Measuring the Resistance to Glymphatic Flow in Humans

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Applied Cognition

Conflict of Interest Disclosures for Speakers

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Learning Objectives

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Upon completion of this activity, participants should be able to:

- Explain how how resistance to glymphatic flow is measured in humans
- Understand the effect that EEG powerbands and hypnogram stages have on glymphatic flow resistance
- Understand the latest in-human translation of preclinical research on glymphatic function

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This presentation is based on the following manuscript in collaboration with listed co-authors

medRxiv
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Cold Spring Harbor Laboratory BMJ Yale

The use of continuous brain parenchymal impedance dispersion to measure glymphatic function in humans

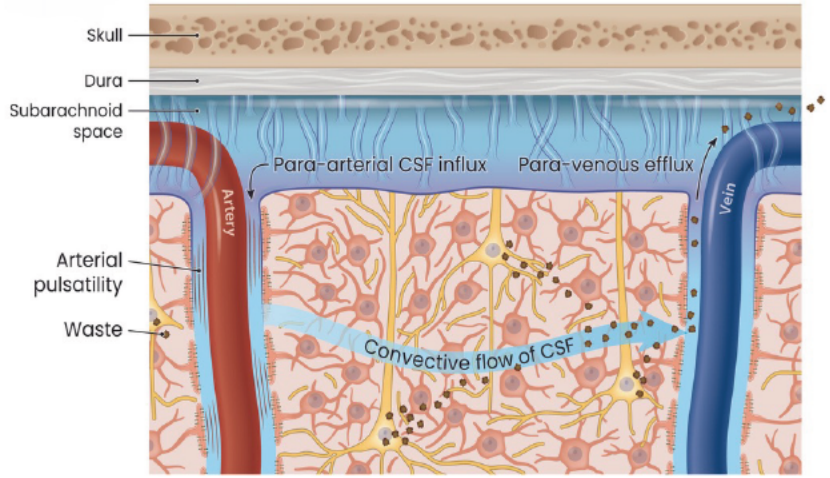
Paul Dagum, Laurent Giovangrandi, Swati Rane Levendovszky, Jake J. Winebaum, Tarandeep Singh, Yeilim Cho, Robert M. Kaplan, Michael S. Jaffe, Miranda M. Lim, Carla Vandeweerd, Jeffrey J. Iliff

doi: https://doi.org/10.1101/2024.01.06.24300933

Glymphatic function

The new biology of sleep

The newly discovered glymphatic system plays a critical role in sleep's cognitive recovery and clearance of neurodegenerative proteins and metabolic waste products.

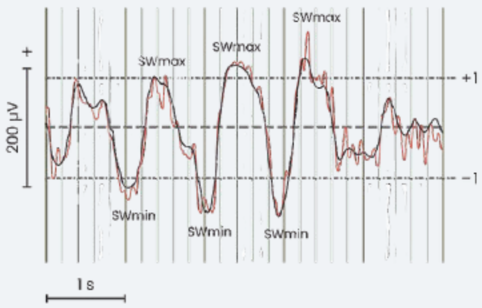


Glymphatic System: A waste clearance pathway in the brain that relies on interchange of cerebrospinal fluid (CSF) and interstitial fluid (ISF).

1

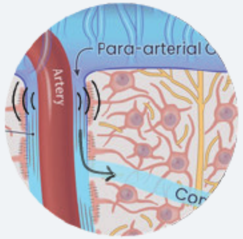
Synchronized Oscillations

The cleaning power of slow wave activity (SWA) during deep sleep is augmented by a 60% increase in the interstitial fluid (ISF) volume created via AQP-channels.



2

Arterial Pulsatility

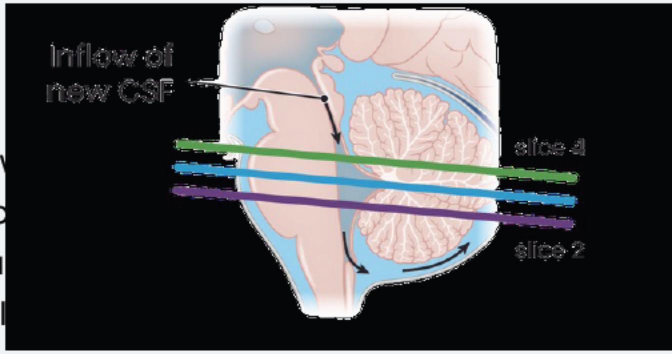


Arterial pulsatility in the brain provides the motive force that moves cerebrospinal fluid (CSF) into the perivascular spaces surrounding major arteries.

3

Pulse waves of CSF

Pulsatile waves of CSF flow increase v
clearance and are entrained to resto
slow wave oscillations by hemodyna
oscillations and neurovascular coupl



What we know about glymphatic function

mostly from rodent work

In mice, glymphatic flow results in 60% shift in fluid from intracellular to interstitial, widening interstitial channels

In mice, high EEG delta power, low beta power and low heart rate increase glymphatic function

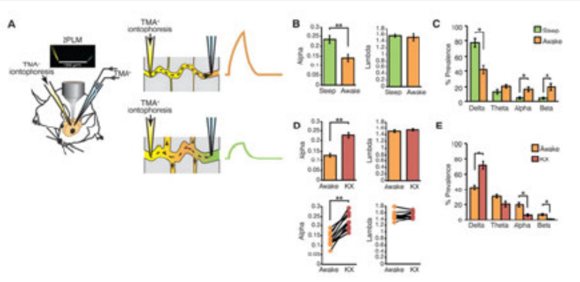
Synchronized neuronal oscillations propagate flow through the large ionic waves they create

Glymphatic function in humans has been demonstrated using intrathecal contrast MRI

1

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie[1,*], Hongyi Kang[1,*], Qiwu Xu[1], Michael J. Chen[1], Yonghong Liao[1], Meenakshisundaram Thiyagarajan[1], John O'Donnell[1], Daniel J. Christensen[1], Charles Nicholson[2], Jeffrey J. Iliff[1], Takahiro Takano[1], Rashid Deane[1], and Maiken Nedergaard[1,†]
[1]Division of Glial Disease and Therapeutics, Center for Translational Neuromedicine, Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY 14642, USA

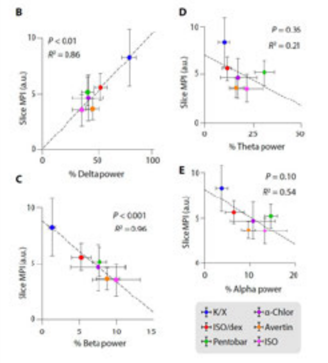


2

SCIENCE ADVANCES | RESEARCH ARTICLE
NEUROPHYSIOLOGY

Increased glymphatic influx is correlated with high EEG delta power and low heart rate in mice under anesthesia

Lauren M. Hablitz[1], Hanna S. Vinitsky[1], Qian Sun[1], Frederik Filip Stæger[2], Björn Sigurdsson[2], Kristian N. Mortensen[2], Tuomas O. Lilius[2,3], Maiken Nedergaard[1,2*]



