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Response to the letter concerning the publication: Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. Mohamed AZ, et al. NeuroImage Clinical 2018 June 5;19:716–726

Abdalla Z. Mohamed[a], Paul Cumming[b,c,d], Fatima A. Nasrallah[a,*]

[a] Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia
[b] Institute of Nuclear Medicine, Inselspital, Bern University, Bern, Switzerland
[c] School of Psychology and Counselling, Queensland University of Technology, Queensland, Australia
[d] QIMR-Berghofer Institute, Brisbane, QLD 4006, Australia

ABSTRACT

In August 2018, Weiner and colleagues raised a red flag concerning certain errors in the tables and figures of our article, "Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. NeuroImage Clinical 2018 Jun 5;19:716–726". We have addressed this in detail in our published "Corrigendum to 'Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury' NeuroImage: Clinical. 19 (2018) 716–726". However, recently Prof. Weiner and colleagues have raised a new issue in indicating that they could not 'replicate our results, despite accurately emulating our methods. We have prepared this letter in response to their recent letter.

Dear Dr. Dickerson

In August 2018, Weiner and colleagues raised a red flag concerning certain errors in the tables and figures of our article, "Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. NeuroImage Clinical 2018 Jun 5;19:716–726" (Mohamed et al., 2018). We have addressed this in detail in our published corrigendum (Mohamed et al., 2019), and have taken steps to ensure that our data analysis pipeline is no longer vulnerable to clerical errors. Happily, our main findings of distinct voxelwise patterns of relatively increased [^{18}F]-AV45 SUVR in long-term PTSD and TBI survivors have withstood re-analysis in our hands. Such focal group differences of small effect size are not at odds with the absent group differences in Prof. Weiner's earlier analysis of the entire cerebral cortex in these study groups (Weiner et al., 2017), as they would surely have been diluted out in the large cortical volume of interest.

One of the major issues raised by Weiner et al. concerned our earlier exclusion of non-Caucasian subjects and the lack of correction for age and APOE4 status. We re-analyzed the data by adding 17 subjects excluded from our earlier analysis due to their ethnicity (results shown in Fig. 1, below). The revised voxelwise findings closely matched Fig. 4 in our original analysis (Mohamed et al., 2018), indicating that ethnicity is not a major factor in our results. The extra 17 subjects distributed among the existing groups as follows: n = 0 (TBI), n = 2 (TBI_PTSD), n = 7 (PTSD), and n = 8 (healthy controls).

In Fig. 1. We see higher relative [^{18}F]-AV45 uptake in the supplementary motor area, cerebellum, and precuneus of the TBI group, in the white matter, the inferior parietal cortex, and the cingulate cortex of the TBI_PTSD group, and in the temporal, occipital, and parietal lobes of the PTSD group, all relative to the healthy control group. Furthermore, we find substantially the same results upon inclusion of additional subjects of non-Caucasian ethnicity, and with the adjustment for APOE4 status and age (Fig. 2, below), tested at the request of Prof. Weiner.

Weiner et al. have gone to considerable trouble to emulate closely our analysis methods using the same subject groups as in our publication, but have not replicated our voxelwise findings. We note two remaining issues that may account for Prof. Weiner's discrepant findings with the same data:

1. Weiner et al. do not specify their method for image registration, i.e., FSL, ANTS, or SPM. Different registration algorithms, software versions, operating systems, and input arguments to the registration commands might subtly alter parametric maps, resulting in false positive or negative findings. As stated, we used FSL 5.0.9, which gives in our hands different results that its updated versions such as 5.0.10, 5.0.11, and 6.0.

2. Whereas we first calculated SUVR maps in the native space, registered to the anatomic template, and then applied smoothing, Weiner

* Corresponding author.
E-mail address: f.nasrallah@uq.edu.au (F.A. Nasrallah).

