Noninvasive and remote measurement of sleep-active glymphatic function in the human brain by dynamic impedance spectro-tomography

Poster: P2-986

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MOTIVATION

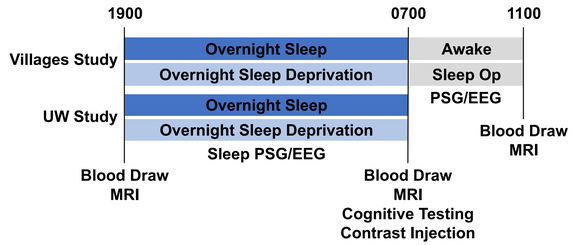
Perivascular glymphatic exchange contributes to the clearance of amyloid β, tau, and α synuclein primarily during sleep. Glymphatic function has been assessed in human populations solely through neuroimaging, including contrast-enhanced magnetic resonance imaging (CE-MRI). Yet these approaches are invasive, and not suitable for widespread clinical implementation. A continuous, non-invasive approach to assessing glymphatic function might permit the identification of patients with glymphatic impairment, and potentially at risk for the development of Alzheimer's disease-related pathological changes. It would also enable the development of interventions targeting glymphatic function.

Using a newly developed investigational medical device (IMD) to measure brain parenchymal resistance to fluid flow by dynamic impedance spectro-tomography, we evaluated the performance of this putative measure of glymphatic function against "gold-standard" CE-MRI across both sleeping and waking states.

METHODS

Twenty-five healthy 55-65 y/o participants were enrolled in a cross-over randomized control clinical trial encompassing one night of sleep/wake followed by a 4hr morning sleep/wake opportunity. T1 MRI was obtained in the morning at 0700 (pre-contrast) and at 1100 (4hr post IV contrast) following the sleep opportunity. The [post-contrast - pre-contrast] ROI differences were used in the analyses. The eight parenchymal ROIs (Frontal gray/white matter (GM/WM), Parietal GM/WM, Temporal GM/WM and Occipital GM/WM) were corrected for the contribution of parenchymal vasculature to the T1 signal. The non-parenchymal regions of interest (ROIs) included CSF ROIs (Ventricles; subarachnoid space, SAS) and blood ROIs (internal carotid artery, ICA; superior sagittal sinus, SSS; confluence of the sinuses, CSS). Participants were instrumented with the IMD to measured continuous changes in brain parenchymal resistance (R). Sleep EEG powerbands, hypnogram, heart rate (HR) and HR variability (HRV) were also recorded by the device. Overnight R, HR, HRV, and EEG powerbands (delta, theta, alpha, beta) were normalized to unity at onset of each observation period. Mixed linear modeling with participant random intercept was performed on the contrast enhancement of the eight parenchymal ROIs treated as spatial measures, Ventricle and CSS (selected as the CSF and blood compartment covariates) and mean overnight parenchymal resistance R, EEG powerbands, HR and HRV as interaction moderators. Models included age, sex and APOE genetic status if their inclusion changed regression coefficients by more than 10%.

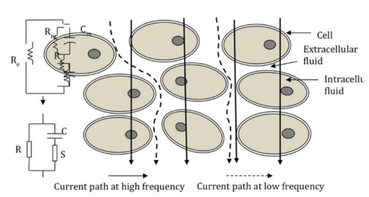
STUDY SCHEMATIC



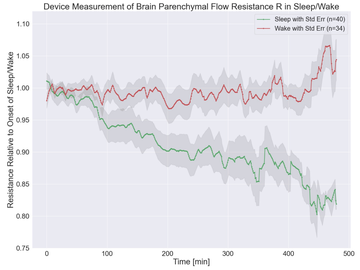
RESULTS

Dynamic Impedance Spectro-Tomography

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



Sleep-Dependent Reductions in Parenchymal Resistance R



Measurement of overnight changes in parenchymal resistance (R) by impedance spectro-tomography showed dramatic reductions in R in the sleeping condition.

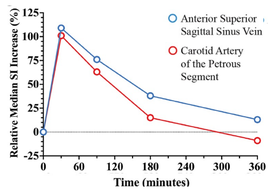
Overnight Decline in R is Driven by Changes in Delta Power

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		

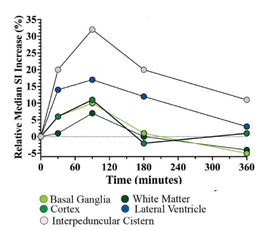
During N2/N3 sleep, multivariate regression of the change in R showed that an increase in EEG delta power, increasing heart rate variability (HRV), and declining heart rate (HR) caused R to decrease faster.

