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Reply to Dr. Ashwin Kumaria

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We are very pleased to read the letter submitted by Dr. Ashwin Kumaria to the journal in response to our research paper *(1)*. We share with the writer an excitement in the potential for a PET based method to estimate the clearance of CSF. As pointed out in Dr. Kumaria's letter, an impaired removal of protein waste may contribute to the development of many neurodegenerative diseases. This hypothesis is supported by an increasing body of preclinical evidence *(2)*. The CSF clearance deficits we observed in the ventricle and superior nasal turbinates in our Alzheimer disease study, are part of the glymphatic pathway, a CSF and interstitial fluid (ISF) communication pathway largely designed for waste removal from brain.

Rodent model studies have identified glymphatic pathway deficits in transgenic Alzheimer mice, in cerebrovascular disease, and brain trauma models. Animal studies have also shown the modifiability of the glymphatic pathway under experimental sleep and exercise conditions *(3)*.

Looking forward, Dr. Kumaria points out promising areas of investigation in human. We offer that another poorly understood area worthy of study is the contribution of the glymphatic system to the presentation of antigens and immune cells to the brain and to their clearance out to the periphery.

Overall, we expect that future functional longitudinal human imaging studies will directly test the hypothesized causal and modifiable relationships between brain CSF and ISF clearance and the accumulation of misfolded proteins, thus creating new therapeutic possibilities for neurodegenerative diseases like Alzheimer's.

Reference:

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3. Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis J. Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. *J Clin Invest*. 2017;127:3210-3219.