therefore possible that a treatment with transdermal auricular vagus stimulation may also be beneficial for patients with neuropathic POTS.

Additionally, and in patients only, norepinephrine concentrations during head-up tilt significantly decreased after water intake, which was associated with an improvement of symptoms. This finding supports the occurrence of the water-induced pressor response and also its assumed mechanisms (Scott et al., 2001; Jordan, 2005; Lu et al., 2012). In summary, the tone of the sympathetic nervous system appears to be down-regulated after water ingestion, and patients with neuropathic POTS therefore experience less arousal and fewer symptoms during head-up tilt, which in turn could be a reason for better cognitive performance.

The present study must be considered with some limitations. First, the study includes a limited sample size, so that the analysis of complex regression models such as a mediation analysis was not possible. Second, all participants had the same procedure during the examination; the order of the conditions (e.g., supine vs. head-up tilt, before vs. after water) was not randomized. Therefore, although we included a control group, we cannot completely exclude the presence of confounding learning and/or fatigue effects. We chose the present study protocol to avoid the possible confounding effect of the known day-to-day fluctuation of symptoms in patients with POTS. Additionally, only patients with neuropathic POTS were included in the study, leading to limited generalizability of the results with respect to other POTS subtypes, especially hyperadrenergic POTS. Previous studies have shown that muscle sympathetic nerve activity peaks 30 min after water intake and that plasma norepinephrine concentrations change at around the same time (Jordan et al., 1999; Scott et al., 2001). The second half of the experiment was therefore started 20 min after water intake to ensure that the expected peak of the water effect occurred during the phase of cognitive testing and catecholamine assessment. Furthermore, the heterogeneity of the underlying etiologies and comorbidities of POTS in our cohort, particularly the presence of gastrointestinal dysmotility, may have had an impact on the results regarding water intake (Dipaola et al., 2020). Finally, the described excessive increase in plasma norepinephrine concentration may not necessarily represent an increase in central sympathetic activity but also a decrease in norepinephrine clearance, as plasma norepinephrine concentration is the result of the balance between norepinephrine release and clearance. The inclusion of indices of cardiovascular autonomic control such as heart rate and blood pressure variability or measurements of muscle sympathetic nerve activity would have allowed a more comprehensive assessment of autonomic function.

The present study provides further evidence for the occurrence of pure orthostatic cognitive deficits in POTS, particularly in relation to working memory function, and found that these were associated with patient-reported symptom severity. In addition, the results show that patients with neuropathic POTS had elevated norepinephrine concentrations independent of body position, with an excessive increase in the upright body position that was related to heart rate and subjective symptom perception. Acute water intake in patients with neuropathic POTS decreased norepinephrine concentrations and heart rate, and improved symptoms, which in turn was associated with better cognitive performance. In conclusion, the results of the present study indicate that orthostatic cognitive dysfunction in neuropathic POTS is associated with the symptom severity experienced by patients and support the use of bolus water drinking for down-regulation of the sympathetic nervous system as the basis of symptomatic treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Kantonale Ethikkommission Bern, Bern, Switzerland. The patients/participants provided their written informed consent to participate in this study.

Author contributions

BR, RM, and WZ'G designed the research. BR, AH, and WZ'G performed all study procedures. EG and PE performed all laboratory analyses and interpretations. BR and WZ'G did the data analysis. All authors contributed with data interpretation. BR and WZ'G wrote the manuscript. All authors discussed the results and revised the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.968725/full#supplementary-material

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