LETTER

REPLY TO WOSTYN ET AL.:

Investigating the spaceflight-associated neuro-ocular syndrome and the human brain in lockstep

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We thank Wostyn et al. (1) for their positive and insightful comments with respect to the association of the symptoms of the spaceflight-associated neuro-ocular syndrome (SANS) and our region-of-interest analysis of the brain's ventricular cerebrospinal fluid (CSF) system after long-duration spaceflight (2). We would like to expand upon some points raised in the commentary. Our data show a substantial and quantifiable expansion of the ventricles. Other anatomical regions of the CSF space such as the chiasmatic and the lamina terminalis cisterns, localized much closer to the optic nerve and eye, also show a clear postflight expansion [for details, please refer to Figure 1a of our previous work (3)]. These changes in the basal CSF cisterns are, however, not quantifiable in the absence of a dedicated human atlas for the regions in question. We see the way forward to clarify the presumed connection between the expansion of the ventricles and SANS in the near future in an observer-independent fiducial-based approach to delineate ocular dimensions and retroorbital distance measurements based on magnetic resonance imaging (MRI) pre- and postflight akin to previous exploratory analyses by Kramer et al. (4), but in an algorithm-driven and observer-independent manner. Hereto, a new population-based template with geodesic shooting for the human eye needs to be built first, followed by a standardized segmentation for the eye, the lens, the tip, and course of the optic nerve. Optimally, all delineated ocular and optic nerve distance measurements would then be investigated together with visual acuity and optical coherence tomography data in an interdisciplinary and collaborative approach. After the comments by Wostyn et al. (1), we would now certainly also include the width of the optic canal as a potentially relevant cofactor in future studies. Since MRI also allows for soft tissue segmentation, one might even additionally investigate meningo-endothelial remodeling of the optic canal in the same context. We are, however, cautious of a narrow optic canal's protective relevance for long-duration space travelers. A recent comparably large study in intracranial hypertension found no clear association for the canal width with severity or asymmetry of papilledema (5).

Two aspects of our data should be kept in mind as we all aim to map the effects of long-duration spaceflight. First, our data might still underestimate the actual intracranial fluid accumulation occurring at the end of long-duration spaceflight in humans since our results are obtained on average almost 10 d after return to Earth. Second, the visual acuity changes occurred in fewer than half of the cosmonauts (5 out of our sample of 11) and all observed visual acuity changes were subclinical. Taken together these facts would speak for a remarkable elasticity and reserve capacity of the tissues neighboring and encompassing the CSF space. Finally, a linear association of SANS with the duration of a single spaceflight has been described (e.g., refs. 6–9), but the additive or cumulative effects in SANS for multimission long-duration exposure to microgravity have only been described anecdotally (10). Future prospective studies should clarify this "dose–response" relationship.

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1 P. Wostyn, T. H. Mader, C. R. Gibson, P. P. De Deyn, The buffering capacity of the brain and optic nerve against spaceflight-associated neuro-ocular syndrome. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 15770–15771 (2019).
2 A. Van Ombergen *et al.*, Brain ventricular volume changes induced by long-duration spaceflight. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 10531–10536 (2019).
3 A. Van Ombergen *et al.*, Brain tissue-volume changes in cosmonauts. *N. Engl. J. Med.* **379**, 1678–1680 (2018).
4 L. A. Kramer, A. E. Sargsyan, K. M. Hasan, J. D. Polk, D. R. Hamilton, Orbital and intracranial effects of microgravity: Findings at 3-T MR imaging. *Radiology* **263**, 819–827 (2012).
5 Y. Farrokhi, S. Sharif Kashani, M. Aghsaei Fard, F. Pakdel, S. Yadegari, Optic canal size in idiopathic intracranial hypertension and asymmetric papilledema. *Clin. Neurol. Neurosurg.* 10.1016/j.clineuro.2019.105376 (2019).
6 N. Alperin, A. M. Bagci, Spaceflight-induced visual impairment and globe deformations in astronauts are linked to orbital cerebrospinal fluid volume increase. *Acta Neurochirurgica Suppl.* **126**, 215–219 (2018).
7 N. Alperin, A. M. Bagci, C. J. Oliu, S. H. Lee, B. L. Lam, Role of cerebrospinal fluid in spaceflight-induced ocular changes and visual impairment in astronauts. *Radiology* **285**, 1063 (2017). Retraction in: *Radiology* https://pubs.rsna.org/doi/10.1148/radiol.2017161981 (2017).
8 A. G. Lee, T. H. Mader, C. R. Gibson, T. J. Brunstetter, W. J. Tarver, Space flight-associated neuro-ocular syndrome (SANS). *Eye (Lond)* **32**, 1164–1167 (2018).
9 T. H. Mader *et al.*, Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. *Ophthalmology* **118**, 2058–2069 (2011).
10 T. H. Mader *et al.*, Optic disc edema in an astronaut after repeat long-duration space flight. *J. Neuroophthalmol.* **33**, 249–255 (2013).