Nature and Science of Sleep

Elevate Series

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RESPONSE TO LETTER

From Brain to Insomnia: Can Neurotrophic Factors Unlock the Sleep Puzzle After Stroke? [Response To Letter]

Guomei Shi[1,2], Xiaorong Wang[2,3], Rujuan Zhou[2,3]

[1]Department of Neurology, Taixing Clinical College of Bengbu Medical College, Taixing, Jiangsu, People's Republic of China; [2]Stroke Center, Taixing People's Hospital, Taixing, Jiangsu, People's Republic of China; [3]Department of Neurology, Taixing People's Hospital, Taixing, Jiangsu, People's Republic of China

Correspondence: Rujuan Zhou, Taixing People's Hospital, No. 1 Changzheng Road, Taixing, Jiangsu, 225400, People's Republic of China, Tel +86 13951158499, Email zhourujuan123@163.com

Dear editor

We are grateful for the attention to our recent study published in *Nature and Science of Sleep*[1] and the insightful feedback by Yang, Pan and Hong.[2] Their letter raised three key points: (1) In early neurological deterioration (END) patients, impaired consciousness (eg, drowsiness, coma) may confound early-onset insomnia (EOI) assessment. The Pittsburgh Sleep Quality Index (PSQI), as a self-report tool, might not be suitable for patients with acute neurological deterioration. (2) The DeLong test was not used to confirm the statistical significance of AUC differences between biomarkers (mBDNF/proBDNF ratio vs mBDNF alone). (3) Subgroup analyses for comorbidities (eg, depression, anxiety) were lacking, potentially confounding the BDNF-EOI association.

We recognize the potential challenge of distinguishing EOI from acute neurological impairments, such as altered consciousness, in patients with END. To address this, our exclusion criteria rigorously excluded individuals with severe aphasia or cognitive deficits that could compromise self-reported sleep assessments (see Materials and Methods). All included participants were clinically evaluated to ensure sufficient cognitive capacity to complete PSQI. Additionally, given the potential impact of specific infarction sites (eg, thalamus, brainstem) on sleep, we meticulously identified lesion locations, including telencephalon, diencephalon, cerebellum, and brainstem. Statistical analysis revealed no significant association between these infarction sites and the occurrence of EOI.

While acknowledging the limitations of relying on subjective sleep measures, objective tools like polysomnography (PSG) were limited to 11 patients due to technical and financial constraints. This limitation is explicitly discussed in the revised manuscript (see Discussion), where we emphasize the need for future studies to incorporate actigraphy or simplified PSG protocols for broader applicability. Importantly, our diagnosis of EOI adhered strictly to ICSD-3 criteria, requiring new-onset sleep disturbances (eg, sleep initiation, maintenance difficulties) in patients without pre-stroke insomnia, thereby differentiating EOI from transient arousal deficits caused by acute brain injury.

We concur with Yang et al's observation regarding the need to statistically validate differences in AUC values among biomarkers. Reanalysis using the DeLong test confirmed that the mBDNF/proBDNF ratio (AUC = 0.778) significantly outperformed mBDNF alone (AUC = 0.686; Z = 2.128; DeLong test: $p = 0.033$), indicating the ratio's superior predictive capability for EOI.

We agree that comorbidities may influence neurotrophin levels. In our multivariate regression model, HAMD (depression) scores were identified as an independent predictor of EOI (OR = 1.429, $p < 0.001$), while HAMA (anxiety) scores showed borderline significance ($p = 0.081$). Subgroup analyses stratified by HAMD scores revealed no significant interaction between neurotrophin levels and depressive status on EOI risk ($p > 0.05$), suggesting partial control of confounding. Future studies should conduct subgroup analyses stratified by comorbidities (eg, anxiety, hypertension, diabetes) or employ mediation models to clarify whether BDNF-EOI associations are independent of comorbidities.

Received: 19 March 2025
Accepted: 19 March 2025
Published: 5 April 2025

Finally, we sincerely appreciate Yang et al for their rigorous review and will incorporate these recommendations into our future research endeavours. We look forward to validating these findings through multicenter longitudinal studies and mechanistic investigations.

Disclosure

The authors report no conflicts of interest in this communication.

References

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https://doi.org/10.2147/NSS.S529220