls, and specific subcortical structures would exhibit prominent volume loss in accordance with postural imbalance in AD patients.

2. Materials and methods

2.1. Participants

This cross-sectional study included the patients who visited the memory clinic of the Keimyung University Dongsan Medical Center for evaluation of cognitive function from December 2010 to March 2012. All participants were the people who were not previously diagnosed as having dementia. Diagnostic work-up included clinical assessment of history taking, neurological examination, laboratory tests, neuropsychological evaluation, postural assessment by CDP, and brain MRI. The AD patients fulfilled the criteria of probable AD of the National Institute of Neurological and Communicative Diseases and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA).[21] Participants with no subjective cognitive complaints and normal cognition were included as controls.

We excluded participants if any of the following criteria were met: age < 55 or >90, a score below 10 on the Mini Mental State Examination (MMSE),[22] MCI fulfilling the criteria defined by Petersen,[23] accompanying conditions that could potentially affect postural control such as parkinsonism, central or peripheral vestibular diseases, diabetes or severe osteoarthritis, other types of dementia rather than AD (i.e., dementia with Lewy bodies), history of psychiatric episodes or substances abuse, lesions in subcortical structures, white matter hyperintensities of Fazekas grade >1,[24] or failure of FMRIBs Integrated registration and segmentation tool (FIRST) image analysis algorithm.[25]

This study was conducted in accordance with regional research regulations and conformed to the Declaration of Helsinki. This study was approved by the medical ethics committee of the Keimyung University Dongsan Medical Center, South Korea, and written informed consent for their clinical data was obtained from all participants for research purposes.

2.2. Neuropsychological assessments

All participants underwent a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery (SNSB),[26] which contains the following sub-domains: attention, language and related function, visuospatial function, visual and verbal memory, frontal/executive function, and MMSE.

2.3. Postural assessment using computerized dynamic posturography

We used CDP (EquiTest version 4.0, NeuroCom, Clackamas, OR) to evaluate postural control quantitatively. It consists of footplate with visual surround and a software program, which measures and records the vertical and horizontal forces exerted by the participant's feet. The assessment has 3 parts of sensory organization test (SOT), motor control test (MCT), and unilateral stance test (UST). The participants were asked to put their barefeet parallel on the footplate while staring straight ahead during testing. The SOT, which assesses the ability of participants to process individual sensory input to maintain balance control under the combined conditions of eye opening status, sway of footplate, or movement of visual surrounds, was performed under the following 6 conditions for 20 seconds twice: (1) eyes-open with fixed footplate and visual surround, (2) eyes-closed with fixed footplate and visual surround, (3) eyes-open with fixed footplate and moving visual surround, (4) eyes-open with sway of footplate and fixed visual surround, (5) eyes-closed with sway of footplate and fixed visual surround, (6) eyes-open with sway of footplate and visual surround. COG sway angle, that is, antero-posterior or medio-lateral, were presented as COG alignment. In addition, an equilibrium composite score, which is calculated by comparing the angular difference between a participant's maximum anterior to posterior COG displacement and the maximum possible sway range of 12.5°. A score of 0 indicates a fall, whereas a score of 100 indicates no sway. The MCT assesses the ability of the automatic motor system to quickly recover following unexpected external disturbances. When footplate moves forward or backward with different speeds of 5 cm/sec (small), 10 cm/sec (medium), or 15 cm/s (large), the time in milliseconds from movement of footplate to initiation of the active force response in a leg was measured, which is defined as latency. The UST was performed with standing on 1 foot on a footplate for 10 seconds 6 times with eyes-open. The participants chose the foot they preferred to stand on. The falling frequencies in each participant, the mean sway velocity in each trial and the mean time to fall in the cases of falling were obtained. CDP was conducted by 1 technical expert (HL), who was blinded to the information of participants, at the vestibular laboratory in the Keimyung University Dongsan Medical Center.