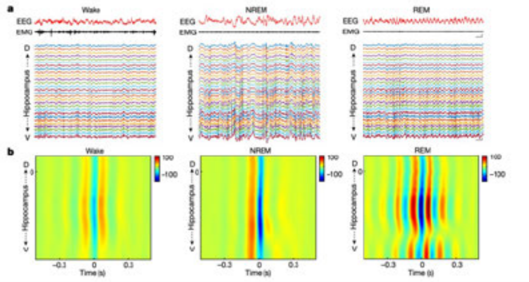
3

Article

Neuronal dynamics direct cerebrospinal fluid perfusion and brain clearance

https://doi.org/10.1038/s41586-024-07108-6
Received: 16 February 2023
Accepted: 23 January 2024

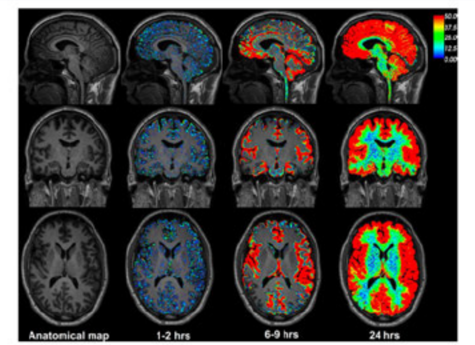
Li-Feng Jiang-Xie, Antoine Drieu, Kesshi Bhasiin, Daniel Quintero, Igor Smirnov & Jonathan Kipnis



4

Brain-wide glymphatic enhancement and clearance in humans assessed with MRI

Geir Ringstad,[1,2] Lars M. Valnes,[3] Anders M. Dale,[4,5,6] Are H. Pripp,[7] Svein-Are S. Vatnehol,[8] Kyrre E. Emblem,[9] Kent-Andre Mardal,[3,10] and Per K. Eide[2,11]



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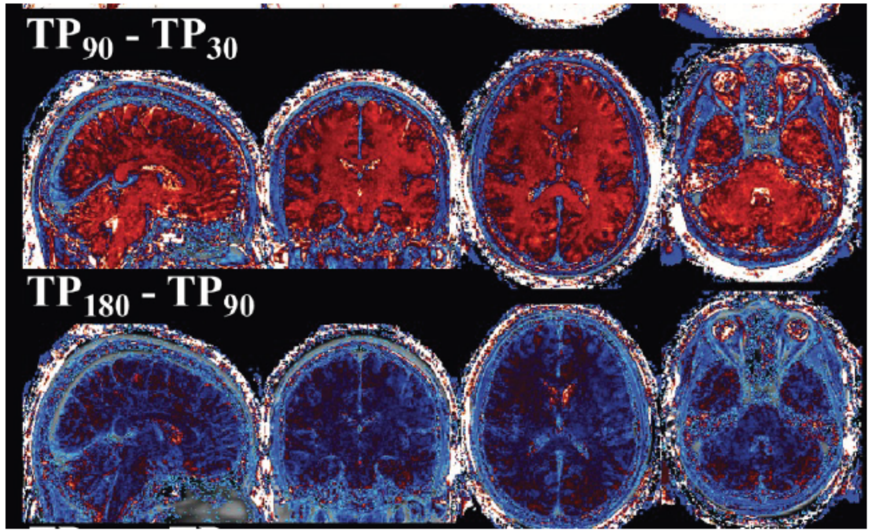
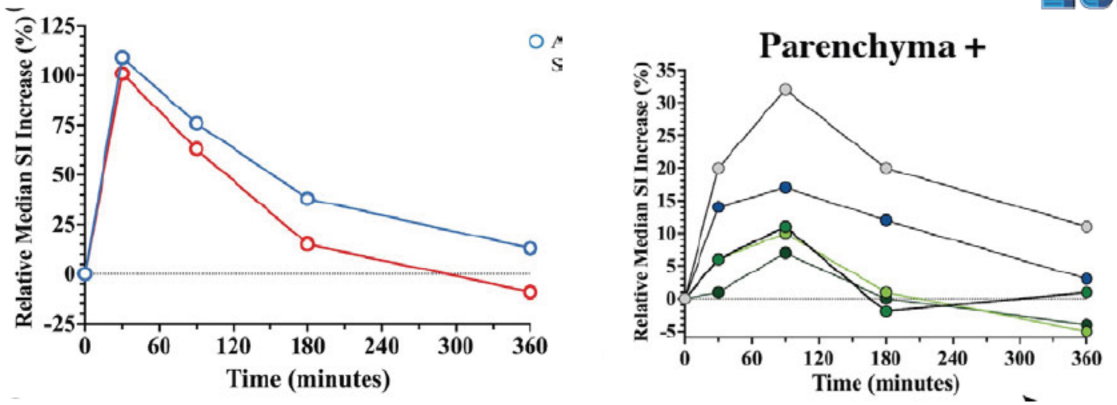
Using intravenous contrast-enhanced MRI to measure glymphatic function in humans

CE MRI is the current benchmark

Quantification approaches for magnetic resonance imaging following intravenous gadolinium injection: A window into brain-wide glymphatic function

Sutton B. Richmond[1] | Swati Rane[2] | Moriah R. Hanson[1] | Mehmet Albayram[3] | Jeffrey J. Iliff[4,5,6] | Dawn Kernagis[7] | Jens T. Rosenberg[8] | Rachael D. Seidler[1,9]



