International Journal of Geriatric Psychiatry

PET measurement of brain acetylcholinesterase activities in cortex and subcortical areas

Dear Professor George Alexopoulos, Professor Alistair Burns,

Editor, *International Journal of Geriatric Psychiatry*

We appreciate the letter concerning our manuscript entitled "Dementia with Lewy bodies can be well-differentiated from Alzheimer's disease by measurement of brain acetylcholinesterase activity – A [^{11}C]MP4A PET study" by Professor Bohnen, and we would like to make a response. We have prepared a reply to the letter by Professor Bohnen and colleagues. We feel that it will be of special interest for the readers of *International Journal of Geriatric Psychiatry*.

(Re: Letter to the Editor by Bohnen *et al.*)

We thank Bohnen and colleagues for thoughtful comments and would like to take this opportunity to add further discussion regarding our paper. We acknowledge that thalamic acetylcholinesterase (AChE) activity, which represents ascending cholinergic pathway from the brainstem pedunculopontine nucleus, might also represent a promising target for discriminating between dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Compared with healthy controls (HC), DLB patients showed reduction in the thalamic k_3 hydrolysis rate of [^{11}C]MP4A (−17.7%), whereas thalamic AChE activity was preserved in AD (+0.1%). However, the coefficient of variation (COV) of thalamic k_3 measured by [^{11}C]MP4A was relatively large (19.3% in 18 HC of the present study and 20.1% in 20 HC of a previous study) (Namba *et al.*, 1999). Although subcortical areas were included in our voxel-based brain analyses, such large COV would be insufficient to detect significant difference in thalamic k_3 between DLB and AD. Furthermore, thalamic k_3 measured by [^{11}C]MP4A showed poor to fair differential diagnostic performance between AD and DLB (area under the curve [AUC] = 0.703, 95% CI: 0.523–0.883) as well as between mild AD and mild DLB (AUC = 0.600, 95% CI: 0.281–0.919). In contrast, COV of thalamic k_3 measured by [^{11}C]MP4P (or PMP) was sufficiently small in the paper by Bohnen and colleagues (10.6% in 14 HC) (Kotagal *et al.*, 2012), although a previous study reported that COV of thalamic k_3 measured by [^{11}C]MP4P (or PMP) was 31% (Koeppe *et al.*, 1999).

Previous PET studies demonstrated that [^{11}C]MP4A is not a suitable tracer for measuring AChE activity in brain regions with extremely high AChE activity, such as in the cerebellum and striatum (Namba *et al.*, 1999). In other words, k_3 estimation measured by [^{11}C]MP4A mainly reflects regional cerebral blood flow, since radioactivity in brain regions with extremely high AChE activity leads to unstable estimation of regional AChE activity in those brain regions. We used [^{11}C]MP4A in the present study because [^{11}C]MP4A showed higher specificity for AChE (94% in autopsied brain of human) compared with [^{11}C]MP4P (or PMP) (86%) (Shinotoh *et al.*, 2004). However, measurement of AChE activity by [^{11}C]MP4A might be unstable in the thalamus, in which AChE activity is moderately high, following the cerebellum and striatum. Having said that, [^{11}C]MP4A is capable of detecting decrements of thalamic *k3* activities when the thalamus is severely impaired, such as in the case of progressive supranuclear palsy patients (−24.0%) (Hirano *et al.*, 2010). [^{11}C]MP4P (or PMP) would be an appropriate tracer for relatively accurate measurement of thalamic AChE activity, as well as the combined evaluation of thalamic and cortical AChE activities.

Conflict of interest

There are no conflicts of interest to be disclosed.

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