2.4. Imaging acquisition and analysis

Brain MRI was performed at the initial visit, using a 3.0 Tesla scanner (Signa, HDxt, GE Healthcare, Milwaukee, WI) with an 8-channel head coil. For measurement of the subcortical volumes, a 3-dimensional, T1-weighted-fast spoiled gradient echo sequence was obtained with acquisition parameters as follows: repetition time/echo time 8.89/3.57 ms; flip angle, 20°; field of view, 250 mm; matrix size, 256×256; 212 sagittal slices; slice thickness, 1.4 mm, no gap. Routine T2-weighted, fast fluid attenuated inversion recovery (FLAIR) and Gradient Echo imaging were also obtained to exclude structural lesions that may affect cognitive function and postural instability such as mass or vascular lesions, and white matter hyperintensities.

All the T1-weighted were processed and analyzed automatically with the tools of the FSL software package (FMRIB Software Library, http://fmrib.ox.ac.uk/fsl/fslwiki/). Using the algorithm FIRST,[25] we segmented the bilateral amygdala, thalamus, hippocampus, GP, NAc, caudate nucleus, and putamen. The left and right volumes of each structure were summed. Examples of subcortical segmentation using FIRST are presented in Fig. 1. Whole brain volume and volumes of each structure, automatically calculated using SIENAX (Structural Image Evaluation using Normalization of Atrophy, Cross-sectional),[27,28] were normalized for head size via volumetric scaling factor, which was calculated by registering the brain

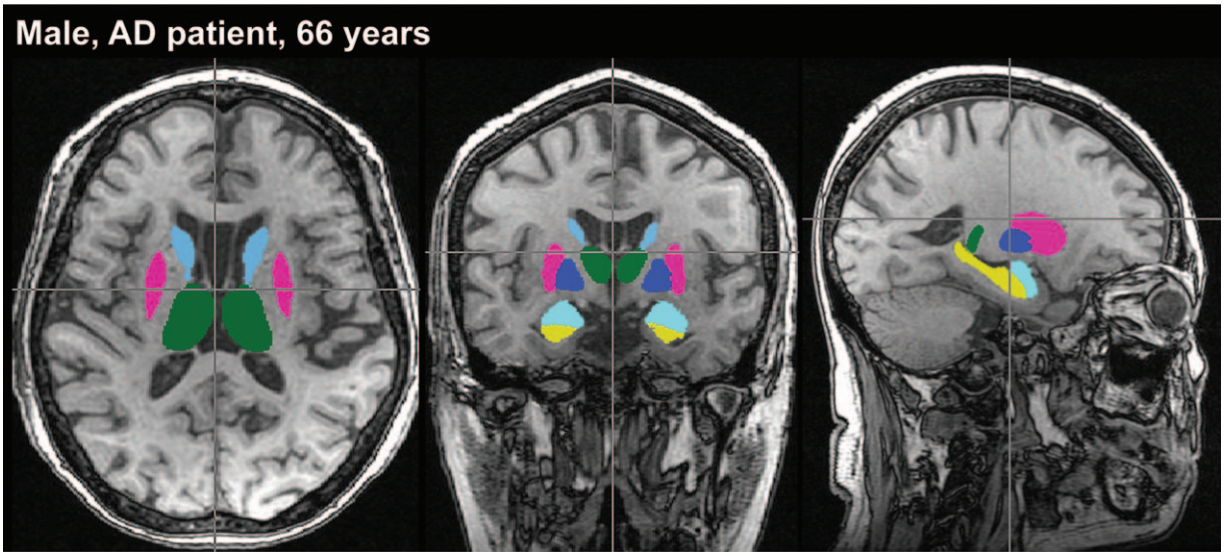

Figure 1. Example of automated segmentation of subcortical gray matter structure using FIRST in AD patient. Segmentations are shown overlaid on the 3D T1-weighted images in 3 orthogonal orientations, corresponding to the axial (left column), coronal (middle column), and sagittal (right column) planes. Colored structures—yellow: Hippocampus; Turquoise: Amygdala; Green: Thalamus; Light blue: Caudate nucleus; Pink: Putamen; Dark blue: Globus pallidus; Orange: Nucleus accumbens. AD = Alzheimer's disease.

image to MNI152 (Montreal neurological Institute, Montreal, Canada) space.