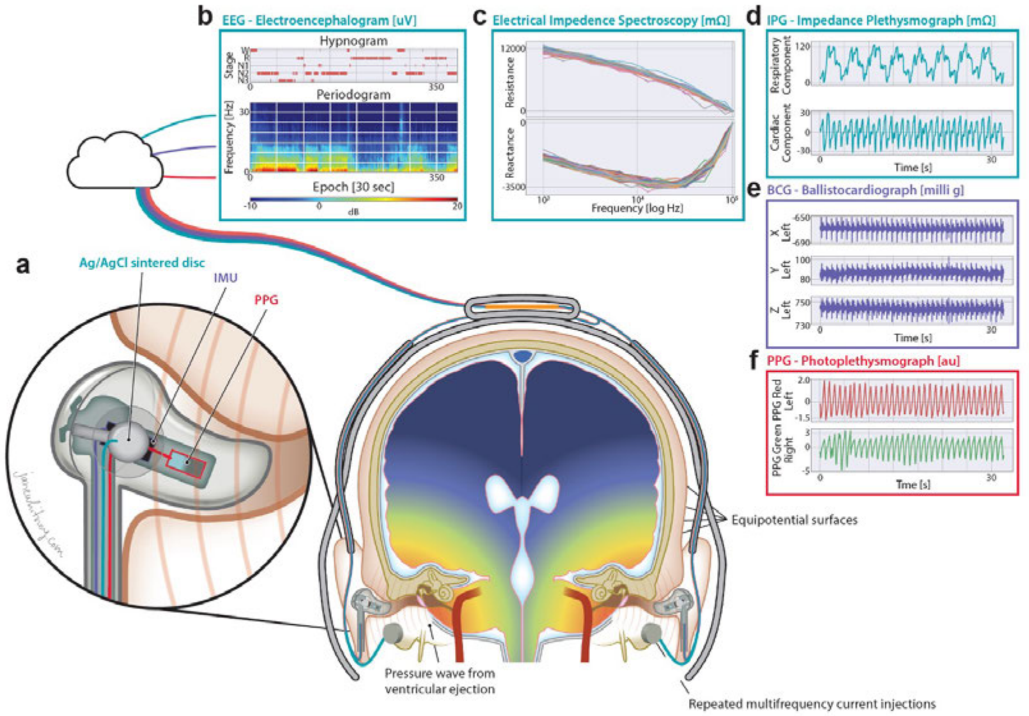


1. 50% of the contrast is cleared from the blood in the first 110 min
2. MRI signal intensity peaks in the brain parenchyma at 90 min
3. Participants maintained supine and awake for the 360 min duration

The lack of continuous in-human measurement of glymphatic function limits our understanding of this transformative biology and its potential in therapeutic discovery

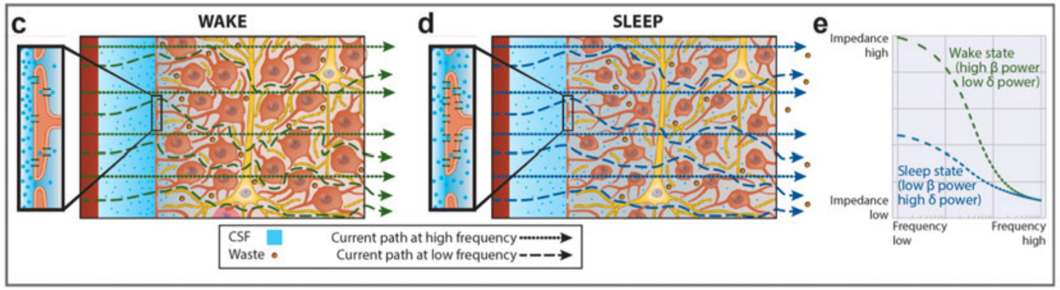
The science of how we measure glymphatic function

Using the latest in microtechnology, biophysics and signal analysis we continuously measure glymphatic flow resistance during sleep



1

We measure resistance to flow using impedance spectroscopy over a broadband range of frequencies using dedicated hardware, allowing for continuous overnight measurements



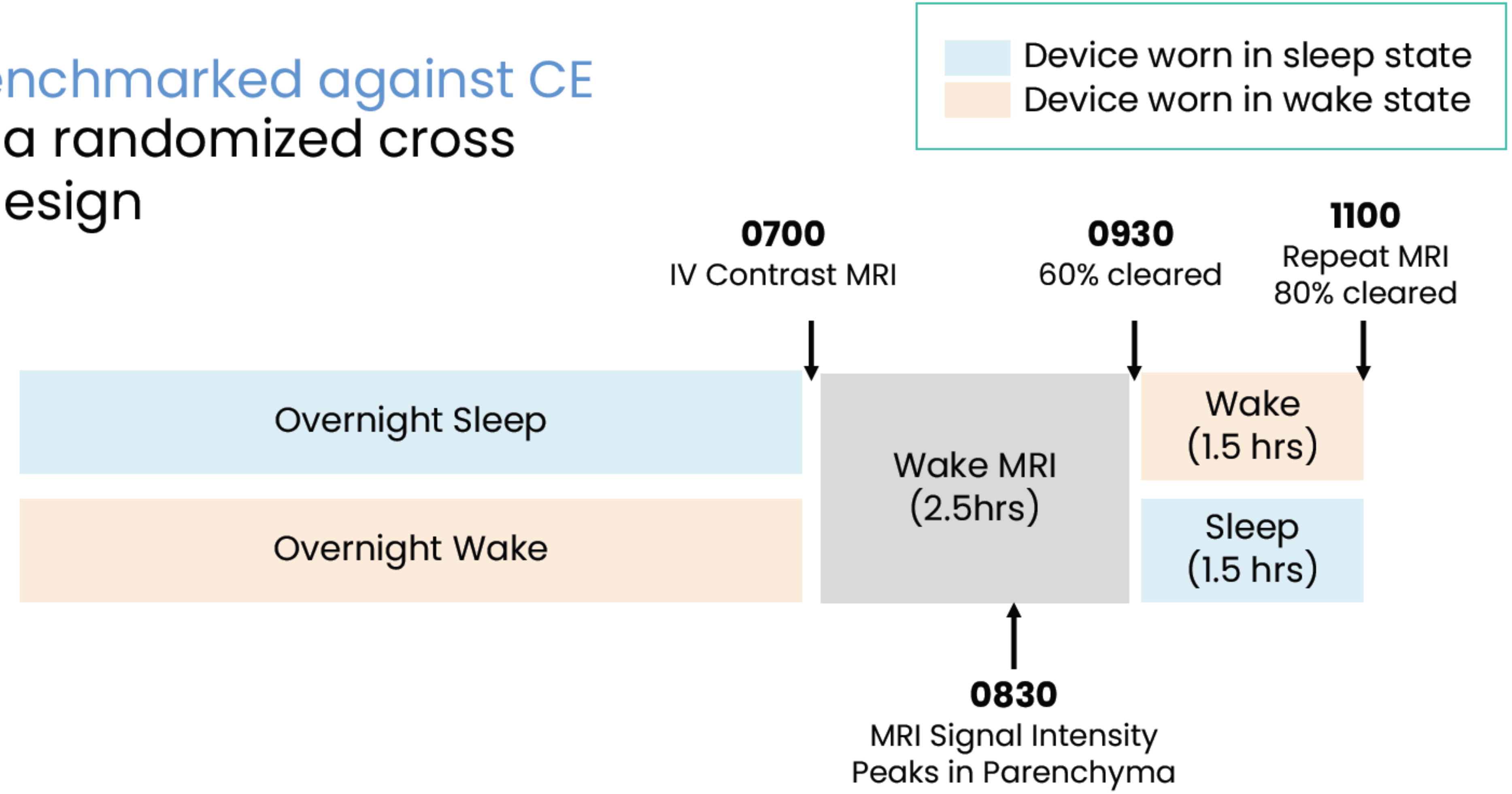
2

We concurrently measure EEG, HR and PTT through novel approaches using miniaturized and simplified instrumentation

Benchmarking Study: Primary Objective

Measuring glymphatic function continuously during sleep which is currently not possible

We benchmarked against CE MRI in a randomized cross over design



Continuous measure of glymphatic flow resistance using multifrequency impedance spectroscopy