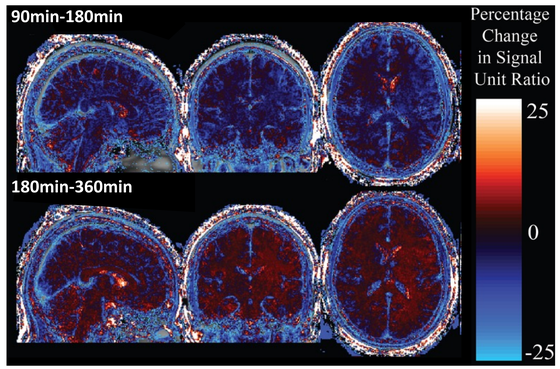
Glymphatic Assessment by Intravenous CE-MRI

Blood Compartments



Parenchymal and CSF Compartments



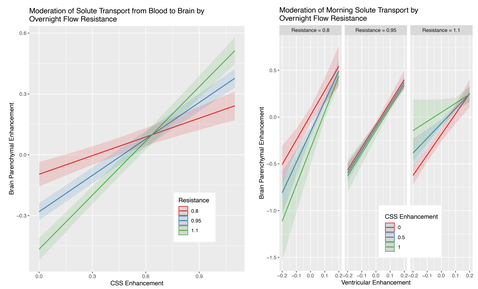


In published studies (Richmond et al. *Eur J Neurosci* 2023), we have demonstrated in healthy young participatns that glymphatic function can be measured by contrast-enhanced (CE)-MRI following intravenous gadobutrol injection. Vascular contrast enhancement peaks at 30 min post-IV gadobutrol injection, declining 90-360 min post-injection. CSF and parenchymal enhancement peaks at 90 min post-injection, reflecting contrast leakage into the CSF, and thence into brain tissue.

T1-weighted imaging was used to map contrast-enhancement following IV injection. Difference images were generated by registering and subtracting T1 scans at 90 and 180 min, and at 180 and 360 min post-injections. These show widespread parenchymal enhancement 3-6 hrs after IV contrast injection.

Parenchymal Resistance R Moderates the Relationship Between CSF and Parenchymal Solute Levels

	Moderation of Morning Brain Solute Transport by Overnight Resistance		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	0.5620	0.1014 – 1.0227	**0.018**
Overnight Resistance	-0.6795	-1.1557 – -0.2032	**0.006**
Morning CSS Contrast	-1.9313	-3.2821 – -0.5804	**0.006**
Morning Ventricular Contrast	3.7912	-0.5751 – 8.1575	0.092
Resistance:CSS	1.9700	0.5821 – 3.3579	**0.006**
Resistance:Ventricles	-1.4521	-5.7700 – 2.8657	0.514
CSS:Ventricles	7.8341	0.8638 – 14.8044	**0.030**
Resistance:CSS:Ventricles	-8.2323	-15.4102 – -1.0545	**0.026**
Random Effects			
σ^2	0.002		
$\tau_{00\ pid}$	0.002		
ICC	0.533		
$N_{\ pid}$	29		
Observations	351		
Marginal R^2 / Conditional R^2	0.872 / 0.940		



In the best-performing mixed linear model, a blood x CSF interaction term moderated by overnight R predicted parenchymal contrast enhancement (ANOVA P<0.001). Lower resistance steepened the relationship between CSF-parenchymal contrast (glymphatic influx) and flattened the relationship between blood-parenchymal contrast (clearance to blood).

MAIN FINDINGS

In a **first-in-human** cross-over randomized control clinical study comparing a continuous measure of dynamic **brain parenchymal resistance R** to gold-standard CE-MRI measures of glymphatic function across sleep and awake states, we observed:

- **R is a robust predictor of glymphatic exchange**, reflected by the movement of contrast from blood and CSF into brain parenchyma.
- Overnight **changes in R are significant moderators of morning brain solute transport**, independent of sleep/wake status.

CONCLUSIONS

Sleep reduces brain parenchymal resistance, R measured by impedance spectro-tomography with an IMD. Overnight changes in R measured by the IMD was a robust predictor of contrast movement from the blood and CSF compartments through the brain parenchyma. These findings begin to validate IMD-derived parenchymal R as non-imaging measure of glymphatic function in the human brain. Detection of glymphatic impairment in real-world settings may permit (i) early identification of individuals at-risk for developing sleep-related Alzheimer's disease pathology, and (ii) enable precision targeted enhancement of glymphatic function to enhance glymphatic function and pathological protein clearance.

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