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## A Letter Concerning A Role for Blood-brain Barrier Dysfunction in Delirium following Non-Cardiac Surgery in Older Adults

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To the Editor,

Devinney et al. <sup>1</sup> highlight a link between blood-brain barrier (BBB) dysfunction and post-surgery delirium in older adults. Using the MADCO-PC and INTUIT studies, they analyzed cerebrospinal fluid (CSF) samples from before and after surgery. CSF-to-plasma albumin ratio (CPAR) was used as a surrogate for BBB dysfunction. In their study, 12.6% of subjects experienced postoperative delirium, with a significant rise in CPAR values post-surgery. This change correlated with delirium and longer hospital stays.

It should be specified that CPAR is an imperfect marker for BBB dysfunction for several reasons. First, CPAR evaluates the blood-CSF barrier (BCSFB) rather than the BBB <sup>2,3</sup>. It's essential to distinguish between the BBB and BCSFB, as they have different diffusion pathways and CSF flow rates. The authors suggest a continuous relationship between CPAR and BBB permeability, referencing a study by Montagne et al. <sup>4</sup> which shows a correlation between CPAR and a specific MRI sequence called "K<sub>trans</sub>". This sequence reflects the efflux rate of gadolinium from blood plasma into the brain's extravascular-extracellular space. Unfortunately, the generalization of these findings established on a population of normal aging subjects or subjects with various causes of cognitive impairment to patients undergoing surgery lacks evidence. Also, as discussed by Reiber and others <sup>5,6</sup>, CPAR doesn't consider CSF flow rate, and factors like reduced CSF production that can alter its values. Since CPAR focuses on albumin (70kDa), lower levels of increased permeability can be missed <sup>7,8</sup>. Olsson et al. <sup>9</sup> also showed that consecutive lumbar punctures within 24h-48h raised CPAR, possibly due to inflammation from the initial puncture.

Furthermore, Devinney's "2-hit" theory for delirium onset lacks data on peri-operative drugs. Indeed, some drugs, especially CYP3A or P-glycoprotein inhibitors <sup>10</sup>, are tied to delirium. Our team found that in conditions with increased BBB permeability, such drugs often appear in patient CSF <sup>11</sup>. Finally, the study omits details on the orthopedic surgeries performed, even though 27.1% of participants had them. Differentiating between spinal surgeries, which could be "neurosurgery" or "orthopedic surgery", is vital. Spinal surgeries might cause inflammation, affecting CSF-albumin levels.

In summary, Devinney's study provides really new insights in the pathophysiology of post-operative delirium. Nevertheless, it has gaps and potential biases. Given the complexities surrounding BBB and BCSFB, a singular approach may not capture the full extent of their dynamics and future studies should consider a multimodal

assessment approach: First, incorporate a broader range of blood biomarkers such as Protein S-100 Beta, Neuron specific enolase, and GFAP. These markers can provide a more comprehensive understanding of BBB and BCSFB integrity and function. Second, utilize advanced MRI sequences allowing to measure “ $K_{trans}$ ”. However, performing an MRI on a patient experiencing delirium is challenging, as their agitation can compromise the quality and safety of the imaging procedure. CT-Perfusion imaging<sup>12</sup> is feasible for agitated patients because it is fast, and allows BBB assessment. Third, account for the potential bias of drugs administered during the peri-operative period.

By integrating these additional measures, future research can offer a more holistic and accurate understanding of BBB and BCSFB dynamics in the context of postoperative delirium. It's essential to interpret the current data with caution, recognizing its limitations, and the potential for various biases. Only with a comprehensive approach can we truly unravel the complexities of BBB and BCSFB in relation to postoperative complications in older adults.

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## Disclosures:

Loïc Le Guennec has nothing to disclose.

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LLG, AB and NW wrote the manuscript.