Response to: 'Correspondence on 'Blood-brain barrier leakage in systemic lupus erythematosus is associated with gray matter loss and cognitive impairment" by Pamuk and Hasni

We thank Dr Pamuk *et al*[1] for their interest in our work,[2] and for providing insights regarding mechanisms that may help explain our findings. Their correspondence highlights the importance of further understanding the processes underlying our main finding: extensive blood-brain barrier (BBB) leakage affects ~25% of patients with systemic lupus erythematosus (SLE) and is linked to smaller grey matter volume and cognitive impairment. We agree that the mechanisms resulting in BBB leakage in SLE remain poorly understood, and that a neuroinflammatory response mediated through the lymphatic system may contribute to BBB pathology.

There is a growing consensus regarding the link between BBB pathology and neuroinflammation,[3] and several hypotheses regarding causality have been proposed. Some experimental evidence suggests that autoimmune-inflammatory mechanisms may interact with the BBB through the systemic circulation at the capillary lumen, causing BBB injury that triggers downstream neuroinflammation.[4] Acting in an amplification loop, neuroinflammation, in turn, further exacerbates BBB injury.[5]

As reviewed by Pamuk *et al*, autoimmune-inflammatory mechanisms may also involve the lymphatic system. Animal data suggest that immune cells from lymphoid structures in the neck may migrate into cerebrospinal fluid (CSF) via lymphatics[6] or through the choroid plexus,[7] and trigger neuroinflammation from the space surrounding the BBB. According to this hypothesis, injury to the BBB occurs not at the capillary lumen, but at the network of glial lymphatic (glymphatic) clearance channels surrounding medium-sized brain vessels.[7]

We agree that further research is needed for elucidating the role of the lymphatic system in neuroinflammation, BBB permeability, and neuropsychiatric SLE (NPSLE). One of the major challenges in such research is the lack of established clinical tools for assessing the function of the CNS lymphatic system in living patients. Until such methods are available, we would like to highlight that quantitative assessment of BBB permeability—using dynamic contrast-enhanced MRI—offers an important tool for clinical diagnosis of BBB leakage and for gaining further insight into the role of BBB pathology in NPSLE.

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