

DISCLOSURE

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Reply: Posterior Cingulate Involvement Does Not Argue Against LATE—And Who Said It Does?

REPLY: In response to our recent article evaluating the potential promise and current limitations of neuroimaging methods in contributing to the premortem diagnosis of limbic-predominant age-related

TAR DNA-binding protein 43 (TDP-43) encephalopathy (LATE) (1), the letter by McCarter et al. not only mischaracterizes the content of our article but also, perhaps more surprisingly, mischaracterizes that of its authors' own prior publications. For example, the letter states, "Recent data suggest that medial temporal, posterior cingulate, and frontal supraorbital hypometabolism are predictors of LATE whereas prominent inferior temporal involvement may be predictive of AD [Alzheimer disease] (4)." Their reference 4 (our article's reference 6) cited here corresponds to a 2020 *Neurology* article, of which 4 of the 5 authors of the present letter served as coauthors. Neither the word *posterior* nor the word *cingulate* occurs once in that entire article. This is understandable given that, in its direct comparison of TDP-43-positive versus TDP-43-negative cases, whereas relative hypometabolism of medial temporal and frontal supraorbital regions was seen in the TDP-43-positive group, not a single voxel of hypometabolism in the 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 (Fig. 2 in that article). Their own article thus fails to support the authors' claim in their letter.

Their letter further states, "Antemortem studies of amnesic dementia cases have demonstrated medial temporal and PCC [posterior cingulate cortical] hypometabolism to be more prominent in amyloid-negative (5) and tau-negative patients (6)," again citing themselves (their reference 6, our reference 11) referencing a 2018 *Brain* article by Botha et al. for which again 4 of the 5 authors of their present letter were coauthors (including one who served as first author and another who served as senior author). In fact, among their autopsy-proven diagnoses, a total of 2 were tau-negative, and both were documented to have hippocampal sclerosis (a feature that not only is unnecessary for LATE to be diagnosed but also 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 4 were amyloid-negative and tau-negative. Moreover, all 8 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. (2). This article examined 408 autopsied participants having LATE or hippocampal sclerosis in a multicenter national neuropathology dataset and reported that LATE with hippocampal sclerosis is neuropathologically distinct from LATE without hippocampal sclerosis (beyond the presence of the sclerosis itself), with the former group not only demonstrating a wider distribution of TDP-43 in the cortex but also harboring more cerebrovascular pathologies. Thus, the prior work of the letter authors had literally no bearing on the pattern of hypometabolism seen in LATE per se, but only on 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 Chételat et al., which, however, had nothing to do with either LATE or TDP-43. Then, combining all of these references together, their letter asserts, "On the basis of these data, an elevated ratio of inferior-to-medial temporal lobe metabolism was proposed as an ¹⁸F-FDG PET marker of LATE, as the authors [that is, Rieger and Silverman (2022)] correctly pointed out"—this time mischaracterizing *our* article. What we pointed out was only that, in their 2020 *Neurology* article tellingly entitled "Utility of FDG PET in Diagnosis of Alzheimer-Related TDP-43 Proteinopathy," the marker distinguished patients who had what was

denoted as an “AD spectrum pathologic diagnosis” with TDP-43 from those who had autopsy-confirmed AD spectrum diagnoses without TDP-43—that is, 2 different variants of the AD spectrum diagnosis—and thus casts no light on 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 2 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. (3), is actually an abstract published in a supplement and representing a conference poster. It is therefore more difficult to fully assess the significance of this study to the present discussion, but in any event the study included only 4 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 and precuneus hypometabolism than the “AD-typical pattern.”

The figure and accompanying remainder of the letter by McCarter et al. is devoted primarily to showing 3 cases of LATE that are less relevant than anecdotal cases might otherwise be. All 3 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). After these cases is a passing mention of 3 more articles (their references 8–10), the first having no direct relationship to imaging and the others having nothing to do with TDP-43 or LATE.

Finally, the entirety of the objection of the letter by McCarter et al. is directed at a single phrase (constituting one-fifth of a sentence of our 2-page article) regarding when LATE may be suspected, namely “... 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–based or posterior cortical atrophy–based causes of dementia less likely). For context, this phrase occurred in the

paragraph immediately after 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 after 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 the posterior cingulate and the occipital cortex, then those are “bases for suspecting this neurodegenerative process.” Their letter thereby commits a basic logical fallacy—that is, 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.

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