

Date: September 14, 2015

To: **Professor Alistair Burns,**

Editor, *International Journal of Geriatric Psychiatry*

Manchester, UK

Re: Letter to the Editor

Re: Recent article by Shimada et al.: "Dementia with Lewy bodies can be well-differentiated from Alzheimer's disease by measurement of brain acetylcholinesterase activity—^[11C]MP4A PET study". *Int J Geriatr Psychiatry*, 2015: in press.

Dear Professor Alistair Burns:

Shimada et al. investigated the potential diagnostic utility of brain acetylcholinesterase (AChE) activity measurement using N-[¹¹C]-methyl-4-piperidyl acetate (MP4A) and 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 to AD subjects. Regional differences in defined volumes-of-interest (VOIs) were significantly lower in DLB compared to AD in all but the anterior cingulate gyrus. By contrast, the largest regional difference between DLB and AD subjects was in the posterior cingulate

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/gps.4373](https://doi.org/10.1002/gps.4373)

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 to AD using another AChE tracer, [¹¹C]methyl-4-piperidiny 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 pedunclopontine 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 pedunclopontine 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 pedunculo-pontine 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 to 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.

References:

Bohnen, N. I., Kaufer, D. I., Ivanco, L. S., Lopresti, B., Koeppe, R. A., Davis, J. G., Mathis, C. A., Moore, R. Y. & Dekosky, S. T. 2003. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Arch Neurol*, **60**, 1745-8.

- Heckers, S., Geula, C. & Mesulam, M. 1992. Cholinergic innervation of the human thalamus: Dual origin and differential nuclear distribution. *J Comp Neurol*, **325**, 68-82.
- Kotagal, V., Muller, M. L., Kaufer, D. I., Koeppe, R. A. & Bohnen, N. I. 2012. Thalamic cholinergic innervation is spared in Alzheimer disease compared to parkinsonian disorders. *Neurosci Lett*, **514**, 169-72.
- Shimada, H., Hirano, S., Sinotoh, H., Ota, T., Tanaka, N., Sato, K., Yamada, M., Fukushi, K., Irie, T., Zhang, M. R., Higuchi, M., Kuwabara, S. & Suhara, T. 2015. Dementia with Lewy bodies can be well-differentiated from Alzheimer's disease by measurement of brain acetylcholinesterase activity-a [C]MP4A PET study. *Int J Geriatr Psychiatry*.
- Wolf, N. J., Jacobs, R. W. & Butcher, L. L. 1989. The pontomesencephalotegmental cholinergic system does not degenerate in Alzheimer's disease. *Neurosci Lett*, **96**, 277-82.

Sincerely,

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