2.5. Statistical analysis

We performed statistical analyses using IBM SPSS statistics for OSX, version 22 (IBM Corp). We compared groups using χ^2 *test*, *t*-test, and analysis of covariance (ANCOVA) corrected for age, gender, and education. For the comparisons between AD subgroups classified by CDP performances, we used *t*-test and ANCOVA with age and gender as covariates. To evaluate the association and to quantify the strength of the association between subcortical structural volume and postural instability in AD, multiple logistic regression analyses for the groups classified by CDP results were performed: the performance of the UST and SOT served as the dependent factors, and the volumes of the subcortical structures as the independent factors. Age and gender served as covariates. Odds ratios (ORs) with 95% confidence interval (CI) are presented. The resulting ORs can be interpreted as an increased association of postural instability for every SD of reduced volume.

3. Results

3.1. Demographic characteristics and subcortical volumes of the participants

Of the initial 154 participants included in the dataset, 10 participants were excluded for the following reasons: 7 participants had a history of long-standing dizziness and 3 participants had severe visual disturbance. Finally, 37 controls (64.4 ± 6.1 years; F/M 26/11) and 107 AD (70.2 ± 8.3 years; F/M 77/30) were included in this study.

Demographic characteristics and subcortical volumes of all participants are presented in Table 1. Significant differences in age, education, and cognitive scores were noted between groups ($P < .001$). ANCOVA with corrections for age, education, gender, and MMSE revealed that all the subcortical structures were smaller in AD than in controls, except for the GP ($P < .001$).

3.2. Posture assessment using CDP

The postural assessment results using CDP were presented in Table 2. For the SOT, the composite score was higher in controls than in AD (78.30 ± 4.62 vs 74.73 ± 7.80, $P = .001$). However, this difference disappeared after adjusting for age, education, gender, and MMSE. The COG alignments in 6 SOT conditions were different, revealing a difference in medio-lateral movement in AD than in controls ($P < .05$). When corrected for age and gender, these differences remained significant only in conditions 3 and 4. The antero-posterior COG alignments were not different between groups. For the MCT, mean latencies in forward and backward conditions did not differ between AD and controls in every conditions. For the UST, AD patients fell more frequently, and mean sway velocities in AD were faster than controls. In patients who experienced falling, mean time to fall was also shorter in AD than in controls, and these results remained significant after adjusting for age, education, gender, and MMSE.

3.3. Postural instability, cognitive function, and subcortical volumes in AD patients

As the significant differences of composite scores in the SOT and falling frequency in the UST were found, patients with AD were divided into 2 groups according to performances on each test and analyzed. For falling frequency in the UST, UST (+) was defined as the cases who fell more than 3 times of 6 total trials and UST (−), as the case of falling less than 4 times. For composite score in SOT, we defined SOT (+) as the cases in the lower 50% of composite score, and SOT (−) as the upper 50%. The comparison between UST (+) and UST (−) as well as SOT (+) and SOT (−) did not reveal any difference in gender, education, height, or weight. A difference in age was noted between groups (UST (+) 71.7 ± 7.8 years, UST (−) 65.5 ± 8.4 years; SOT (+) 73.4 ± 6.8 years, SOT (−) 66.7 ± 8.4 years, all $P < .05$). A difference in MMSE score was found only between UST (+) and UST (−) (19.8 ± 4.5, 22.4 ± 4.0 respectively, $P < .05$) (Table 3).

Table 1

Demographic features and normalized brain volume in each group.

Demographics	Control (n = 37)	AD (n = 107)	*P*
Gender, men/women, women %*	11/26 (70.3)	30/77 (72)	NS
Age, y	64.4 ± 6.1	70.2 ± 8.3	*P* < .001
Education, y	10.7 ± 4.1	6.1 ± 4.7	*P* < .001
Height, cm	157.8 ± 6.4	156.0 ± 8.5	NS
Weight, kg	58.4 ± 6.7	57.0 ± 9.0	NS
MMSE	26.6 ± 2.6	20.5 ± 4.5	*P* < .001
Normalized volume (cm^3)			
Hippocampus‡	9.3 ± 1.2	8.3 ± 1.4	*P* < .001
Thalamus†	19.3 ± 1.4	18.0 ± 1.9	*P* < .001
Caudate nucleus	9.0 ± 0.8	8.4 ± 1.0	*P* < .001
Putamen†	11.2 ± 1.0	10.2 ± 1.4	*P* < .001
Globus pallidus	4.4 ± 0.6	4.2 ± 1.0	NS
Nucleus accumbens†	1.0 ± 0.3	0.8 ± 0.3	*P* < .001
Amygdala†	3.6 ± 0.5	3.2 ± 0.6	*P* < .001

All data are represented as (mean ± sd) unless indicated otherwise.
MMSE = mini mental state examination, NS = nonsignificant.
* chi-square test. For the normalized brain volume, univariate general linear model analyses with corrections for age, education, gender, and MMSE score were performed.
† *P* < .001.
‡ *P* < .05.

