

Horizontal Versus Longitudinal Axis of the Hippocampus: Metabolic Differentiation as Measured with High-Resolution PET/MRI

TO THE EDITOR: With great interest we read the recent article by Cho et al. entitled “Substructural Hippocampal Glucose Metabolism Observed on PET/MRI” (1). In that work the authors performed high-resolution ^{18}F -FDG PET and structural MRI of the hippocampus in a group of 5 healthy subjects. Among the hippocampal subfields, the highest ^{18}F -FDG uptake was consistently found in the dentate gyrus and cornu ammonis (CA) 4. This report is the first such structural/functional study benefiting from the latest advances in spatial resolution and is therefore of special relevance. However, we wish to suggest an additional data analysis, which from our point of view is essential to implicitly address the issue raised by the authors, that is, substructural hippocampal glucose metabolism.

The hippocampus is a limbic region with a very complex anatomy and function. Based on the predominant cell type, cell origin, and connectivity, the hippocampus is typically segmented into the dentate gyrus; CA1, CA2, CA3, and CA4 fields; and subiculum. This organization, which roughly fits the horizontal axis of the structure, is considered fundamental to hippocampal function, and numerous studies have focused on the above cytoarchitectural subdivisions to explain functional specialization within the hippocampus. Growing evidence indicates, however, the presence of functional differentiation also along the longitudinal, or antero-posterior, axis of the hippocampus. This concept, initially based on animal data, has recently been supported by in vivo neuroimaging studies. Specifically, several investigators have reported a relationship between neuroimaging indices of the anterior hippocampus and episodic memory performance (2–4).

As for ^{18}F -FDG PET, Ouchi et al. (5) found glucose metabolism to be higher in the head than in the body or tail parts of the hippocampus in a group of 8 healthy subjects (mean age of 58 y). In contrast, patients with pure amnesia or with mild Alzheimer dementia showed significantly decreased metabolism in the hippocampal head only. The authors of that study suggested that the energy consumption subserving synaptic transmission through the perforant pathway was higher in the anterior hippocampus, so as to maintain appropriate cognitive functions such as episodic memory. They also claimed that metabolic depression in this region can cause the memory dysfunction seen in amnesic patients. Indeed, the principal input from multimodal association neocortical areas occurs mainly in the anterior parts of the hippocampus, through the perforant pathway arising in the entorhinal cortex. Integrity of the perforant path is a major prerequisite for normal memory function, such that disruption of this path, as occurs very early in the course of Alzheimer disease, causes profound memory impairment (6).

Unfortunately, Cho et al. did not mention the age of their subjects. This is important, as the hippocampal subfields are differently prone to age-dependent processes (7), although the lack of atrophy in the MR images suggests that the subjects were

relatively young. More importantly, the authors did not assess glucose metabolism along the longitudinal axis of the hippocampus, that is, separately for the hippocampal head, body, and tail. Such data would be of great interest for understanding the neurobiology of hippocampal function, as the rank order of metabolic rates might prove to be more distinct along the longitudinal axis of the hippocampus than along the horizontal axis investigated in the study.

Although hippocampal glucose metabolism has been already mapped by Ouchi et al. (5), the improved spatial resolution of the instrumentation possessed by Cho et al. presents distinct advantages. Specifically, the lesser effects of partial volume in the ^{18}F -FDG images, and the nearly perfect coregistration afforded by the hybrid PET/MRI system, make their approach particularly appropriate for studying hippocampal metabolism at the substructural level.

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DOI: 10.2967/jnumed.110.085084

REPLY: We very much appreciate the comments and suggestions of Yakushev and Fellgiebel on our paper (1), which was the first in a series we are publishing on in vivo human molecular imaging using our newly introduced ultra-high-resolution PET-MRI fusion system (2). Like Yakushev et al. (3), we have also noticed the importance of longitudinal differential metabolic activities, and we are preparing several experiments along that line. The results of some of these have already been reported (4).

Our paper was the first to demonstrate the capability of the new PET-MRI system for functional and metabolic study of the hippocampus not only along the horizontal axis but also along the longitudinal axis. In addition, the system measures and localizes the activity with the precision of 7.0-T MRI resolution—that is, resolution on the order of a few hundred microns, well suited to the study of subhippocampal activity. Consequently, with PET-MRI, one can measure functional and metabolic activity at a resolution sufficient to differentiate the subfields of the hippocampal regions—the dentate gyrus; cornu ammonis (CA) 1, CA2, CA3, and CA4; and subiculum—which could not previously be measured by any means. This in vivo human molecular imaging at subhippocampal resolutions will undoubtedly facilitate further exploration of not only the hippocampus but also many vital deep brain structures, such as the thalamus and brainstem, which have delicate structures requiring a similarly high-resolution imaging capability (5).

We wholeheartedly agree that analysis of the longitudinal axis of the hippocampus will clearly shed light on the mysteries of the hippocampal subfields. As suggested by Yakushev et al. (3), the previous ¹⁸F-FDG PET study of Ouchi et al. was limited in measurement of the glucose metabolism in the hippocampus mainly because of the poor resolution of the PET and MRI (1.5 T) scanners they used at that time (6). Studies can undoubtedly be extended to many cognitive neuroscience areas and to hippocampus-related diseases such as dementia and Alzheimer disease. We have already extended our hippocampal activity study to memory and dementia studies, which will certainly include investigation of the longitudinal axis of the hippocampus as suggested by Yakushev et al.

Age-dependent effects were purposely ignored in our study, because we were interested in performing a base study on young, healthy subjects. However, we will certainly extend our studies to age dependency, as well as to various disorders such as Alzheimer's disease. Assessment of age-dependent metabolic changes in the hippocampus will require large numbers of subjects. Our previous work was only to introduce the potential of the new state-of-the-art ultra-high-resolution PET-MRI system for studies of subhippocampal metabolic function. We fully agree that study of the longitudinal axis for age-dependent changes should be pursued, because such

changes would be more sensitive to age, as has been observed in many previous studies (3,7,8).

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DOI: 10.2967/jnumed.110.085407