A WEARABLE DEVICE FOR CONTINUOUS ASSESSMENT AND MEASUREMENT OF SLEEP-RELATED CRANIAL FLUID DYNAMICS AND EEG

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INTRODUCTION

Sleep-active glymphatic exchange supports the clearance of interstitial proteins and solutes, including amyloid beta, tau, and alpha synuclein, whose mis-aggregation is implicated in the pathogenesis of neurodegenerative and neurotraumatic conditions. Glymphatic function is currently understood as the process of perivascular solute exchange between the external cerebrospinal fluid and the internal interstitial fluid compartments. Current approaches for assessing glymphatic function in both rodents and humans involve intrathecal gadolinium-based contrast agent injection followed by serial MRI scans. A non-invasive translational approach for measuring glymphatic function has the potential to improve our understanding of sleep physiology, elucidate its role in brain disorders and expose new targets for intervention. We report on our clinical findings of a new non-invasive investigational medical device to measure glymphatic function.

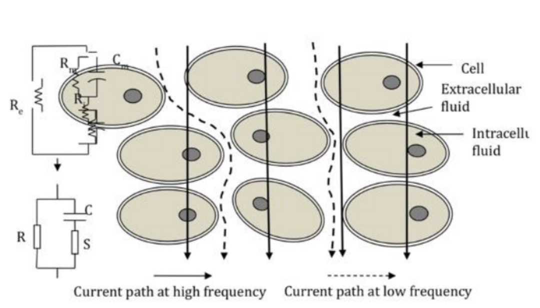
METHODS

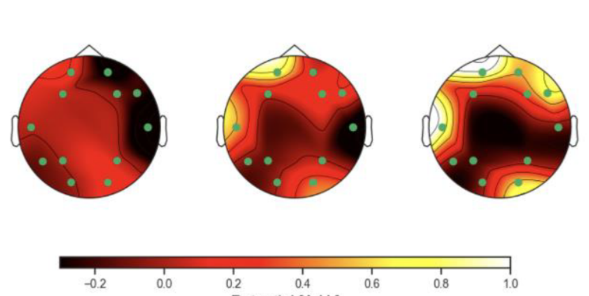
Twenty-seven healthy 50-65 y/o participants were enrolled into a cross-over randomized control clinical trial encompassing one night of sleep and one night of sleep deprivation. During both nights, participants were instrumented with an investigational medical device designed to capture continuous changes in brain parenchymal resistance and cranial fluid dynamics using electrical impedance spectroscopy. The device also captured concurrent EEG and neurovascular parameters. To determine if measured cranial fluid dynamics were explained by sleep/wake physiology, multivariate linear regression on EEG and cardiovascular measures was performed.

Dynamic Impedance Spectro-Tomography

To **measure dynamic shifts in compartment volumes, or glymphatic flow,** the device repeatedly injects minute currents over a wide range of spectral frequencies and transcranial injection electrodes. Over different electrodes, it measures the phase shift of the returned currents, the complex-valued Faradaic impedances and resulting **brain parenchymal resistance R.**

