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April 11th, 2019

Bing Wu, PhD
Review Editor
JoVE

Dear Dr. Wu,

We are delighted to submit our revised manuscript, "***In Vivo* Imaging of Cerebrospinal Fluid Transport through the Intact Mouse Skull using Fluorescence Macroscopy**" for your consideration (Reference # JoVE59774).

We present a manuscript that describes a detailed methodology for macroscopic tracking CSF influx in vivo. In addition to other methods to studying CSF influx into the brain, we believe that in vivo transcranial macroscopic imaging helps us to better understand glymphatic influx. While 2-photon microscopy has a superior spatial resolution, the field of view is limited and requires an intensive surgical procedure. MRI also gives insight to whole brain CSF dynamics, but it lacks the spatial and temporal resolution. Our method has enhanced spatial resolution compared to MRI and does not require the rigorous surgery that 2-photon microscopy often does. Transcranial macroscopic imaging through the whole mouse brain gives us great insight into CSF influx in real-time and allows for many adaptations, including TBI, which can be seen in our results.

We would like to thank you for giving us the opportunity to revise our manuscript. The editorial comments and concerns directed us to take the time to further improve our manuscript.

Our revisions include the following:

1. All protocol steps are now in the proper tense, with no use of personal pronouns
2. Removed all highlighting from cautions and notes
3. Protocol steps were reduced to 4 lines or fewer, unless indicated
4. We have added a co-author, Xiaowei Wang. She was influential in preparing the re-submission and Dr. Wang has reported no conflicts of interest.

Please find our reply to the reviewer comments in an accompanying file.

Best regards,

With best regards,

A handwritten signature in cursive script that reads 'Maiken Nedergaard'.

Maiken Nedergaard
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Co-Director, Center for Translational Neuromedicine