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TAUB INSTITUTE for research on ALZHEIMER'S DISEASE and the aging brain

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PLOS
1160 Battery Street
San Francisco, CA 94111

TO: Editorial staff at PLOS Biology
RE: Manuscript Submission, Research Article

We are pleased to submit the manuscript entitled "Chemogenetic attenuation of neuronal activity in the entorhinal cortex reduces Aβ and tau pathology in the hippocampus" by Rodriguez *et. al.* to PLOS Biology. This manuscript is a revised version of our previously submitted manuscript [PBIOLOGY-D-19-00723R1] and is submitted along with a full response to four reviewers' critiques and comments (Rodriguez *et al* – PLOS Biology – Response to Reviewers), Supplemental Table 1 and Appendix 1.

Manuscript Summary

In this revised manuscript, we describe experiments using a novel transgenic mouse line created to investigate the relationship between amyloid beta (Aβ) accumulation and tau pathology in vivo. Specifically, we test the hypothesis that hAPP/Aβ leads to overactive neuronal signaling and impaired network function in the entorhinal cortex, and that this hyperactive phenotype aggravates local tau pathology and promotes acceleration of tau accumulation into the hippocampus. Importantly, we demonstrate that attenuating this hyperactive phenotype in the EC using chemogenetics (DREADDs activation) results in reduced hAPP/Aβ as well as pathological tau accumulation in downstream, synaptically connected HIPP subfields. Our results strongly support the hypothesis that Aβ-associated neuronal hyperactivity is a key driver of AD pathology, and that combating this aberrant neuronal firing can be an effective approach to ameliorating Aβ and tau accumulation in the brain.

Response to Reviewers Summary

We are happy to report that we have now included new data from additional mice to studies throughout this revised manuscript, resulting in increased sample sizes and more robust statistical analyses on a per mouse basis. Importantly, all electrophysiology and brain harvesting for IHC processing was performed in a balanced manner across genotypes. The electrophysiology data from the newly added mice was collected at the same time as the mice whose original data appeared in the original manuscript. Single-unit and local field potential analysis was performed at a later time. Likewise, brain harvesting for newly added mice in Figures 4-5 was performed at the same time as mice that appear in the original manuscript. Brain sectioning, immunostaining and image analysis for the new mice was completed at a later time unless otherwise noted.

We would greatly appreciate it if the same reviewers were contacted to review our revised manuscript. However, in the event that this is not possible, we have included a list of researchers that we would like to have included in the review process based on technical expertise, as well as researchers who should be excluded based on competing research interests.

Sincerely,
S. Abid Hussaini

We would like to **exclude** the following researchers from the review process based on competing research interests:

Bradley T Hyman (Harvard University / Massachusetts General Hospital)
David Holtzman (Washington University of St. Louis)
Joanna Jankowsky (Baylor College of Medicine. Houston, Texas)

Reviewers to *include* with relevant experience:

Lennart Mucke (Gladstone Institute, San Franscisco) lennart.mucke@gladstone.ucsf.edu
- expert on hAPP/J20 mouse model
- expert on hyperactivity

Jaime Grutzendler (Yale University) jaime.grutzendler@yale.edu
- expert in dynamics of AD pathology
- recent publication history using DREADDs in AD mouse models

Jorge Palop (University of California – San Francisco) jorge.palop@ucsf.edu
- has published extensively w/ hAPP/J20 mice
- technical expertise in electrophysiology

John O'Keefe (University College London) j.okeefe@ucl.ac.uk
- expert in hippocampus and entorhinal cortex
- expert in vivo electrophysiology and research interests in AD

Arthur Konnerth (Technische Universitat Munchen) office-konnerth.med@tum.de
- expert in cortical population activity
- published extensively on Aβ-associated neuronal hyperactivity