$$Glymphatic\ Flow = \frac{\Delta Pressure}{R}$$



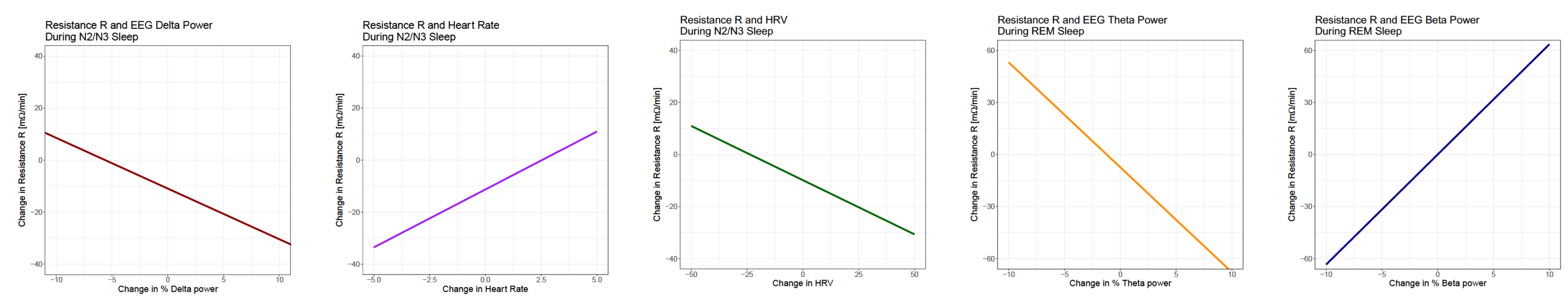


EEG and Cardiovascular Predictors of Resistance R During N2 and N3 Sleep

Predictors	*Estimates*	*CI*	*p*
(Intercept)	-11.36	-20.22 – -2.51	**0.012**
Change in % Delta Power	-1.95	-3.73 – -0.17	**0.032**
Change in HRV [ms]	-0.42	-0.69 – -0.14	**0.003**
Change in HR [bpm]	4.46	0.38 – 8.53	**0.032**
Observations	361		
R^2 / R^2 adjusted	0.042 / 0.034		

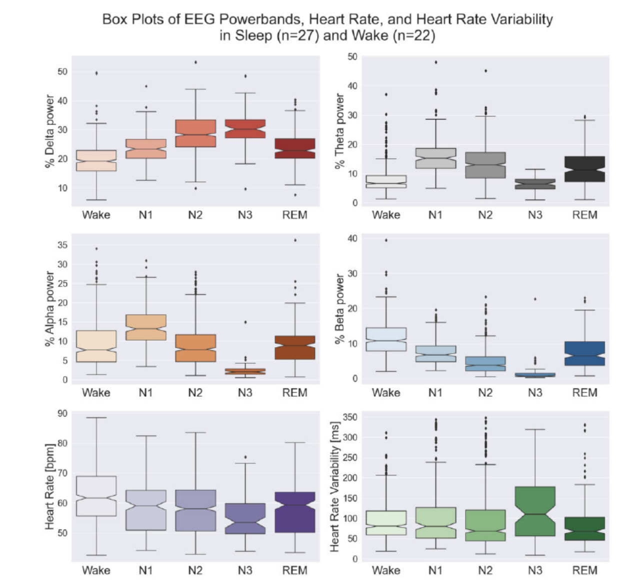
EEG Predictors of Resistance R During REM Sleep

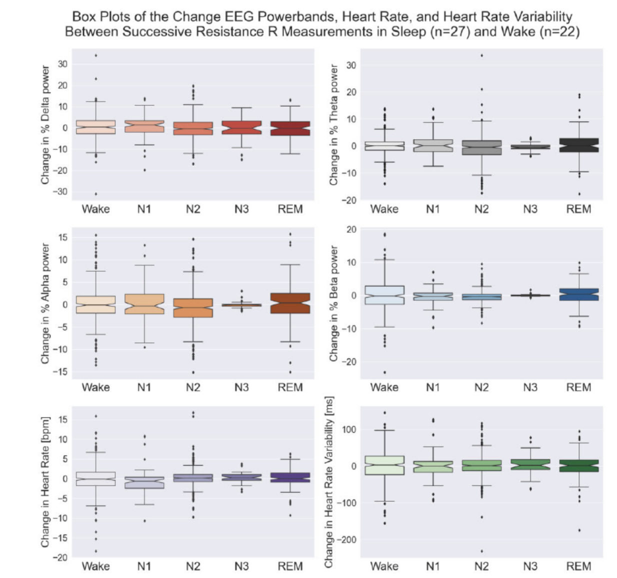
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-8.08	-22.47 – 6.31	0.268
Change in % Theta Power	-5.35	-9.00 – -1.70	**0.004**
Change in % Beta Power	6.92	0.65 – 13.18	**0.031**
Observations	101		
R^2 / R^2 adjusted	0.080 / 0.062		