Comparisons of cognitive function between UST (+) and UST (–) revealed that language, visuospatial, verbal and visual memory, frontal-executive functions, and MMSE were worse in UST (+) than in UST (–) (all $P < .05$). When corrected for age, gender, and MMSE, these differences remained same in all cognitive domains. Comparing SOT (+) with SOT (–), SOT (+) showed worse performances in verbal memory and frontal executive function, which remained significant after correction for age, gender, and MMSE (Table 3).

We compared subcortical volumes between UST (+) and UST (−). Putamen and nucleus accumbens were smaller in UST (+) than in UST (−) ($P < .05$). Correcting for age, gender, and MMSE showed significant volume loss of nucleus accumbens only (Table 3). Comparing SOT (+) with SOT (−), SOT (+) exhibited smaller volume in the thalamus, hippocampus, and NAc, but only NAc had significant volume loss after adjusting for age, gender, and MMSE ($P < .05$). Multiple logistic regression showed that smaller volume of the NAc was associated with postural instability (OR [95% CI], 17.85 [2.60–122.80] for UST, 42.85 [6.06–302.47] for SOT) (Table 4).

4. Discussion

The main finding of current study is that falling frequency in the UST and composite score in the SOT as markers of postural instability were associated with NAc volume loss in AD. Additionally, postural instability and the volume loss of all subcortical structures, except for GP, were much severe in AD compared with controls, and the AD subgroups of poorer postural instability assessed by falling frequency in the UST and composite score in the SOT showed worse cognitive function.

Numerous researchers have demonstrated increased frequencies of falling and severe postural instability in AD compared with cognitively normal elderly.[1,29] Considering the fact that even people with MCI or SCI have impaired balance [6,7,30] and various parameters of balance control were associated with the severity of cognitive dysfunction,[3,6,7] assessment of postural instability in AD might provide a clue for an earlier diagnosis of AD and a method to provide further individualized management. However, many of these studies[5,8–10] used self-reported questionnaires for falling or simple tests of walking abilities for given time, which provided limited information about participant performances. Thus, we adopted CDP for quantitative assessment of balance control in AD and hypothesized that CDP performance might be more impaired in AD than in controls as in the previous reports. As expected, we observed that AD exhibited more severe postural instability than controls. Although previous studies that evaluated posture control in AD quantitatively confirmed poor balance in AD, results were inconsistent regarding individual parameters of posturography. One study of balance features in AD and MCI demonstrated that the antero-posterior sway was the most frequently involved parameter,[7] but in another, the medio-lateral sway was affected more.[30] In the current study, AD showed more severe medio-lateral sway in every SOT condition. However, these significances remained only in conditions with sway of referenced visual and surface (condition 3 and 4, respectively), after correcting for age and gender. Significant sway in these 2 conditions is possibly attributed to the fact that other conditions are too easy (i.e., condition 1 and 2) or too complicated (i.e., conditions 5 and 6) to discriminate AD and controls. In addition, lower composite scores in SOT were noted in AD compared with controls, indicating more tendencies to fall with the change in sensory input in AD.

A few previous reports of the value of unilateral stance in AD are available.[31,32] In our study, AD showed higher falling frequency, faster sway velocity and shorter time to fall than in

Table 2

Computerized dynamic posturography (CDP) results.