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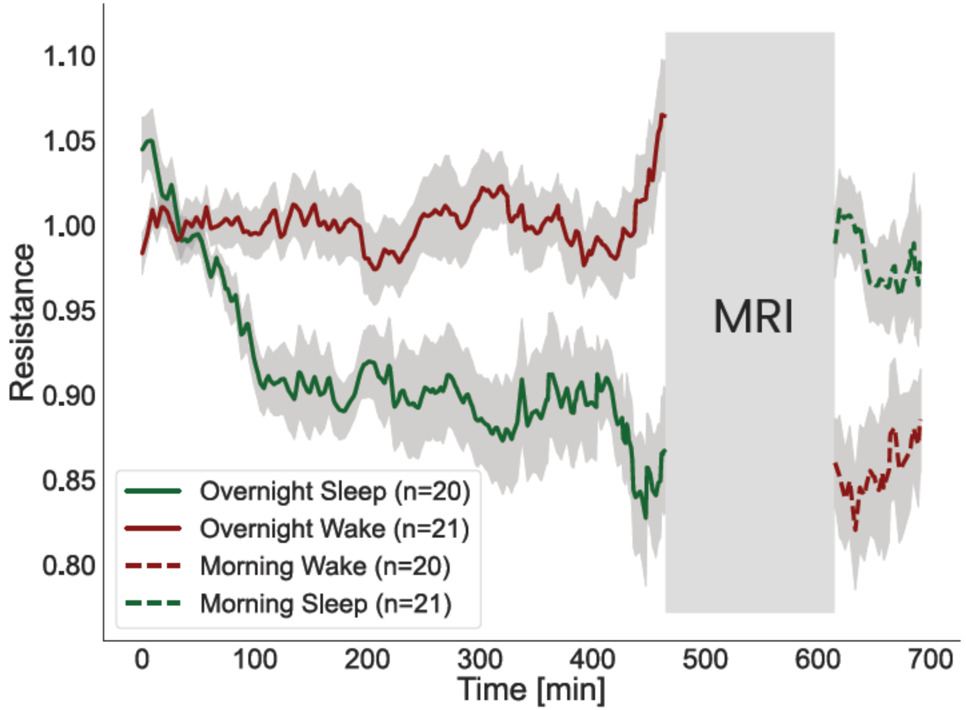
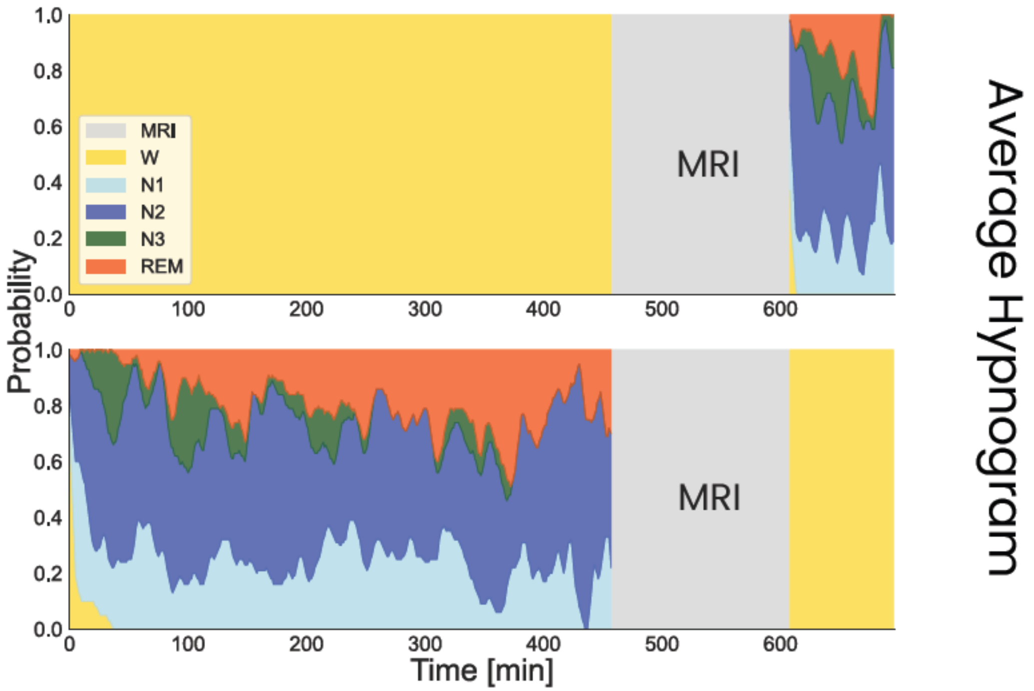