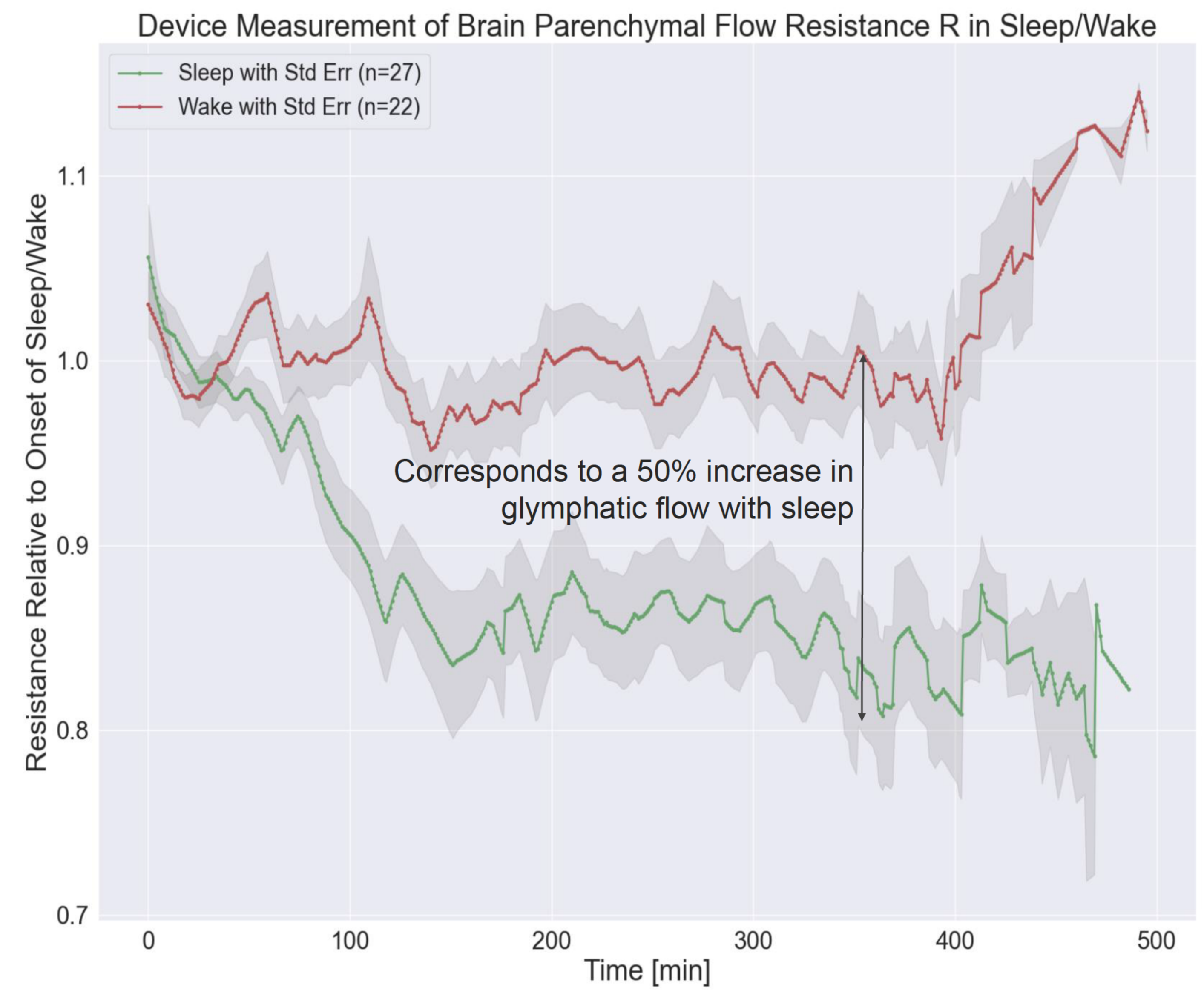


MAIN FINDINGS

- First-ever continuous measure in humans of changes in brain-fluid compartment volumes identified as glymphatic flow
- Sleep lowered resistance to cranial fluid flow, versus wake ($p < 0.005$)
- Fluid flow occurred during N2, N3 and REM sleep, and was associated with changes in EEG delta, theta, beta power, heart rate and heart rate variability