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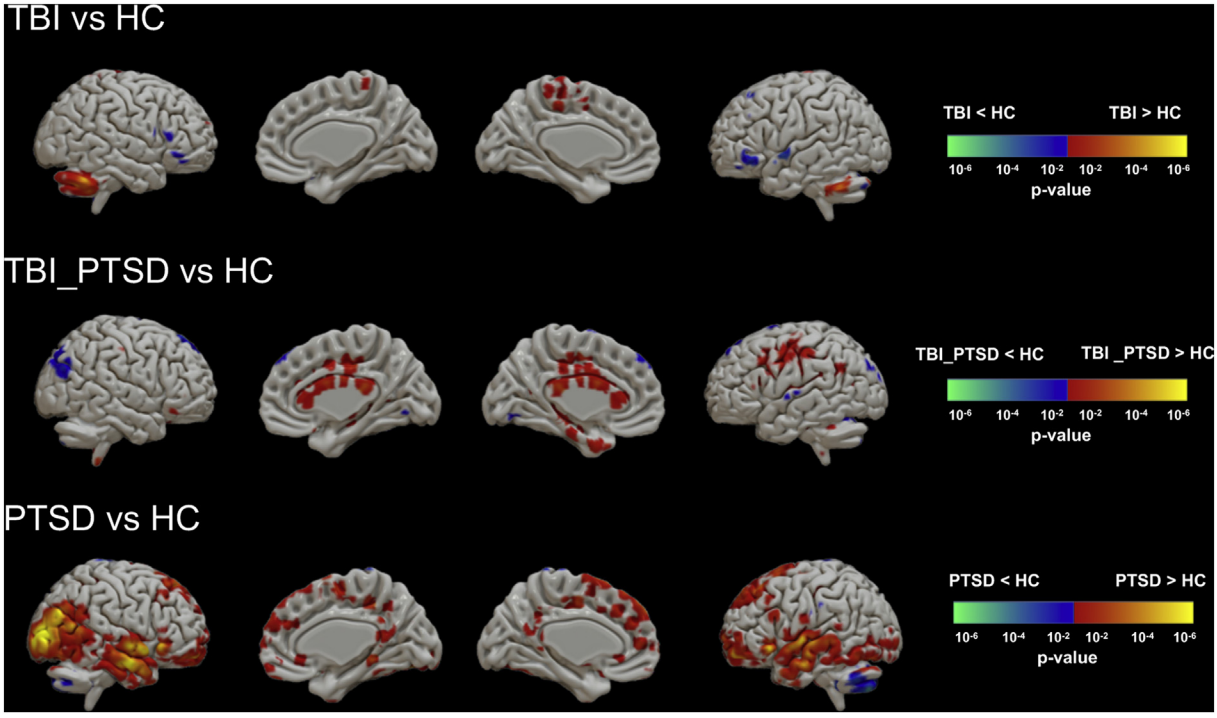

Fig. 1. This figure shows the adjusted results of the original Fig. 4 of (Mohamed et al., 2018) after adding the 17 subjects who were excluded in our earlier analysis because of their non-Caucasian ethnicity. The total number of subjects is then: n = 21 (TBI), n = 31 (TBI_PTSD), n = 64 (PTSD), and n = 65 (healthy controls).

