

# Prediction of Treatment Response to Donepezil using Automated Hippocampal Subfields Volumes Segmentation in Patients with Mild Alzheimer's Disease

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Previous studies reported some relationships between donepezil treatment and hippocampus in Alzheimer's disease (AD). However, due to methodological limitations, their close relationships remain unclear. The aim of this study is to predict treatment response to donepezil by utilizing the automated segmentation of hippocampal subfields volumes (ASHS) in AD. Sixty four AD patients were prescribed with donepezil and were followed up for 24 weeks. Cognitive function was measured to assess whether there was a response from the donepezil treatment. ASHS was implemented on non-responder (NR) and responder (TR) groups, and receiver operator characteristic (ROC) analysis was conducted to evaluate the sensitivity, specificity, and accuracy of hippocampal subfields in predicting response to donepezil. The left total hippocampus and the CA1 area of the NR were significantly smaller than those of the TR group. The ROC curve analysis showed the left CA1 volumes showed highest area under curve (AUC) of 0.85 with a sensitivity of 88.0%, a specificity of 74.0% in predicting treatment response to donepezil treatment. We expect that hippocampal subfields volume measurements that predict treatment responses to current AD drugs will enable more evidence-based, individualized prescription of medications that will lead to more favorable treatment outcomes.

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**Key Words** Hippocampal subfields volumes, Donepezil, Alzheimer's disease, Treatment response.

## INTRODUCTION

Alzheimer's disease (AD) is a chronic and disabling disorder associated with substantial impairment, decreased quality of life in the older adults. As there is no treatment available which could modify the disease process, the mainstay of the treatment of AD has been symptomatic management using the acetylcholinesterase inhibitors (ChIEs) and glutamate antagonists.<sup>1</sup> Among the ChIEs, the donepezil is used worldwide for cognitive and behavioral management of AD. Although the donepezil has been clinically recognized to stabilize cognition for 6 to 12 months, a large proportion of AD patients

experience cognitive decline even after the initial intervention.<sup>2</sup> Possibly the reason for these differences in treatment responsiveness are due to various factors such as racial, ethnic, genotype disparities, clinical stage of dementia, co-morbidities, concomitant medication, functional and structural neuronal substrates.<sup>2-5</sup> However, fundamental reason for this variability is not well understood, but this is essential for understanding etiologies of AD and enhancing effective strategies for management of AD.

As the hippocampus is the core brain region playing a major role in memory function, its atrophy is frequently suggested as an important biomarker of AD trajectory. In this regard, a previous study showed reduced hippocampal volumes and deformations of the cornu ammonis region 1 region (CA1) and subiculum subfields were correlated with a poorer response to donepezil treatment.<sup>6</sup> However, a longitudinal study did not prove the volumetric and shape change associated with treatment response of donepezil in AD patients.<sup>7</sup> These might be attributable to small sample sizes and the methodological limitations of their analyses (3D surface mapping).

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Moreover, resemblance of hippocampus to a 'Swiss roll' hindered 3D surface mapping from delineating subtle differences between the subfields.<sup>8</sup> To overcome the aforementioned methodological limitations, we used the subfield volume segmentation to elaborate the subtle changes of the hippocampus during the donepezil treatment in AD.

The aim of this study is to explore the anatomical differences between the treatment responders and non-responders to 24 weeks donepezil treatment of AD. In addition, we also attempted to identify the hippocampal subfields which could predict the treatment response of 24 weeks of donepezil treatment in the patients with AD.

## METHODS

### Subjects

Sixty-four AD patients were recruited in this study. The inclusion criteria are as follows: 1) a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) criteria,<sup>9</sup> 2) a score on the Clinical Dementia Rating Scale (CDR)=0.5 or 1.<sup>10</sup> Subjects who had other neurological or psychiatric conditions and those taking any psychotropic medications were

excluded. The study was approved by Institutional Review Board of the Catholic University of Korea. Written informed consent was obtained from all subjects and their guardians.