Test		Control (n = 37)	AD (n = 107)	*P*
UST	Falling frequency on EO*	1.49 ± 1.92	4.67 ± 1.84	*P* < .001
	Mean sway velocity on EO*	1.14 ± 0.31	1.33 ± 0.43	*P* < .05
	Mean time to fall on EO†	4.55 ± 2.36	3.02 ± 2.17	*P* < .05
SOT	Composite score	78.30 ± 4.62	74.73 ± 7.80	*P* < .05
MCT (latency, ms)	Small-backward	146.89 ± 16.64	149.07 ± 16.60	NS
	Medium-backward	140.68 ± 16.55	140.51 ± 14.84	NS
	Large-backward	138.78 ± 15.79	137.94 ± 14.11	NS
	Small-forward	152.03 ± 20.22	154.39 ± 16.99	NS
	Medium-forward	140.14 ± 15.48	140.89 ± 14.74	NS
	Large-forward	137.16 ± 15.97	139.02 ± 14.38	NS

AD = Alzheimer's disease, CDP = computerized dynamic posturography, EO = eyes-open condition, MCT = motor control test, NS = nonsignificant, SOT = sensory organization test, UST = unilateral stance test.
All data are represented as (mean ± sd) unless indicated otherwise.
* *P* < .001 on correcting for age, education, gender, and MMSE score.
† *P* < .05 on correcting for age, education, gender, and MMSE score.

Table 3

Demographic features, normalized brain volume and cognitive function in AD subgroups classified by CDP performances.

Demographic	UST (+) n=81	UST (−) n=26	*P*	SOT (+) n=56	SOT (−) n=51	*P*
Gender, men/women, women %	21/61 (74.1)	9/17 (65.4)	NS	18/38 (67.9)	12/39 (76.5)	NS
Age, y	71.7±7.8	65.6±8.4	$P<.05$	73.4±6.8	66.7±8.4	.000
Education, y	5.7±4.6	7.5±5.0	NS	6.7±5.3	5.5±4.0	NS
Height, cm	157.8±8.5	156.5±8.5	NS	157.1±9.0	154.8±7.8	NS
Weight, kg	57.5±8.8	55.6±9.5	NS	55.5±9.1	58.7±8.7	NS
Normalized volume, cm^3						
Hippocampus	8.2±1.4	8.48±1.3	NS	8.0±1.1	8.6±1.6	$P<.05$
Thalamus	17.8±2.0	18.4±1.7	NS	17.4±1.6	18.5±2.1	$P<.05$
Caudate nucleus	8.3±1.0	8.6±1.0	NS	8.3±1.0	8.4±1.0	NS
Putamen	10.1±1.5	10.7±1.1	$P<.05$	10.0±1.3	10.5±1.4	NS ($P=.05$)
Globus pallidus	4.2±1.1	4.1±0.4	NS	4.1±1.0	4.3±0.9	NS
Nucleus accumbens	0.7±0.3	0.9±0.2	$P<.05$†	0.7±0.2	0.9±0.3	$P<.001$*
Amygdala	3.2±0.6	3.3±0.6	NS	3.2±0.6	3.3±0.6	NS
Cognitive function, total score						
MMSE, 30	19.8±4.5	22.4±4.0	$P<.05$†	20.1±4.7	20.8±4.3	NS
Attention	4.5±1.1	4.9±1.1	NS	4.6±1.0	4.6±1.2	NS
Language, 60	29.2±10.8	38.5±7.7	.000†	30.3±10.9	32.8±10.9	NS
Visuospatial function, 32	16.7±10.2	22.5±10.1	$P<.05$†	17.0±10.4	19.3±10.6	NS
Verbal memory, 36	11.3±4.2	14.5±3.8	$P<.05$†	11.1±4.4	13.3±3.9	$P<.05$*
Visual memory, 32	2.2±2.9	5.3±5.4	$P<.05$†	2.6±3.2	3.4±4.4	NS
Frontal-executive function, 120	39.4±21.3	57.1±27.4	$P<.05$†	33.1±19.2	55.3±23.5	.000†

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

AD=Alzheimer's disease, CDP=computerized dynamic posturography, NS=nonsignificant, SOT=sensory organization test, UST=unilateral stance test, UST(+)=the group with a falling frequency more than 3 in UST, UST(−)=the group with a falling frequency less than 4 in UST. For the normalized brain volume and cognitive function, ANCOVA with correction for age, gender, and MMSE score were performed.

* $P<.05$.

† $P<.001$.

controls. Additionally, these UST parameters were correlated with cognitive dysfunction in selective domains as well as general cognition such as MMSE. This finding is consistent with a previous study demonstrating that an abnormal 1-leg balance test was a marker of more advanced dementia.[32] From previous and current studies, the UST may be a useful tool for differentiating AD from people with normal cognition and could serve as an important marker of the poor cognitive function.

