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Dementia with Lewy bodies can be well-differentiated from Alzheimer's disease by measurement of brain acetylcholinesterase activity—[11C]MP4A PET study

Shimada *et al.* investigated the potential diagnostic utility of brain acetylcholinesterase (AChE) activity measurement using N-[^{11}C]-methyl-4-piperidyl acetate (MP4A) and positron emission tomography (PET) in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) (Shimada *et al.*, 2015). These investigators found greater reductions in cortical AChE hydrolysis rates in DLB compared with AD subjects. Regional differences in defined volumes-of-interest (VOIs) were significantly lower in DLB compared with AD in all but the anterior cingulate gyrus. By contrast, the largest regional difference between DLB and AD subjects was in the posterior cingulate gyrus. The authors conclude that PET measurement of cortical AChE activity may be useful for the differential diagnosis between DLB and AD. Consistent with these findings, we previously reported greater cortical AChE reductions in DLB compared with AD using another AChE tracer, [^{11}C]methyl-4-piperidinyl propionate (PMP) (Bohnen *et al.*, 2003). We found that cortical AChE activity was relatively preserved in patients with AD except for more severe involvement of the inferior lateral temporal cortex. Our findings of partial group overlapping values of regional cortical AChE activity agrees with the current Shimada *et al.* paper, where based on their plotted AChE data points, PET would have a good (89.7%) but not perfect diagnostic accuracy in distinguishing DLB from AD. Furthermore, cholinergic cortical losses will become more prominent with advancing severity of disease in AD making AChE PET likely a better test in patients with mild to moderate rather than severe stage of dementia for the distinction of DLB from AD.

There are two major brain cholinergic projection systems. The first arises in the basal forebrain complex, including the nucleus basalis of Meynert, providing the principal cholinergic input of the cortical mantle and is known to degenerate in DLB and AD as shown in the paper by Shimada *et al.* The second arises in the pedunculopontine nucleus, a brainstem locomotor center, and provides cholinergic inputs to the thalamus, cerebellum, basal ganglia, other brainstem nuclei, and the spinal cord (Heckers *et al.*, 1992). AChE PET imaging assesses cholinergic terminal integrity with cortical uptake reflecting largely basal forebrain function, and thalamic uptake principally reflecting pedunculopontine nucleus integrity. It is unclear from the Shimada *et al.* paper whether their voxel-based brain analysis was limited to the cortical VOIs or also included subcortical areas, such as the thalamus.

Previous post-mortem studies have shown that there is selective loss of basal forebrain neurons in AD, with relative sparing of the brainstem pedunculopontine cholinergic neurons (Woolf *et al.*, 1989). We recently reported on brainstem–thalamic cholinergic nerve terminal integrity in patients with AD, DLB, and other groups (Kotagal *et al.*, 2012). Compared with normal controls (NC), prominently reduced thalamic k3 hydrolysis rate was noted in subjects with DLB (−17.4%), whereas brainstem–thalamic AChE was preserved in AD (−0.7%). We agree with Shimada and colleagues that AChE PET may be useful for the differential diagnosis between DLB and AD but would advocate selection of brainstem–thalamic AChE nerve terminals in addition to cortical enzyme activity for more robust group discrimination.

Conflict of interest

None declared.

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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.