### Donepezil treatment

Study participants were prescribed donepezil at a dose of 5 mg/day for the first 28 days; the dose was increased to 10 mg/day thereafter. After the 24-week study period, those who presented with 2 points or more improvement in Mini-Mental Status Examination (MMSE) from baseline were grouped as responders in the previous study.<sup>11</sup>

### MRI acquisition

Imaging data were collected with a 3-Tesla Siemens Verio scanner located in the St. Vincent Hospital. The T1 weighted three dimensional magnetization prepared rapid gradient-echo (MPRAGE) sequences parameters were as follows: TE=2.5 ms; TR=1900 ms; inversion time (TI)=900 ms; flip angle (FA)=9°; FOV=250×250 mm; matrix=256×256; and voxel size=1.0×1.0×1.0 mm<sup>3</sup>. T2-weighted MRI sequences were as follows: TE=91 ms; TR=3700 ms; flip angle (FA)=150°; FOV=220×220 mm; matrix=448×448 in plane resolution, and 3-mm slice thickness.

**Table 1.** Demographic and clinical characteristics of study participants

	TR (N=38)	NR (N=26)	p value
Age (years±SD)	69.8±4.1	71.1±6.5	NS
Education (years±SD)	9.5±4.3	9.6±3.7	NS
Sex (M:F)	14:24	10:16	NS
CDR	0.8±0.3	0.8±0.3	NS
CDR-SB	4.8±1.5	4.5±2.2	NS
Total ICV (mm <sup>3</sup> ±SD)	136,3931±143,029.5	1,356,751±116,598.8	NS
Left normalized volume (mm <sup>3</sup> ±SD)			
Total hippocampus	2,131.9±239.3	1,901.9±229.9	<0.0001
CA1	1,112.2±170.6	937.1±146.3	<0.0001
CA2	12.0±2.1	11.6±3.2	NS
CA3	47.5±4.4	47.1±4.4	NS
DG	625.6±94.0	572.4±111.2	NS
SUB	334.4±43.1	333.6±25.8	NS
Right normalized volume (mm <sup>3</sup> ±SD)			
Total hippocampus	1,965.4±336.7	1,893.7±218.6	NS
CA1	1,017.2±207.9	980.0±184.9	NS
CA2	12.2±4.3	13.2±4.3	NS
CA3	39.9±9.6	37.5±9.3	NS
DG	600.4±113.6	551.9±114.5	NS
SUB	295.5±44.0	311.0±29.6	NS

TR: treatment responder, NR: treatment non-responder, SD: standard deviation, CDR: Clinical Dementia Rating, CDR-SB: CDR sum-of-box, MMSE: Mini Mental Status Examination, ICV: intracranial volume