Previous studies on motor latency during posturography in AD demonstrated contradictory findings. Some studies revealed a significant correlation between motor latency and cognitive function,[33,34] but others failed to show a definite association between these factors.[35] We could not find any significant differences in mean latency in MCT between AD and controls, suggesting that AD patients had relatively preserved efferent motor copy system compared with controls. A further study is needed to resolve this issue.

In the current study, we found the poorer cognitive performances in AD subgroups with more severe postural instability, classified by CDP performances. Besides the studies of relationship between motor latency and cognition described above, there were evidences that cognitive dysfunctions in selective domains as well as general cognition such as MMSE would contribute to the falling or gait disturbance in AD. Executive function[34] or attention,[36,37] as well as visuospatial function[37] was suggested to be risk factors for falling and postural instability. Consistent with these observations, our exploratory analyses demonstrated that the group with higher falling frequencies in UST [UST (+)] had poorer performances in all cognitive domains we assessed, and the group with lower composite score in the SOT [SOT(+)] was poorer in verbal memory and frontal-executive function. These findings suggest that postural instability might be an important marker of the poor cognitive function in addition to the prediction of further

Table 4

Multiple logistic regression analyses in AD patients.

	UST(+)			SOT(+)		
	R square	Odds ratios (95% CI)	*P*	*R* square	Odds ratios (95% CI)	*P*
Thalamus	0.035	1.227 (0.94–1.60)	NS	0.112	1.424 (1.11–1.82)	$P<.05$
Hippocampus	0.010	1.154 (0.83–1.60)	NS	0.06	1.388 (1.03–1.88)	$P<.05$
Caudate	0.025	1.374 (0.86–2.20)	NS	0.005	1.139 (0.77–1.69)	NS
Putamen	0.06	1.465 (1.00–2.14)	$P<.05$	0.048	1.339 (0.99–1.81)	NS
Globus pallidus	0.003	0.884 (0.53–1.46)	NS	0.025	1.347 (0.85–2.08)	NS
Nucleus accumbens	0.132	17.847 (2.59–122.80)	$P<.05$†	0.214	42.827 (6.06–302.47)	$P<.001$†
Amygdala	0.008	1.339 (0.62–2.89)	NS	0.005	1.219 (0.64–2.33)	NS

AD=Alzheimer's disease, CI=confidence interval, NS=nonsignificant, SOT (+)=composite score in the sensory organization test, UST (+)=falling frequency in the unilateral stance test with eyes-open.

† $P<.05$ on correcting for age, gender, and MMSE score.

cognitive decline, which is consistent with previous results of the role of abnormal 1-leg balance test in AD.[31,32]

From the increasing evidences that cognitive dysfunction could be related to subcortical structures in AD[14,38] and postural instability,[34,35,37] we hypothesized the role of subcortical gray matter on postural instability via connection to the cortex or hippocampus, especially in AD. Subgroup analyses classified by CDP performances in AD demonstrated smaller volumes of putamen and NAc in UST(+), and of the thalamus and NAc as well as hippocampus in SOT(+). In addition, associations between falling frequencies in the UST and NAc volumes, as well as composite score in the SOT and NAc volume were noted. Indeed, the subcortical structure, especially NAc as a part of basal ganglia, might be closely related to postural instability in AD.

The vestibular system, which is responsible for generating vestibulo-spinal reflexes, had a role in cognition.[39] Through processing of spatial information such as the cues from personal and extra-personal spaces, the vestibular system is involved in maintaining balance. The relation between vestibular function and cognition is based on the cortical-subcortical network.[37] Five vestibular pathways[39] which are related to cognition have been proposed: (1) a vestibulo-thalamo-cortical pathway, (2) a pathway from dorsal tegmentum to entorrhinal cortex via thalamus, (3) a pathway from nucleus reticularis to hippocampus, (4) a pathway via cerebellum and thalamus, (5) a pathway to basal ganglia. Among them, our finding, which showed the associations between NAc volume reduction and postural instability, supports the basal ganglia hypothesis. As a part of basal ganglia, the NAc contributes to vestibular function through internal spatial representation as well as spatial learning and memory with the connections with limbic areas.[16,17,39,40]

NAc is located in the region where the caudate nucleus and the putamen meet the septum pellucidum. Within the networked connections in the basal ganglia, NAc receives input via the mesolimbic dopaminergic projections from the VTA and substantia nigra, and glutamatergic projections from the amygdala, hippocampus, thalamus, and prefrontal cortex.[41] The main output from the NAc project to thalamus, substantia nigra-ventral tegmental area, GP, amygdala.