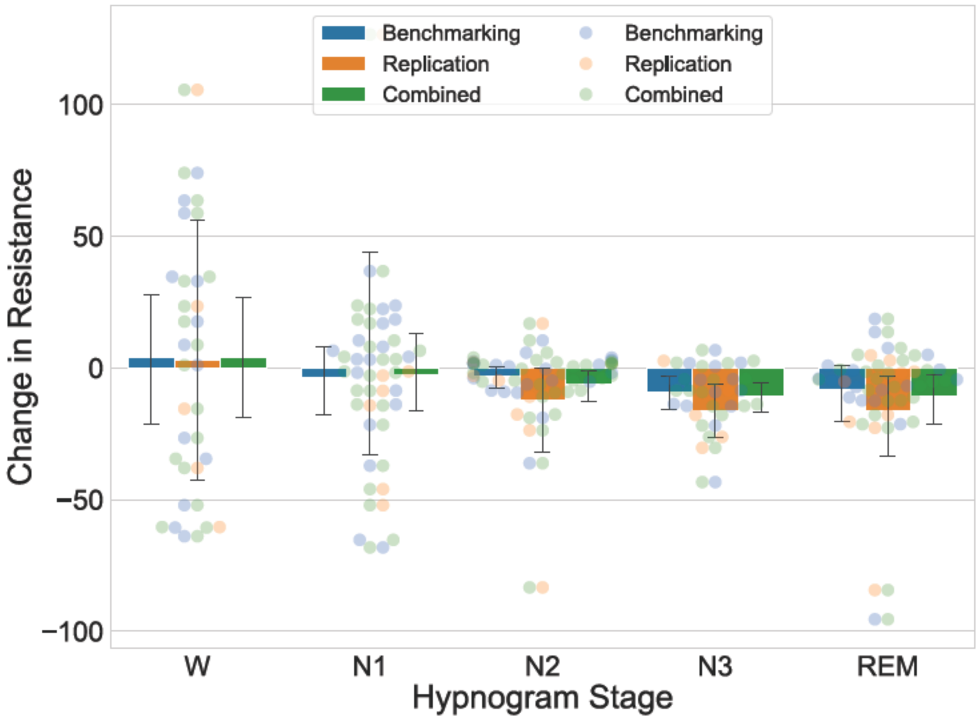


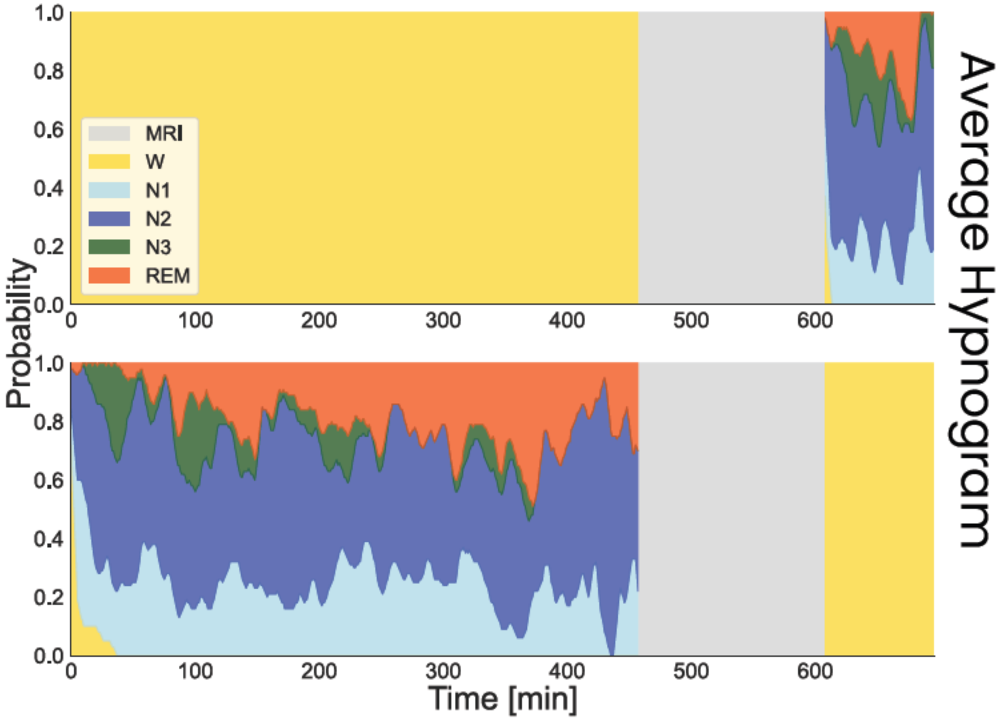
Resistance decreased with overnight sleep versus wake ($p<0.001$)

In morning, resistance increased with wake but did not return to prior evening value ($p<0.01$)

Following overnight wake, resistance decreased with sleep recovery ($p<0.01$)

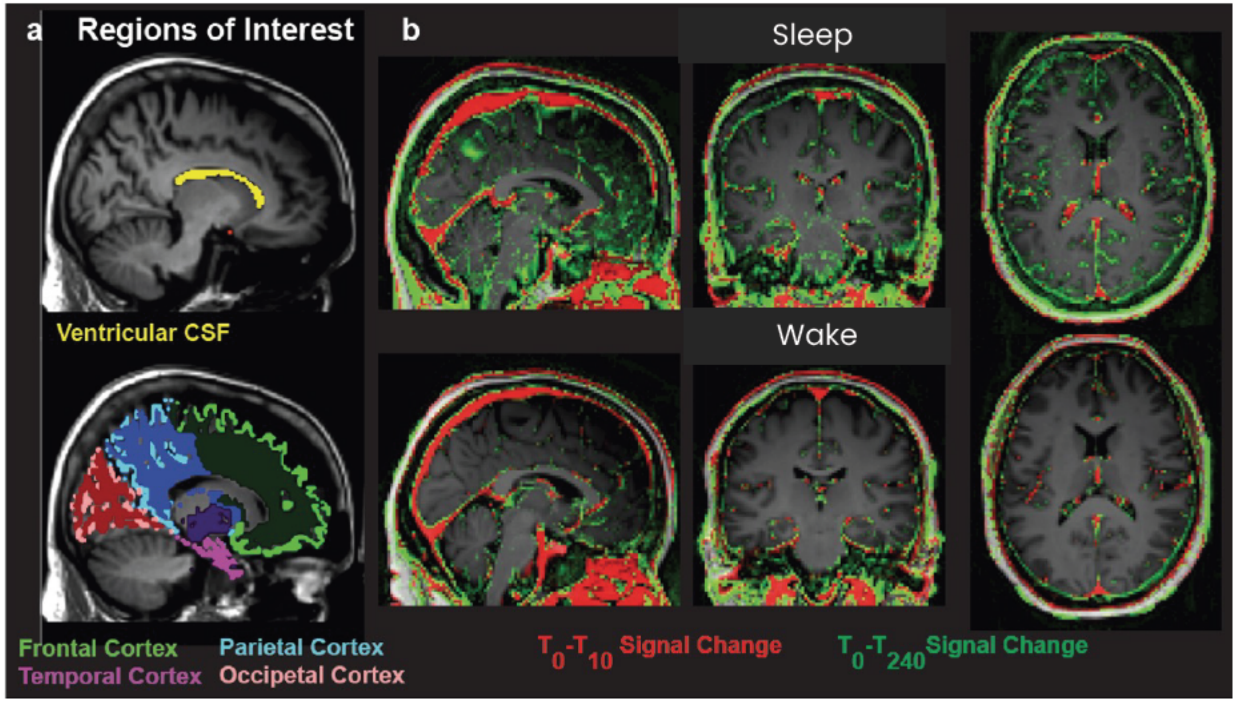
Decrease in resistance occurred during N2, N3 and REM sleep but not N1 or Wake (combined studies, $p<0.05$)





Does glymphatic flow resistance explain changes in MRI signal intensity within and between sleep and wake states?

Our null hypothesis was that sleep active physiology has no effect on the signal and that it can be explained entirely by blood and CSF contrast, and biological confounders