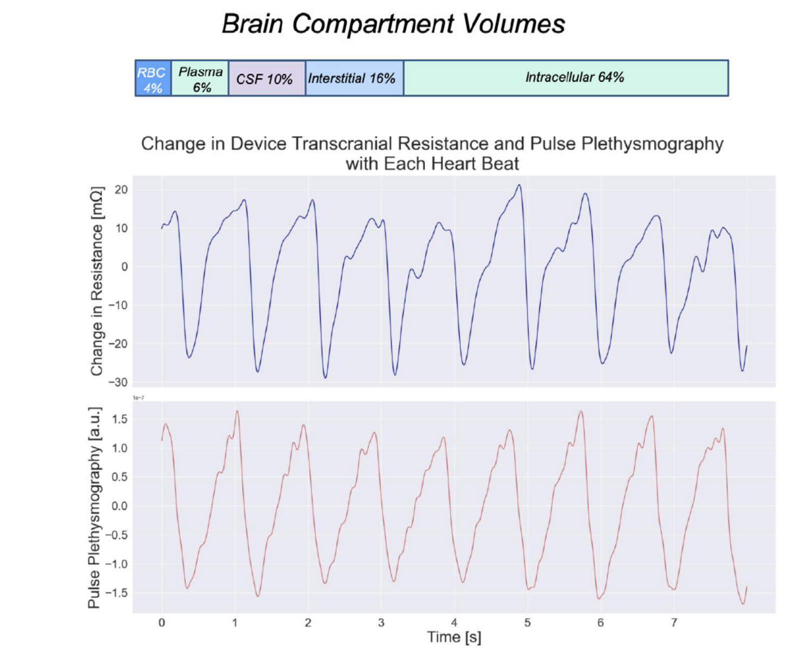






RESULTS

Sleep lowered brain parenchymal resistance by 13.1% compared to wake and induced a corresponding 30.1% increase in brain interstitial fluid volume ($p<0.005$). The decrease occurred during N2/N3 and REM sleep. During N2/N3 sleep, multivariate regression of the change in resistance R on EEG and cardiovascular physiology showed that an increase in EEG delta power (resp. increase in HRV and decrease in HR) caused R to decrease faster ($p = 0.032$, resp. $p = 0.003$ and $p = 0.032$). During REM sleep, multivariate regression on EEG and cardiovascular physiology showed that an increase in EEG theta power (resp. decrease in beta power) caused R to decrease faster ($p = 0.004$, resp. $p = 0.031$).



Resolution of Dynamic Measurements from the Device

- The brain comprises four compartment volumes: intracellular, interstitial, CSF and blood
- With each heart beat, approximately **1 tablespoon of arterial blood enters the brain**
- The device's **transcranial resistance measurement detects it as a peak-to-peak decrease of 30 to 40 mOhms**
- The **changes in overnight sleep** that occur in the brain-compartment volumes are in the **thousands of mOhms**

CONCLUSIONS

Sleep induces changes in brain parenchymal fluid dynamics that are measurable using dynamic impedance spectroscopy and spectrotomography. These changes are associated with N2, N3 and REM sleep changes in EEG band power and cardiovascular physiology. This investigational medical device may provide a pathway for the non-invasive assessment of glymphatic function in human populations in real-world settings. Detection of glymphatic impairment in real-world settings may permit (i) early identification of individuals at-risk for developing a neurodegenerative disorder, and (ii) enable precision targeted enhancement of glymphatic function to restore protein clearance and reverse neuropathology.

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