




# Voxel-Based Morphometry Analysis of Structural MRI for Differentiation Between Dementia with Lewy Bodies and Alzheimer's Disease [Letter]

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Shohei Inui <sup>1,2</sup>  
Keita Sakurai <sup>1</sup>  
Yoshio Hashizume <sup>3</sup>

<sup>1</sup>Department of Radiology, Teikyo University School of Medicine, Tokyo, Japan; <sup>2</sup>Department of Radiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; <sup>3</sup>Choju Medical Institute, Fukushima Hospital, Aichi, Japan

## Dear editor

We read the article entitled “Differentiation Between Dementia With Lewy Bodies And Alzheimer’s Disease Using Voxel-Based Morphometry Of Structural MRI: A Multicenter Study” by Matsuda et al with great interest.<sup>1</sup> The authors recruited 239 patients with dementia with Lewy bodies (DLB) and 385 patients with Alzheimer’s disease (AD), and evaluated the utility of Voxel-Based Specific Regional Analysis System for Alzheimer’s Disease (VSRAD<sup>®</sup>) for their differentiation. They also emphasized the value of dorsal brainstem (DBS) atrophy in addition to medial temporal lobe (MTL) atrophy. As the authors noted, to differentiate AD from DLB is important in the clinical setting to select appropriate pharmacotherapy. Considering the difficulty of using indicative biomarkers including dopamine transporter SPECT in all patients, it is beneficial to reinforce the supportive feature MRI using voxel-based morphometry for the differential diagnosis.

However, we have some concerns. From our experience using VSRAD in clinical and research settings, MRI scan parameters especially the magnetic field strength of MR scanners exert an influence on the analysis outcomes. A previous study revealed that there was a more than two-fold difference between medial temporal Z-score values calculated against normal controls scanned with 1.5T and 3.0T.<sup>2</sup> The difference in the magnetic field strength of MR imagers may introduce a methodological bias and degrade the generalization performance of the model. In this study, the authors constructed the training and test data from images acquired with 1.5T imagers only and those acquired with both 1.5T and 3.0T imagers, respectively, to calculate the Z-scores with VSRAD. Instead, we recommend either of the following strategies for a more unbiased analysis: 1) construct the training and test data from images obtained with 1.5T imagers only and evaluate them with a hold-out method, 2) construct both the training and test data from both of the images obtained with 1.5T and 3.0T imagers and evaluate them with a cross validation approach. Model refinement with the above-described strategy would enable elimination of the methodological bias and might enhance the generalization performance and applicability of the constructed model to clinical practice.

The constructed decision tree for differentiation of DLB and AD ranked the degree of MTL atrophy as the most important feature (the 1st node of the decision tree). However, MTL atrophy is not a specific finding of AD, and various

Correspondence: Keita Sakurai  
Department of Radiology, Teikyo University  
School of Medicine, 2-11-1 Kaga, Itabashi-  
ku, Tokyo 173-8605, Japan  
Tel +81-3-3964-1211  
Email ksak666@yahoo.co.jp

neurodegenerative disorders, including some DLB, even pure form, can show an atrophic change similar to that of AD.<sup>3</sup> As expected, approximately 41% of cases with DLB were mislabeled as AD in this study. The results of this study reconfirmed the necessity of taking account of imaging features other than relative preservation of MTL for their differentiation.

Another limitation of this study was that it was restricted to a situation in which only clinically-diagnosed AD and DLB were included to evaluate the utility of this analytical method. However, the proportion of AD and DLB in patients with neurodegenerative dementia is estimated to be merely one half.<sup>4</sup> Pathologically-confirmed imaging studies have reported that non-AD/DLB neurodegenerative disorders including argyrophilic grain disease (AGD), TDP-43 proteinopathy (TDP) and progressive supranuclear palsy (PSP) can show MTL and DBS atrophy mimicking that of AD and DLB (i.e., MTL atrophy of AGD and TDP, and DBS atrophy of PSP).<sup>5</sup> These easily mistaken atrophic changes can cause erroneous analytical results when directly applied to the clinical setting. Considering the wide spectrum of dementia-related neuropathologies, it would be ideal to develop

more sophisticated analytical methods to differentiate various dementias and validate them using pathologically-confirmed cases.

## Disclosure

The authors report no conflicts of interest in this communication.

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