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The Inflammatory Response to Surgery and Sleep Fragmentation

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We thank the correspondents for their interest in our work and appreciate the invitation to respond.

The correspondents suggest that our research should have exposed a *proportional relationship* between interleukin-6 (IL-6) levels and the degree of cognitive impairment. We certainly agree that there is an *association* between upregulated IL-6 transcription with postoperative cognitive decline after surgery in rodents. Dong *et al* have suggested a causal relationship between the two in “wounded” older rodents¹. However, we are unaware of any reports of *quantitative proportionality* between the amount of behavioral change with varying levels of IL-6. While we have not addressed this hypothesis directly we consider it unlikely that such a constant ratio exists because of the interplay of a multitude of factors governing complex behavior such as learning and memory. Our previous work has uncovered several different causal factors², each of which is individually capable of influencing cognition. For example, the translocation of bone marrow-derived monocytes into the brain, a prerequisite for postoperative cognitive decline³, requires HMGB1-mediated MCP-1 expression² with no precise quantitative relationship to hippocampal IL-6 transcription.

We agree with the correspondents’ concern that we did not exhaustively assess memory paradigms, but we stated this caveat in the opening paragraph in the Discussion section of our report⁴.

Regarding the correspondents’ contention that we should not invoke preconditioning as a speculation for the observed dissociation between behavior and neuroinflammation, the examples they provided are not in the sleep domain in the surgical setting. The sleep model used in this study is characterized by rebound REM sleep and an increase in the deeper stages of NREM sleep. Rebound sleep following sleep disruption has been causally related to subsequent neuroprotection by reducing the expression of inflammatory mediators⁵.

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Conflicts of interest: none

SV and MM helped prepare the manuscript.

We hope that our response has allayed the correspondents' remaining concerns about our study.

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