### Hippocampal subfield volumes segmentation

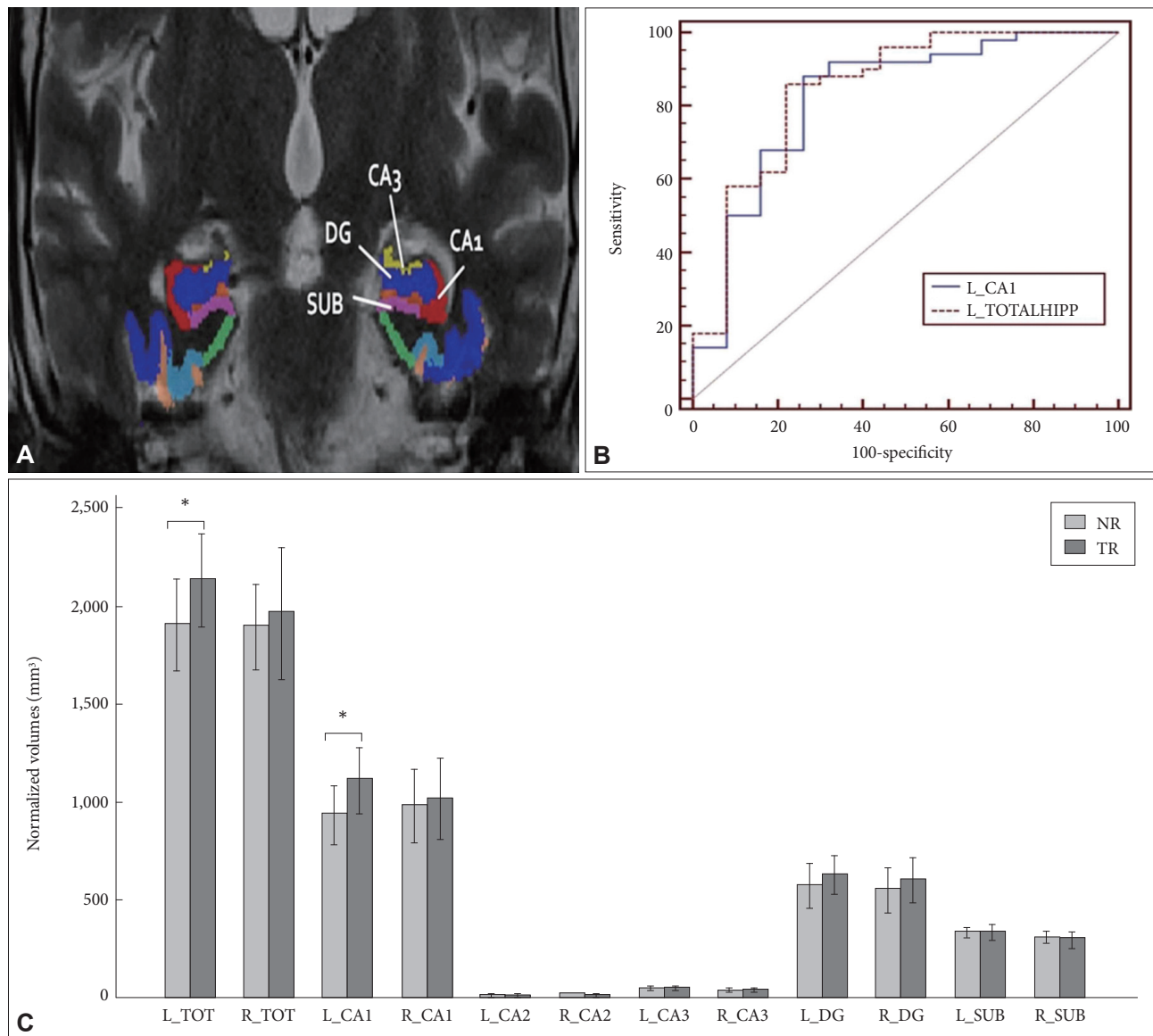
Segmentation of the hippocampal subfields was performed with the ASHS (<http://www.nitrc.org/projects/ashs/>). This method uses a combination of a multi-atlas image segmentation algorithm and a learning-based bias correction technique.<sup>12</sup> Each subject's T2-weighted image was registered to a set of manually labeled atlases with deformable registration, and the candidate segmentations provided by the atlas package were combined into a single consensus segmentation based on similarity-weighted voting. Finally, the corrective learning classifiers trained to detect the voxels mislabeled by the above approach were applied to the consensus segmentation. The fol-

lowing subfields were defined: cornu ammonis 1 region (CA1), 2 region (CA2), 3 region (CA3), 4 region (CA4), dentate gyrus (DG), and subiculum (SUB).

### Statistical analysis

Descriptive statistics were performed using demographic and clinical scores from the neuropsychological tests. Student t-tests were used to assess statistical differences of continuous variables, and Chi-square tests were used to assess dichotomous variables of the treatment responder group and the non responder group.

In line with other volumetric analyses, raw volumes of each



**Figure 1.** (A) Segmentation scheme used for hippocampal subfields segmentation used in this study; (B) The predictive performances of baseline hippocampal subfields volume measurements in 24 weeks donepezil treatment in the patients with AD (C) Group differences of baseline hippocampal subfields volumes between the TR and the NR groups. AD: Alzheimer's disease, TR: treatment response, NR: treatment non-response, L-CA1: left cornu ammonis region 1 region, L-TOTALHIPP: left total hippocampus, L: left, R: right, TOT: total hippocampus, CA1: Cornu ammonis region 1, CA2: Cornu ammonis region 2, CA3: Cornu ammonis region 3, DG: dentate gyrus, SUB: subiculum.