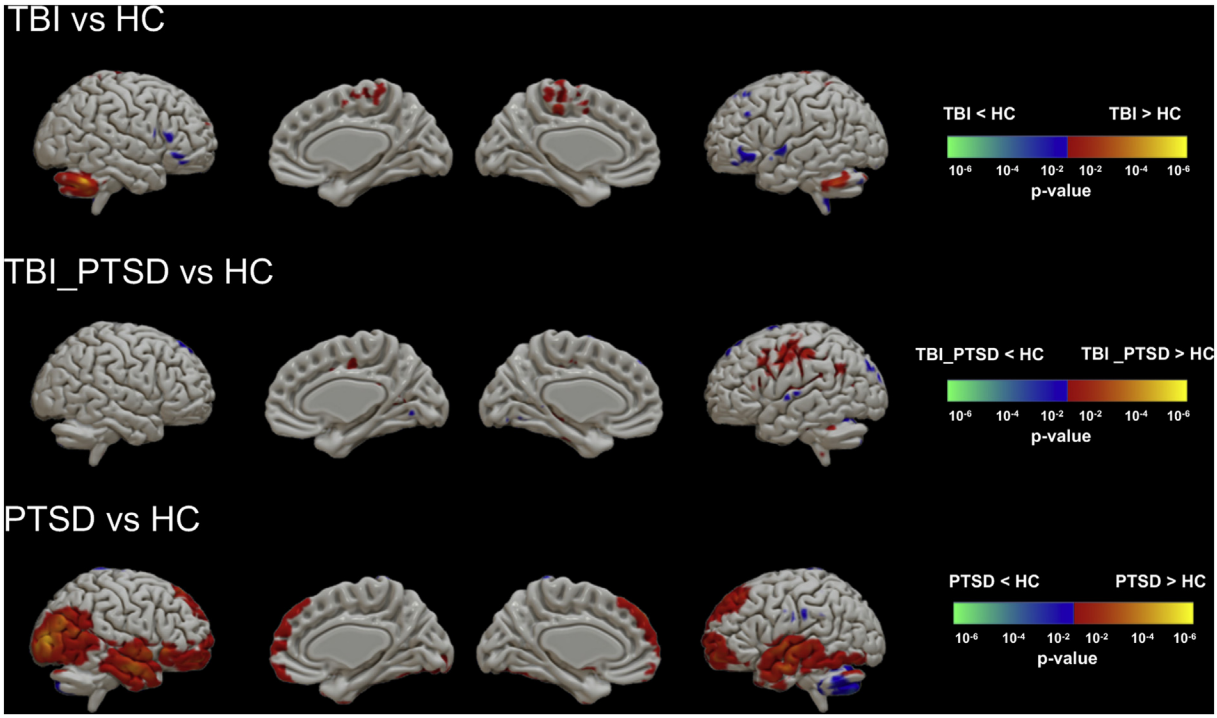

Fig. 2. This figure shows the same contrasts in Fig. 4 from (Mohamed et al., 2018), but with the addition of 17 subjects who were excluded in our earlier analysis because of their non-Caucasian ethnicity, and with results further adjusted for APOE4 status and age. The white matter finding in the TBI_PTSD group disappeared after these adjustments. However, the findings of relatively higher [^{18}F]-AV45 uptake in several cortical regions of the PTSD group, including the temporal, occipital, and parietal cortex remained, as did the increased relative uptake in the supplementary motor area, cerebellum, and precuneus of the TBI group.

et al. calculated their SUVR maps after registration and smoothing, which likely results in different biases due to resampling.

In general, if PET results are so very sensitive to minor methodological differences, one might suppose that the tracer and methods are not completely fit to detect reliably real group differences of small effect size. In this case, various re-analyses seemingly chatter around a sensitivity limit established by the low specific binding of [^{18}F]-AV45, a first-generation amyloid tracer. This issue is not without precedent in PET imaging; consider the unreliable quantitation of [^{18}F]-fallypride

binding to dopamine $D_{2/3}$ receptors in the cerebral cortex, where the BP_{ND} is only 0.5 (Smith et al., 2019). Returning to our topic of amyloid imaging, florbetaben, florbetapir, and flutemetamol all have similar sensitivity and specificity for the diagnosis of Alzheimer's disease (Morris et al., 2016), and might be similarly insensitive for detecting the small group differences encountered in our analysis of TBI and PTSD survivors. We can hope that improved amyloid tracers such as fluselenamyl, which has higher affinity for amyloid and lower non-specific binding in the white matter (Sundaram et al., 2016), should help resolve this present issue. Furthermore, PET investigations of amyloid in conditions other than Alzheimer's disease should also accommodate the range of biophysical properties of different kinds of amyloid deposits (Shoghi-Jadid et al., 2005).

Indeed, the limits of sensitivity of present PET methods may be the most important matter arising from this inquest, and one of general interest to the readership of NeuroImage Clinical: if two similar and valid approaches to data analysis give disparate results, then we must be operating at the limit of the sensitivity of the methods. High sensitivity is obtainable at the cost of false positive findings (Frackowiak et al., 1996), but false negatives may arise from factors such as choice of reference region, the precise extent of smoothing, or the filtration of individual parametric maps. We perceive a need for objective measures of the sensitivity of a given method, perhaps obtainable through simulations over a wide range of cluster and effect sizes.

Respectfully,

Fatima A Nasrallah PhD. Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia.

Paul Cumming PhD, Institute of Nuclear Medicine, Inselspital, Bern University, Bern, Switzerland; School of Psychology and Counselling, Queensland University of Technology, Queensland, Australia.

Abdalla Z Mohamed MSc, Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia.

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