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Title:
Posterior Cingulate Involvement Does Not Argue against LATE -- and Who Said It Does?

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In response to our recent article evaluating potential promise and current limitations of neuroimaging methods in contributing to the premortem diagnosis of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) *(1)*, the letter by McCarter et al. *(2)* not only mischaracterizes the content of our article, but also, perhaps more surprisingly, mischaracterizes that of its authors' own prior publications. For example, it states, "Recent data suggest medial temporal, posterior cingulate, and frontal supraorbital hypometabolism are predictors of LATE whereas prominent inferior temporal involvement may be predictive of AD (4)." Their reference 4 (our article's reference 6) cited here corresponds to a 2020 *Neurology* article, of which four of the five authors of the present letter to the editor served as co-authors. Neither the word "posterior" nor "cingulate" occurs once in that entire article; this is understandable given that, in its direct comparison of TAR DNA-binding protein 43 (TDP-43)-positive versus TDP-43-negative cases, while relative hypometabolism in the TDP-43-positive group of medial temporal and frontal supraorbital regions was seen, not a single voxel of hypometabolism in posterior cingulate cortex was identified, even at the statistical criterion (quite loose for this kind of analysis) of $p<0.001$ uncorrected for multiple comparisons (Figure 2 in that article). Their own article thus fails to support the authors' claim in their letter.

Their letter further states, "Antemortem studies of amnestic dementia cases have demonstrated medial temporal and posterior cingulate cortical hypometabolism to be more prominent in amyloid negative (5) and tau negative cases (6)," again citing themselves (their reference 6, our reference 11) referencing a 2018 *Brain* article by Botha et al. for which again four of the five authors of their present letter were co-authors (including one who served as first author and another who served as senior author). In fact, among their autopsy-proven diagnoses, a total of two were tau-negative, and both of them were documented to suffer from hippocampal sclerosis -- a feature that is not only unnecessary for LATE to be diagnosed, but that was present in only 22% of TDP-43-positive cases in their own larger autopsy series published in the abovementioned *Neurology* article -- and even including their non-autopsy-proven cases, a total of only four were amyloid-negative/tau-negative. Moreover, all eight of the TDP-43 positive cases identified on autopsy were confounded by the concomitant presence of hippocampal sclerosis (perhaps reflecting the selection bias imposed by the inclusion criteria). The importance of this confound is made all the more clear by a recent article by Gauthreaux et al. *(3)*, examining 408 autopsied participants in a multicenter national neuropathology data set having LATE and/or hippocampal sclerosis, and reporting that LATE with hippocampal sclerosis is neuropathologically distinct from LATE without hippocampal sclerosis (beyond the presence of the sclerosis itself), with the former group demonstrating not only TDP-43 that is more widely distributed in the cortex, but also that harbors more cerebrovascular pathologies. Thus, the prior work of the letter authors had literally no bearing upon the pattern of hypometabolism seen in LATE *per se*, but only upon the pattern seen in patients with hippocampal sclerosis, about whom they (properly) had previously confined their comments.

The other source (their reference 5) that the authors cite in their letter as supporting their thesis is an excellent 2016 article by Chetelat et al., which however had nothing to do with either LATE or TDP-43. Then combining all of these references together, their letter asserts, "Based on these data, an elevated ratio of inferior-to-medial temporal lobe metabolism was proposed as an FDG-

PET marker of LATE, as the authors [i.e., Rieger and Silverman (2022)] correctly point out" – this time mischaracterizing *our* article, as what we had pointed out was only that the marker distinguished patients with what their 2020 *Neurology* article denoted as an "AD spectrum pathologic diagnosis" *with* TDP-43 from those with autopsy-confirmed AD spectrum diagnoses *without* TDP-43 -- i.e., two different variants of the AD spectrum diagnosis, in their article tellingly entitled "Utility of FDG-PET in diagnosis of Alzheimer-related TDP-43 proteinopathy," and thus casts no light upon the population of LATE subjects who lack coexistent AD spectrum pathology, since none was included in their study. It is of course entirely unsurprising that two separate diseases characterized by processes capable of occurring independently and both attacking medial temporal structures preferentially, would lead to worse medial temporal hypometabolism for the same degree of inferior temporal hypometabolism associated with AD, in those instances when both diseases concomitantly occur (and, for that matter, when LATE occurs concomitantly with hippocampal sclerosis).