hippocampal subfield and the whole hippocampus (corresponding to the sum of the three subfields) were normalized by the total intracranial volume (TIV) to account for inter-individual variability in head size (normalized volume=1000× raw volume/TIV). Binary logistic regression with receiver operator characteristic (ROC) analysis was implemented to assess the sensitivity, specificity, and accuracy of hippocampal subfields to predict treatment response to donepezil treatment with the age, gender and education as covariates. All statistical analyses were conducted with the use of the MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

## RESULTS

### Demographic data

After 24 weeks donepezil treatment, the 38 (59.3%) study participants who showed response were classified as the treatment responder (TR) group. The other 26 (40.7%) subjects were classified as the treatment non-responder (NR) group. There were no significant baseline demographic and clinical characteristics between the TR group and the NR group. However, score changes of MMSE from baseline to 24 weeks were significantly different between TR group and NR group.

### Hippocampal subfields volumes segmentation

The hippocampal subfields volumes of left total hippocampus and the CA1 area were significantly different between the TR group and the NR group ( $p < 0.001$ ) (Table 1). The ROC curve analysis showed the left CA1 volumes showed highest area under curve (AUC) of 0.85 with a sensitivity of 88.0%, a specificity of 74.0%, a positive predictive value (PPV) of 77.2% and a negative predictive value (NPV) of 86.0% (Figure 1). The left total hippocampus volume showed AUC value of 0.84 with a sensitivity of 86%, a specificity of 78.0%, a PPV of 79.6% and a NPV of 84.8% (Figure 1). However, the other regions of the left SUB, CA2, CA3 and all the right hippocampal subfields volumes could not reached the AUC > 0.5.

## DISCUSSION

To our knowledge, this is the first study of hippocampal subfield analysis in predicting treatment response to donepezil. According to our results, left total hippocampal volume and more significantly, left CA1 volume showed good validity in predicting response to donepezil. Regarding our results showing statistically significant association between left hippocampal volume and treatment response but not in the right hippocampal volume, a recent meta-analysis indicated that this asymmetry could be a state-dependent marker in AD.<sup>13</sup>

There have been numerous attempts to predict response to

ChIEs. Digit symbol substitution test, medial temporal lobe atrophy and hippocampal structure change have all been purported to be potential predictors for ChIEs treatment.<sup>14-17</sup> In our results, not only the left hippocampal volume but also, CA1 significantly predicted donepezil response, and this harbors several clinical implications. CA1 has been suggested to be a major target of neuronal loss in AD patients, and it was associated with the disease severity and duration.<sup>18,19</sup> Previous animal studies proposed a possibility of close link between cholinergic modulation and CA1. Acetylcholine was crucial in maintaining long-term potentiation in CA1 region, consequently affecting synaptic plasticity of CA1 pyramidal neurons.<sup>20-22</sup>

Hippocampal subfield analysis has been frequently implemented to explore regional vulnerability of hippocampus in normal aging and AD patients.<sup>23-29</sup> Indeed, many previous studies proposed disparate vulnerability of hippocampal subfield volumes to AD pathology, thus the importance of measuring subfield volumes rather than volume as a whole has been accentuated.<sup>25</sup> Moreover, validity of measuring hippocampal volumes in foretelling of conversion from mild cognitive impairment to AD has been discussed.<sup>30,31</sup> We believe our results are in line with the aforementioned studies, with possible implications of applying automated hippocampal subfield analysis in the monitoring of AD patients.

There are several limitations in our study that must be taken into consideration. First, inherent methodological limitations of neuroimaging and pertinent analytic methods are inevitable. Disparities in defining boundaries for hippocampal subfields can result in varying outcomes. Indeed, one study discussed differences in anatomical definition of hippocampal subfields, especially prominent in CA1.<sup>25</sup> Second, our result 24-week design could be considered too short to reflect the treatment response of donepezil and resultant sustained changes in hippocampal volumes. However, a 24-week design has been frequently adopted to predict the treatment response of donepezil.<sup>32-34</sup> One study with an identical design as our study indicated that 63% of donepezil-treated group showed improvement in cognition.<sup>33</sup> Third, homogeneity of our study participants makes the results difficult to generalize.

In conclusion, we expect that hippocampal subfields volume measurements that predict treatment responses to current anti-dementia drugs will enable a more evidence-based, individualized prescription of medications that will lead to more favorable treatment outcomes.

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