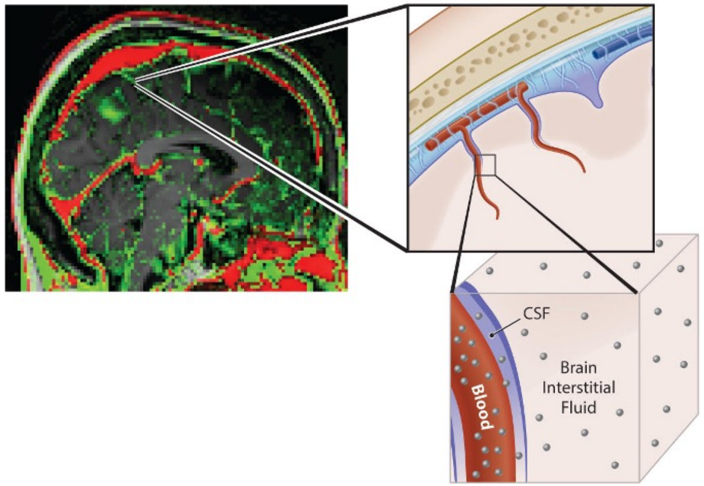
null hypothesis

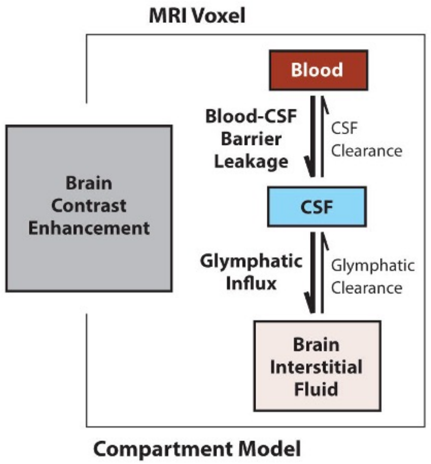
Predictors	*Estimates*	*CI*	*p*
(Intercept)	34.1338	1.8407 – 66.4269	**0.041**
ICA	6.8897	1.6506 – 12.1287	**0.011**
Ventricles	181.7404	154.1633 – 209.3174	**<0.001**
age	-0.2226	-0.7334 – 0.2882	0.398
gender [male]	-1.8408	-4.6085 – 0.9269	0.198
APOEe4 [TRUE]	0.1313	-3.0403 – 3.3029	0.936
Random Effects			
σ^2	94.372		
$\tau_{00\ ROI}$	13.118		
N_{ROI}	8		
Observations	198		
Marginal R^2 / Conditional R^2	0.767 / NA		

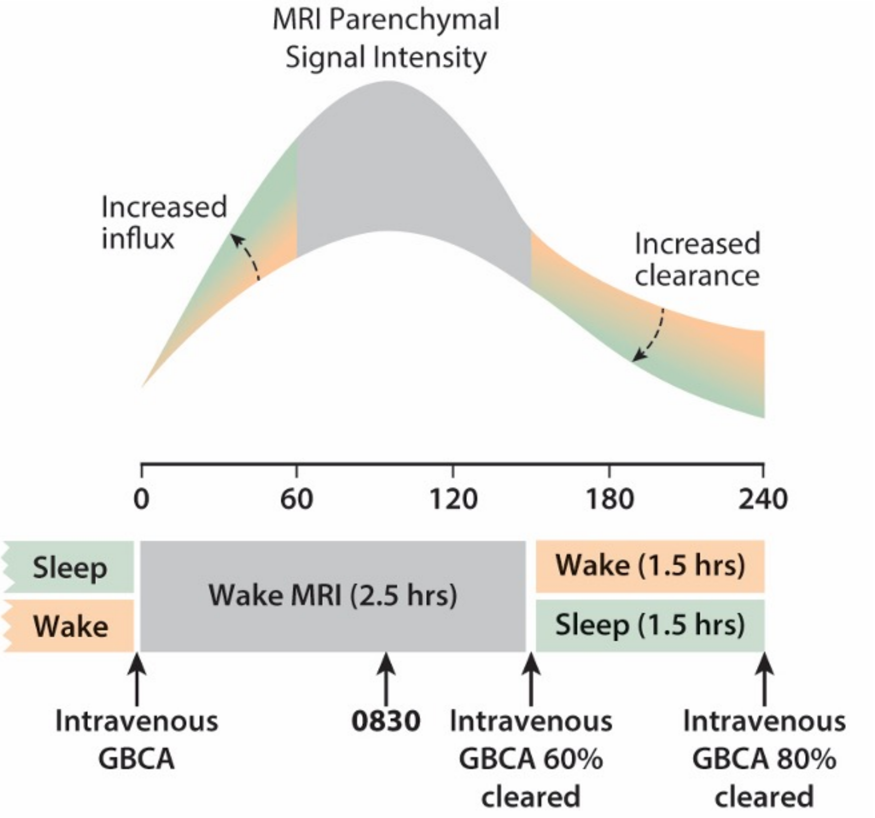
Under the glymphatic hypothesis CSF influx and clearance increase with elements of sleep active physiology

The cross-over design allowed us to test this hypothesis in both the overnight and the morning interventions

Increased CSF influx will increase MRI signal intensity







Increased CSF clearance will decrease MRI signal intensity

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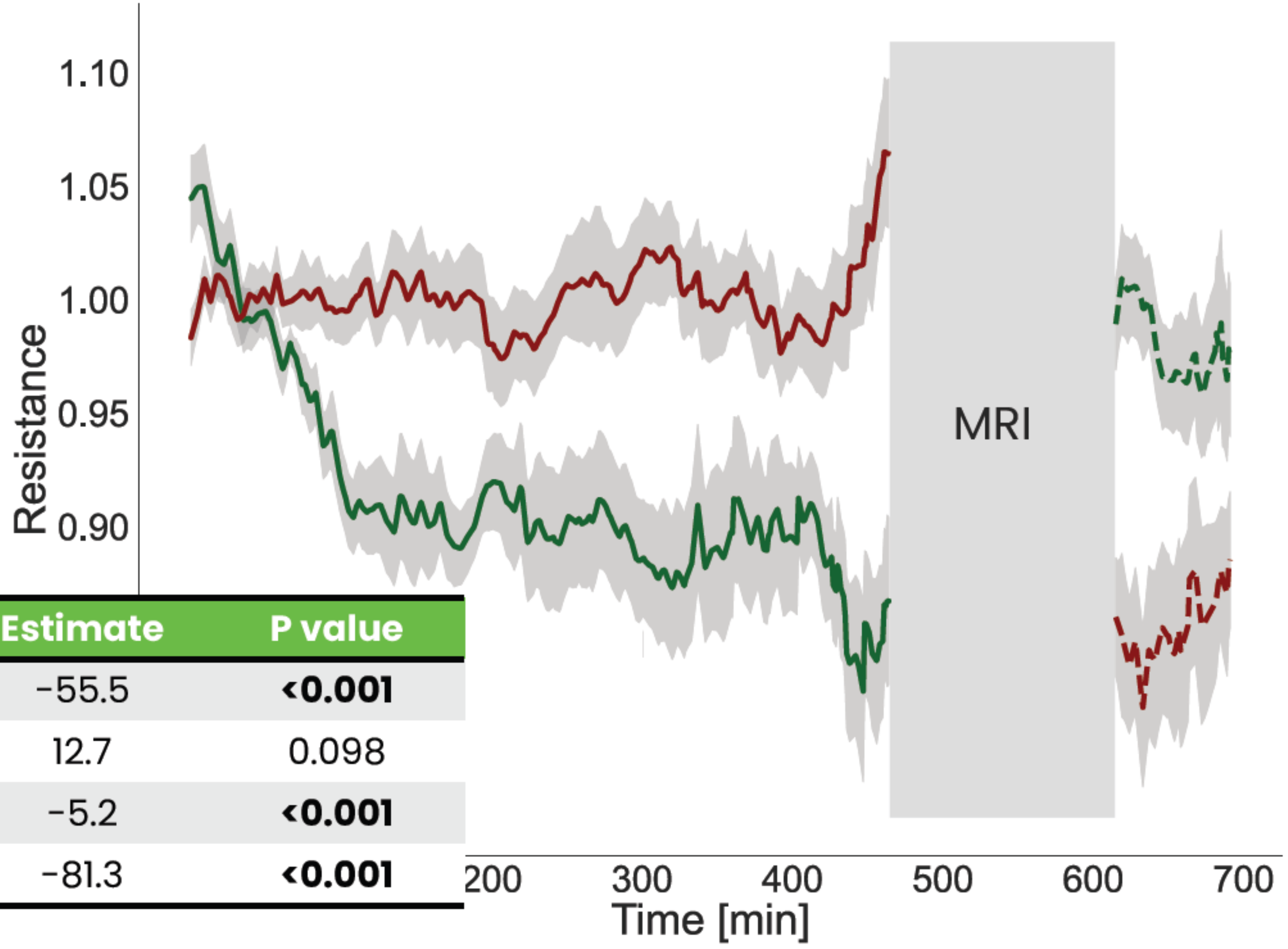
Glymphatic flow resistance predicts MRI signal intensity

