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Is Hippocampal Volumetry Really All That Matters?

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I read with interest the recent article in AJNR, "Predictive Utility of Marketed Volumetric Software Tools in Subjects at Risk for Alzheimer Disease: Do Regions Outside the Hippocampus Matter?"[1]

It is an interesting study, yet I will elaborate below why I do not fully agree with the conclusions of this article: "Therefore, future prognostic studies in mild cognitive impairment, combining such tools with demographic and other biomarker measures, are justified in using hippocampal volume as the only volumetric biomarker."[1]

The authors demonstrated that 2 different MR volumetry software packages provide equivalent results with respect to hippocampal volumetry. As a consequence, the conclusion is justified that the postprocessing software does not systematically bias the MR morphometry results, at least for the 2 implemented software packages.

The second finding is that hippocampal atrophy alone performed as well as the additionally performed analysis of other anatomic regions. However, it must be noted that the regions used in the tested software packages are anatomically defined regions that only partially overlap with the established Alzheimer disease (AD) signature regions (ie, those regions that are consistently found to be abnormal in AD).[2,3] Because of partial volume effects, these large anatomic regions are not necessarily the most sensitive regions for this specific purpose. The current study assessed 3D T1 voxel-based morphometry (VBM)–derived gray matter concentration, whereas the more demanding analyses of 3D T1-derived cortical thickness and related volume estimates are generally more sensitive with less interindividual variability.[4] A direct comparison between the presented VBM-type hippocampal volumetry and cortical thickness–derived volumetry (eg, in AD signature regions) was not performed. Consequently, I challenge the conclusion that hippocampal volume can be suggested as the only volumetric biomarker because the authors did not demonstrate that the presented hippocampal volumetry outperforms, for instance, AD signature regions.

When looking into the data in more detail, the area under the curve (AUC) for hippocampal volumetry is 0.69 or 0.68, depending on the software. In the abstract, this is not noted, yet it is stated in the manuscript that the AUC was 0.76 and 0.68 for the Alzheimer's Disease Assessment Scale–13 (ADAS-13) and the Mini-Mental State Examination (MMS), respectively. The MMS is a very simple and fast clinical test that costs almost nothing and can be done everywhere. The MMS performed as well as the much more time-consuming and expensive hippocampal volumetry. Moreover, the MMS worked in all cases, whereas MR hippocampal volumetry was impossible in 30% of cases. Based on the provided results, it can be concluded that MR volumetry provided no added value with respect to the simple and established MMS. The ADAS-13 clearly outperformed hippocampal volumetry. So, playing the devil's advocate, one might conclude that hippocampal MR volumentry is useless because it provided no added value.

Moreover, the dataset is derived from the Alzheimer's Disease Neuroimaging Initiative dataset, a strongly preselected dataset with "super-patients" and "super-controls" excluding all microvascular lesions. Such microvascular lesions contribute to cognitive decline and are very frequent in this age group in typical clinical populations.[5] MR parameters are strictly standardized in this dataset, yet in clinical application, even small modifications of MR parameters significantly bias estimated volumetry results.[6] Therefore, I might speculate that the presented results for MR morphometry in this current article are over-optimistic with respect to typical real-world clinical applications. I would like to repeat that already in this specific and preselected sample, the simple MMS performed as well as MR volumetry, and the ADAS-13 even outperformed MR volumetry.

Personally, I do believe that MR volumetry can provide added value. Yet, I argue that simple hippocampal volumetry is not the best MR biomarker, notably for the detection of individual cases. On average, there is a normal interindividual variation in hippocampal volume of approximately 20% in controls, but also in patients with mild cognitive impairment (MCI) and AD,[7] whereas the disease-related change (eg, for patients with MCI versus controls) is in the range of 7%. This means that direct hippocampal volumetry may identify a substantial volume difference of 7% at the group level, yet because of the larger interindividual variability of approximately 20% per group, this measure is of limited use for the diagnosis of individual cases. Moreover, the current results of hippocampal atrophy are not compared with

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patterns of atrophy, such as the AD signature regions mentioned above, DTI,[8,9] arterial spin labeling,[10-12] and, ideally, a combination of multiple MR parameters and advanced data analysis.[13]

Finally, MR imaging in dementia is used for more than discriminating MCI/AD versus controls, but should also include a differential diagnosis between various types of dementia. This differential diagnosis can be challenging, particularly in the early stages of the disease. As indicated by the authors, future treatment trials of MCI should therefore also discriminate Alzheimer type–MCI/AD pathology from other types of dementia to include only the desired treatment group. For example, behavioral variant frontotemporal dementia (bvFTD) is characterized by predominant frontotemporal atrophy, yet, in most cases, has associated mesiotemporal atrophy. Consequently, hippocampal atrophy alone cannot discriminate AD versus bvFTD, but the volumetry assessment of atrophy pattern has added value. This means that hippocampal volumetry alone might lead to the false inclusion of patients with bvFTD in MCI/AD trials. In Lewy body dementia, hippocampal volumetry will be noncontributive. However, because of the pathologic overlap with Parkinson disease, susceptibility-weighted imaging of nigrosome 1 has added value,[14,15] and quantitative volumetric assessment tools for nigrosome 1 based on quantitative susceptibility mapping are under development. Likewise, vascular pathology often coexists with, for example, AD pathology and cannot be detected by using hippocampal volumetry alone, and volumetric tools exist to assess vascular burden.

In summary, I agree with the conclusion that the 2 tested software tools provide equivalent results for hippocampal volumetry. Hippocampal volumetry alone was as good as the analysis of a predefined anatomic region, with the limitation that anatomically defined regions are not necessarily the most sensitive approach for this specific purpose. I disagree with the statement that hippocampal volumetry alone can be suggested as the only volumetric biomarker for future prognostic studies. This is not supported by the presented results and is an oversimplification of the available evidence.

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