Letter to the Editor

Letter to the Author, concerning the publication: Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. Mohamed AZ, et al. Neuroimaging Clinical 2018 Jun 5;19:716–726

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A B S T R A C T

Over the past six months, we have been in discussion with you and the authors of a recent publication in NeuroImage: Clinical (Amyloid pathology fingerprint differentiates posttraumatic stress disorder and traumatic brain injury. Mohamed AZ, et al. Neuroimaging Clinical 2018 Jun 5;19:716–726). We raised a variety of methodological concerns with Mohamed and colleagues and discussion about these concerns led to their preparation of a corrigendum to be published in NeuroImage: Clinical.

We appreciate that the authors were responsive to our concerns and made a number of changes as noted in the corrigendum. Ultimately, however, the corrigendum does not address the primary conclusions of the study, which we were unable to replicate. We are troubled by the publication of results that cannot be replicated using identical methods and participant data.

This is a letter to the authors to address these concerns.

Dear Dr. Dickerson,

Over the past six months, we have been in discussion with you and the authors of a recent publication in *NeuroImage: Clinical* (Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. Mohamed AZ, et al. Neuroimaging Clinical 2018 Jun 5;19:716–726). We raised a variety of methodological concerns with Mohamed and colleagues and discussion about these concerns led to their preparation of a corrigendum to be published in *NeuroImage: Clinical*. The corrigendum addressed a variety of errors throughout the study, but it did not change the primary conclusion of the study, which is that individuals with both PTSD and TBI and those with PTSD alone have increased Aβ deposition relative to controls (those without PTSD or TBI) based on data from Vietnam War Veterans enrolled in the DOD-ADNI study. This conclusion is based on a voxel-wise analysis of amyloid burden that identified some clusters in which individuals with both PTSD and TBI or with just PTSD had higher amyloid burden than the controls (Mohamed et al., Fig. 4). When evaluated at the regional level (e.g. averages of parietal, cingulate, frontal, and temporal regions), there were no significant differences between groups (Fig. 5).

We were surprised by these findings, because we have examined the same dataset and found that the PTSD group actually had a lower percentage of cortical amyloid burden compared with controls after accounting for age, education and APOE ε4 status (Weiner MW et al. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 2017). A key argument of the Mohamed et al. study is that their voxelwise analyses reveal important regionally-specific group differences that are not apparent at the composite region level.
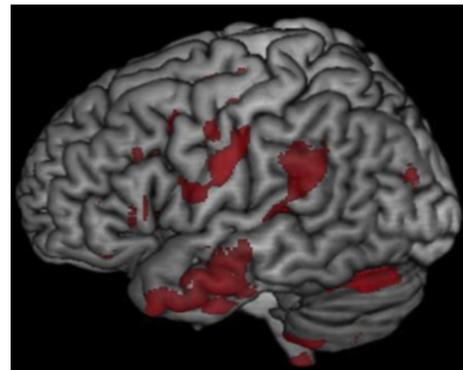

We agree that the examination of regional differences that differ from the global cortical summary measure is a reasonable and informative approach. However, we were unable to replicate the primary voxelwise findings shown in Fig. 4 of Mohamed, et al. using the exact

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same participants (provided to us by the authors) and the image processing methods described in the study. Our methods were as follows: 1) we spatially normalized the florbetapir images by applying the warping parameters calculated from the T1 image transformation to the MNI template; 2) we smoothed the PET images by 6 mm as described in the study and intensity normalized by the cerebellum (white + grey matter); 3) we carried out two-sample unpaired t-tests using FSL randomize nonparametric permutations with 1000 permutations; and 4) we examined results at a TFCE correction of $p < .05$ (with no FWE correction and no explicit cluster threshold, which differed from the original publication where a cluster threshold was utilized). We examined all of the contrasts reported by Mohamed et al. in Fig. 4, and were unable to identify any similar pattern of results, even when modifying the statistical threshold. In particular, unlike Mohamed et al., we found no significant voxels for the PTSD > Control comparison or for the TBI > Control comparison. We did identify some voxels reaching significance for the TBI_PTSD > Controls comparison, but the voxels we identified (shown at right) did not resemble the pattern reported by Mohamed et al.
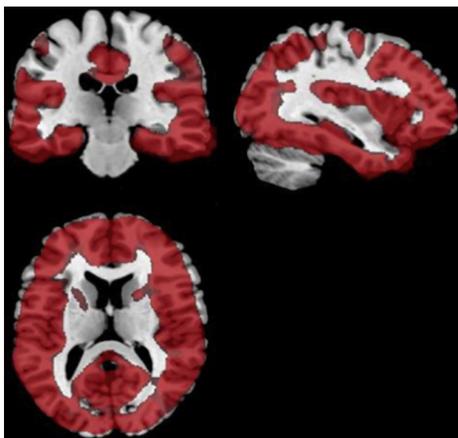
Finally, to verify that our image processing methods were valid and we could obtain results for an expected pattern, we performed a two-sample unpaired t-test with the same parameters as the above analysis, contrasting APOE $\varepsilon4$-positive vs APOE $\varepsilon4$-negative ADNI DOD subjects (regardless of PTSD/TBI/Control status), and observed elevated amyloid throughout the brain except for somatosensory cortex in APOE $\varepsilon4+$ participants compared with their APOE $\varepsilon4-$ counterpart (shown at left).

When we shared our results with you and with the authors, they suggested that the differences in our voxel-wise findings and those in their published manuscript might be due to influential differences in procedures, but this is hard to understand since we followed the methods as described in the manuscript, and used the subject IDs they provided. They also suggested that the methods used to correct for multiple comparisons at the voxelwise level may explain the discrepancy, but we examined the voxelwise results at multiple levels of statistical significance and found that the statistical criterion did not account for the discrepancy.

We appreciate that the authors were responsive to our concerns and made a number of changes as noted in the corrigendum. Ultimately, however, the corrigendum does not address the primary conclusions of the study, which we were unable to replicate. We are troubled by the publication of results that cannot be replicated using identical methods and participant data.

Data availability statement

Datasets related to this article can be found in the following citation:
Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. Mohamed AZ, et al. Neuroimaging Clinical 2018 Jun 5;19:716–726.