Sleep is necessary to lower resistance and promote glymphatic flow

But low resistance is sufficient to induce glymphatic flow independent of the sleep/wake state



Predictor	Estimate	P value
Resistance	-55.5	**<0.001**
Delta power	12.7	0.098
Beta power	-5.2	**<0.001**
HR	-81.3	**<0.001**

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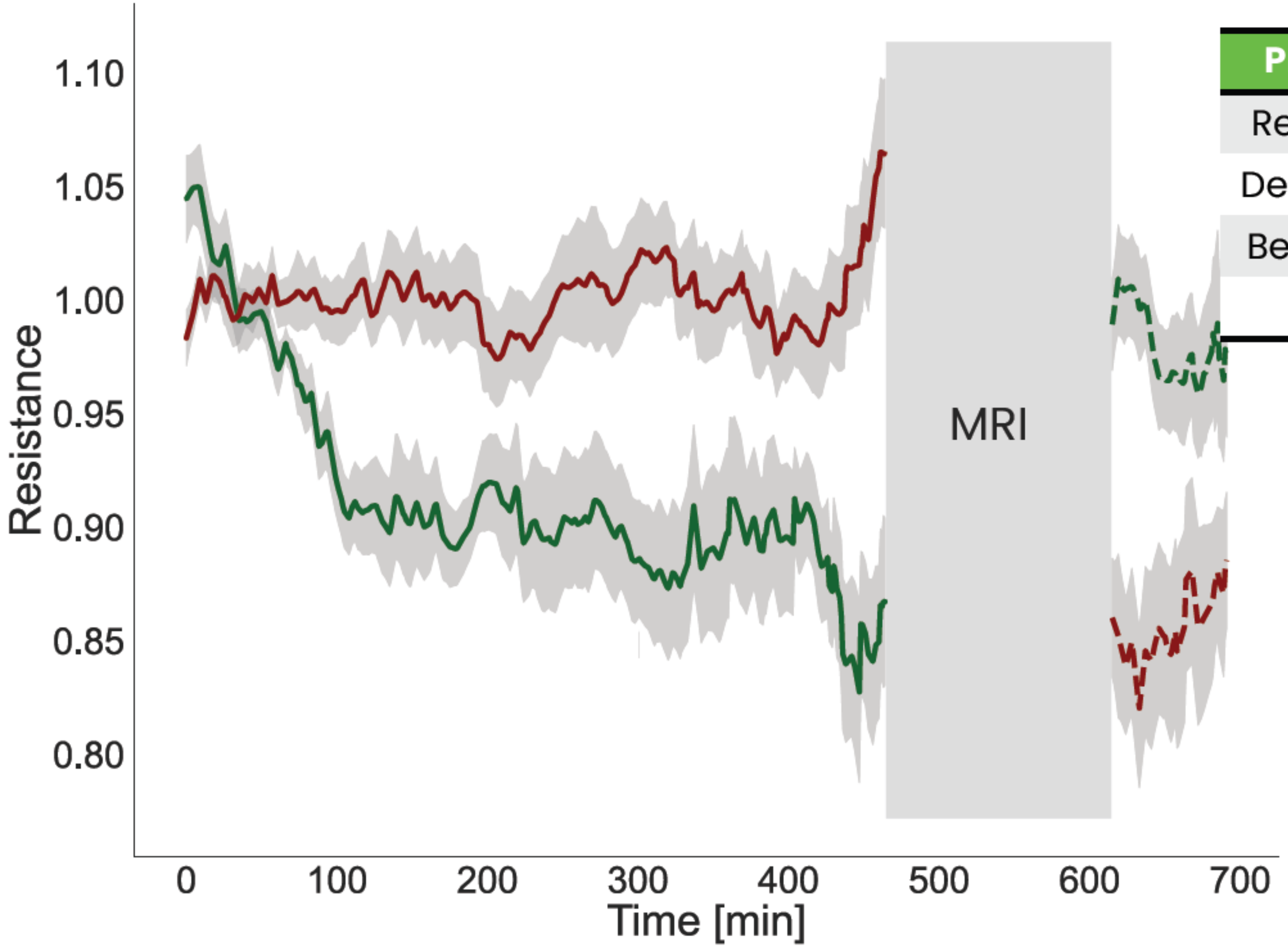

Predictor	Estimate	P value
Resistance	56.6	**<0.001**
Delta power	-39.4	**<0.001**
Beta power	-2.7	0.59
HR	72.9	**<0.001**