Next, the letter's cited reference 7, by Grothe et al. *(4)* is actually an abstract, published in a Supplement representing a conference poster, so it is more difficult to fully assess its significance to the present discussion, but in any event only included four TDP-43-positive cases without hippocampal sclerosis. Moreover, even granting that limitation, it is evident from visual inspection of the poster online, that the "TDP-43-typical" pattern displayed there demonstrated substantially less extensive posterior cingulate/precuneus hypometabolism than the "AD-typical pattern."

The figure and accompanying remainder of the letter by McCarter et al. is primarily devoted to showing three cases of LATE that are less relevant than anecdotal cases might otherwise be, as all three cases are confounded by the concomitant presence of hippocampal sclerosis… again demonstrating the authors' lack of an evidentiary basis for their comments about posterior cingulate hypometabolism in LATE (other than when LATE and hippocampal sclerosis are both present)… followed by passing mention of three more articles (their references 8-10), the first having no direct relationship to imaging, and the latter two having nothing to do with TDP-43 or LATE.

Finally, the entirety of the objection of the letter by McCarter et al. to our article is directed at a single phrase (constituting one-fifth of one sentence of our two-page article), namely that "…a pattern of diminished regional cerebral metabolism that is posterior-predominant but nevertheless differs from AD in lacking as marked a defect of posterior cingulate" activity, in cases when occipital metabolism is also relatively preserved (thus making Lewy body- or posterior cortical atrophy-based causes of dementia less likely) – which, for context, occurred in the paragraph immediately following our paragraph stating, "A definitive diagnosis of LATE will likely not be possible in the premortem setting, however, without neuroimaging that specifically includes assessment of limbic structures with a clinically available tracer for TDP-43 that is sensitive and specific" and immediately following a sentence indicating that this is in reference to scans of patients with "an AD-like clinical picture in older adults." As we point out in our article, the TDP-43 proteinopathy of LATE often coexists with other processes such as amyloidopathy, tauopathy and hippocampal sclerosis, and it also occurs in the absence of those additional processes. We obviously then would not suggest that the presence of posterior cingulate hypometabolism would exclude the presence of LATE, given that the presence of LATE does not exclude the presence of other pathologies that affect posterior cingulate metabolic activity; rather, we suggest that when

other clinical and metabolic features we described are present in the absence of hypometabolism of both posterior cingulate and occipital cortex, then those are "bases for suspecting this neurodegenerative process." Their letter thereby commits a basic logical fallacy – i.e., confusing an if-then statement (if no posterior cingulate or occipital hypometabolism, then LATE) with its inverse (if posterior cingulate or occipital hypometabolism, then not LATE) – which is to say, we agree with the title of their letter, but it has nothing to do with our published article.

No potential conflicts of interest relevant to this article exist.

References

1. Rieger AC, Silverman DHS. Is it too soon to know when it's LATE? *J Nucl Med.* 2022;63:180-182.

2. McCarter SJ, Jones DT, Jack Jr. CR, Lowe V, Botha H. Posterior cingulate involvement does not argue against LATE. *J Nucl Med.* Epub ahead of print.

3. Gauthreaux KM, Teylan MA, Katsumata Y, et al. Limbic-predominant age-related TDP-43 encephalopathy: medical and pathologic factors associated with comorbid hippocampal sclerosis. *Neurology*. 2022;98:e1422-e1433.

4. Grothe MJ, Lang C, Nho K, et al. A topographic imaging biomarker of TDP43 pathology in amnestic dementia based on autopsy-derived FDG-PET patterns. *Alzheimer's Dement*. 2019;15:7 P61-P62 *Supplement*.