Transcranial Electrical Stimulation and EEG to improve CSF Clearance in Sleep Restriction

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BACKGROUND

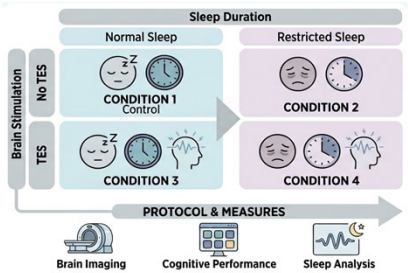
Cerebrospinal fluid (CSF) circulation and its exchange with interstitial fluid (ISF) are critical components of the brain's waste clearance system and overall homeostasis. Impaired CSF flow has been linked to the accumulation of toxic proteins, such as amyloid ($A\beta_{42}$) and tau, which cause cognitive impairment. It is well established that CSF-ISF mediated clearance is a sleep-active process. Active-duty military personnel often require performing cognitively demanding tasks without the ability to get adequate sleep.

In this study, we leverage the Wireless Interface Sensor Pod (WISP) device, a wireless EEG headband designed to enhance CSF-ISF clearance through transcranial electrical stimulation (tES) under conditions of restricted sleep.

OBJECTIVES

1. To assess whether sleep restriction slows subarachnoid CSF flow that is upstream of the CSF-ISF mediated exchange of metabolic waste products.
2. To determine whether WISP-induced stimulation, known to increase slow wave sleep, increases CSF oscillations during sleep restriction to normalize clearance to the same efficiency as natural sleep of 7-9 hours.

METHODS



Study Population Goal: 14 cognitively normal adults (8M; age 22 ± 2 years) with undergoing 4 condition: N: Natural sleep, R: Restricted natural sleep of 4 hours, RT: Restricted sleep of 4 hours with stimulation, NT: Natural sleep with stimulation or sham-control

Imaging: All MRI measurements were conducted between 0700–0900 hours on a Philips MR7700 3T scanner and a 32-channel head coil. Participants underwent a 3D T1w and IVIM MRI for CSF displacement in terms of diffusion *D* (laminar CSF flow), pseudo-diffusion *D** (incoherent shaking or stirring of CSF), and pseudo-diffusion fraction *f* (fraction of CSF experiencing incoherent motion).

Statistics: A Two-Way Repeated Measures Analysis of Variance (RM-ANOVA) will evaluate the primary within-subject factors: Sleep Status (Natural vs. Restricted) and TES Administration (With vs. Without) with statistical significance thresholds set at α=0.05. *For now, only plots for visualization are shown and observations are stated.*

RESULTS

We show data from 3 participants; 001,003,004, for whom MRI analysis was completed. They were 18-year old male, 23-year old male, and 21-year old female respectively. All of them were right-handed with >10 years of education.

Figure 1: Representative figure showing *D*, *D** in the subarachnoid space and one slice showing *D*, *D** in the whole brain. *f*, fraction of tissue displaying incoherent motion characterized by *D** is shown in the entire brain. Based on the map for *f*, *D** is highest in the subarachnoid CSF and ventricles.

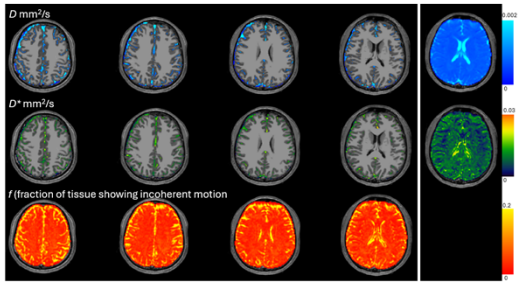


Figure 2: Intravoxel incoherent motion (IVIM) parameter trajectories across N, R, and RT experimental conditions for individual participants. Significant variability is observed between participants and conditions with a consistent downward trend in *D* and *f* with sleep restriction.

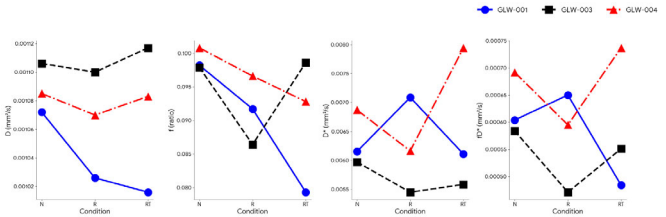
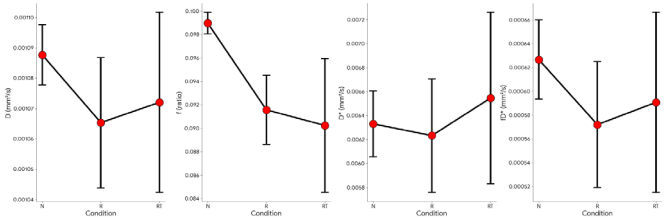


Figure 3: Group-level mean and standard error of the mean (SEM) for IVIM parameters across N, R, and RT conditions. There is a distinct decrease in the amount (*f*) of CSF showing oscillatory behavior with sleep restriction.



DISCUSSION

Aggregate data indicates a consistent downward trend in *D** as experimental conditions progress from N to R. This is in line with our hypothesis and other studies that sleep restriction will reduce the magnitude of CSF oscillatory behavior potentially impairing the glymphatic clearance processes necessary for sustenance of cognitive processes.

While the current analysis provides an encouraging proof-of-concept for trends at a group level for sleep restriction and sleep restriction with tES, the study is currently limited by a small sample size (n=3). Consequently, we are underpowered to draw definitive statistical conclusions, and completing participant analyses is critical to achieving the study's established power targets for rigorous final analysis.

It is also likely that the fraction, *f*, of the fluid showing oscillatory behavior may change with no change in the oscillations (*D**) itself. The individual variability may be better understood by changes in *f*, *D** and the product *fD**.

Whether these upstream measures of CSF circulation are markers of clearance can only be ascertained using plasma or CSF biomarkers that are transported by this system and include $A\beta_{42}$, $A\beta_{40}$, $ptau_{217}$, etc.

CONCLUSION

1. Sleep restriction reduced MRI-derived CSF oscillatory motion across participants.
2. tES demonstrated a restorative trend, increasing CSF oscillatory behavior during sleep restriction, but the response is variable across individuals. Efficacy of tES and paradigms of tES may also play a role in the observed individual variability.
3. IVIM-derived metrics provide a promising non-invasive biomarker of upstream CSF physiology. How these relate to clearance of metabolic wastes from the brain and ultimately to cognition remains to be tested.
4. Larger, adequately powered findings will be available upon study completion to determine whether enhancing CSF oscillations improves brain waste transport and downstream cognitive health.

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