Transmission of the vestibular signal can be achieved through the vestibular-striatal pathway, in which projection fibers from vestibular nucleus to the thalamus synapse with projection fibers into the putamen and striatum.[42] The vestibular sensory input is represented in the part of striatum including NAc.[43] With changes in vestibular signaling, several neurochemical changes, such as of dopamine (DA), GABA, acetylcholine, were found in the striatum. Animals with vestibular deficit showed changed in DA activity or DA receptors and resultant GABAergic responses in the striatum.[43] Conversely, administration of glutamate antagonists reduced locomotion and DA agonist injection into the NAc enhanced locomotor activity.[44] DA is important in detecting changes in familiar information.[45] NAc is an area with higher DA turnover than other striatal structures and high concentration of acetylcholine.[41] In addition, striatal DA enhances activation of NMDA receptors[17] and decreased DA or increased cholinergic activities enhance the production of GABA.[43] These findings suggested that dysfunction of the NAc results in the changes of DA activity and subsequent neurochemical changes, which might be related to vestibular or locomotor deficit as well as well-known neurological and psychiatric conditions such as depression, Parkinson's ds, and drug addiction.[41] Also, functional or neurochemical changes resulted from the volume loss of NAc, which has rich connections with neighboring cortex, might be responsible for mood and behavioral changes in AD.

Spatial navigation requires a continuous representation of the location and body motion with vestibular and visual cues. There was a study that showed striatal neuronal firing induced by specific egocentric movements (e.g., body turning, or forward movement).[17] Retailleau et al[16] suggested that NAc lesions impaired the acquisition of conditioned place preference through the connection with hippocampus, which lead to imbalance or falling. Also, Ferretti et al[40] found the role of the ventral striatum in allocentric learning by intra-accumbens injection of glutamatergic antagonist and Stiles and Smith[43] suggested that vestibular signals use together with sensorimotor inputs in the striatum for body and limb control. Our findings suggest that volume reduction of NAc connected with hippocampus and vestibular structures may impair spatial memory processing through encoding of spatial information, thus leading to postural instability in AD.

Our study has a number of strengths and limitations. One of the strengths is the strict inclusion criteria to eliminate the possibility of other factors affecting postural control, such as mild white matter hyperintensities, and history of falling or vertigo. Additionally, we excluded individuals with subjective cognitive impairment. Despite strict inclusion criteria, we enrolled relatively large numbers of participants. As FIRST, an automated method for subcortical volume extraction, is known to be superior in assessing basal ganglia, this type of approach could be more reliable, considering our goal of defining the role of subcortical structures. Among the possible limitations, first is the fact that we could not reveal the changes of brain volume and CDP performance according to the changes in cognitive function given that our study was cross-sectional in nature. Although our point was to identify the brain structure related to posture control in given time point, adding follow-up information of brain imaging and CDP would be useful in assessing the relations between the factors, and predicting prognosis. Second, the number of controls was small as this study was performed in memory-clinic of the university hospital with strict inclusion criteria. Third, we could not include number of drugs daily taken as confounder. Fourth, we arbitrarily defined poor performance of falling frequency in the UST (UST (+)) and composite score in the SOT (SOT (+)). However, no established criteria are available for the classification of postural instability according to the performance in CDP. Further studies to resolve this issue are necessary. Finally, combining our findings with functional neuroimaging such as diffusion-tensor imaging or PET, and cortical structural data would add powerful interpretations to our subcortical structural imaging study.

In conclusion, we confirmed subcortical volume reduction and poorer balance control in AD compared with controls and found that only NAc volume had significant association with postural instability in AD. In addition, falling in the UST might be an important marker for postural instability in AD. Despite these conclusions, further longitudinal studies with CDP, cognition, and functional neuroimaging would clarify the value of the NAc volume on the given time point in posture control, which would benefit from therapeutic physical intervention in the clinical fields.

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