Glymphatic flow resistance predicts MRI signal intensity

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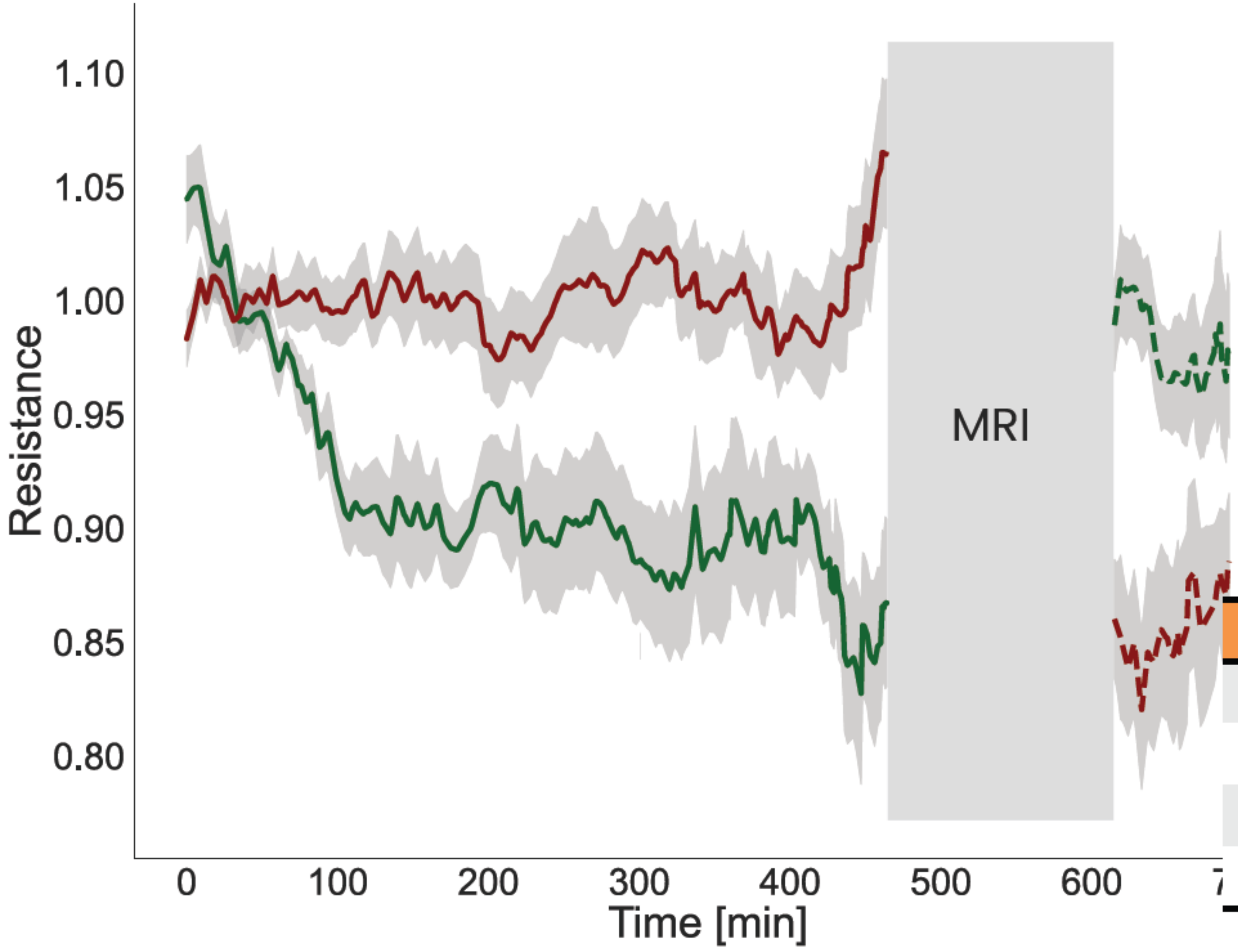


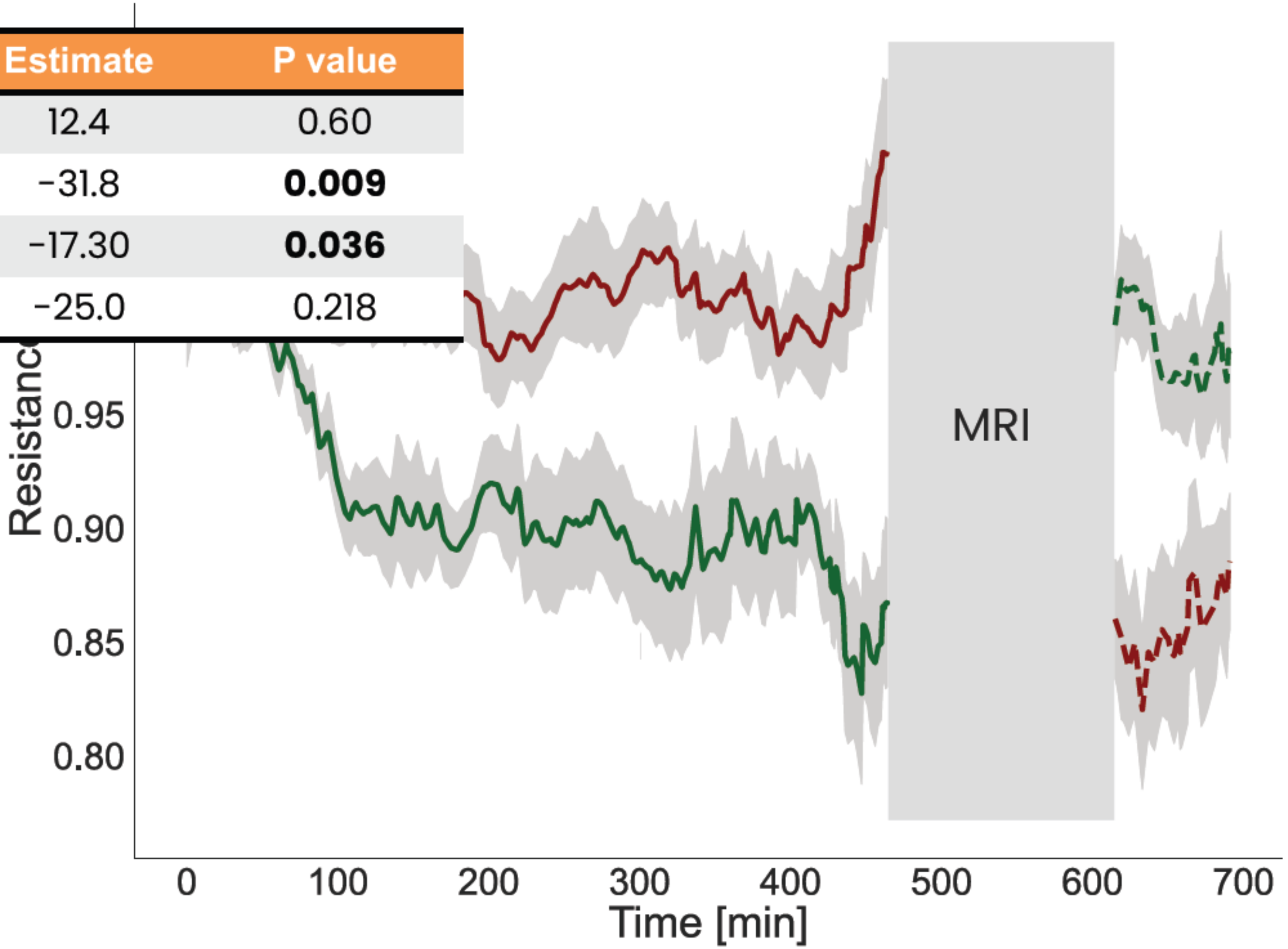
Predictor	Estimate	P value
Resistance	25.3	0.071
Delta power	-22.5	**<0.001**
Beta power	-21.1	**<0.001**
HR	230.9	**<0.001**

Glymphatic flow resistance predicts MRI signal intensity

Sleep is necessary to lower resistance and promote glymphatic flow

But low resistance is sufficient to induce glymphatic flow independent of the sleep/wake state

Predictor	Estimate	P value
Resistance	12.4	0.60
Delta power	-31.8	**0.009**
Beta power	-17.30	**0.036**
HR	-25.0	0.218



Glymphatic flow resistance predicts MRI signal intensity

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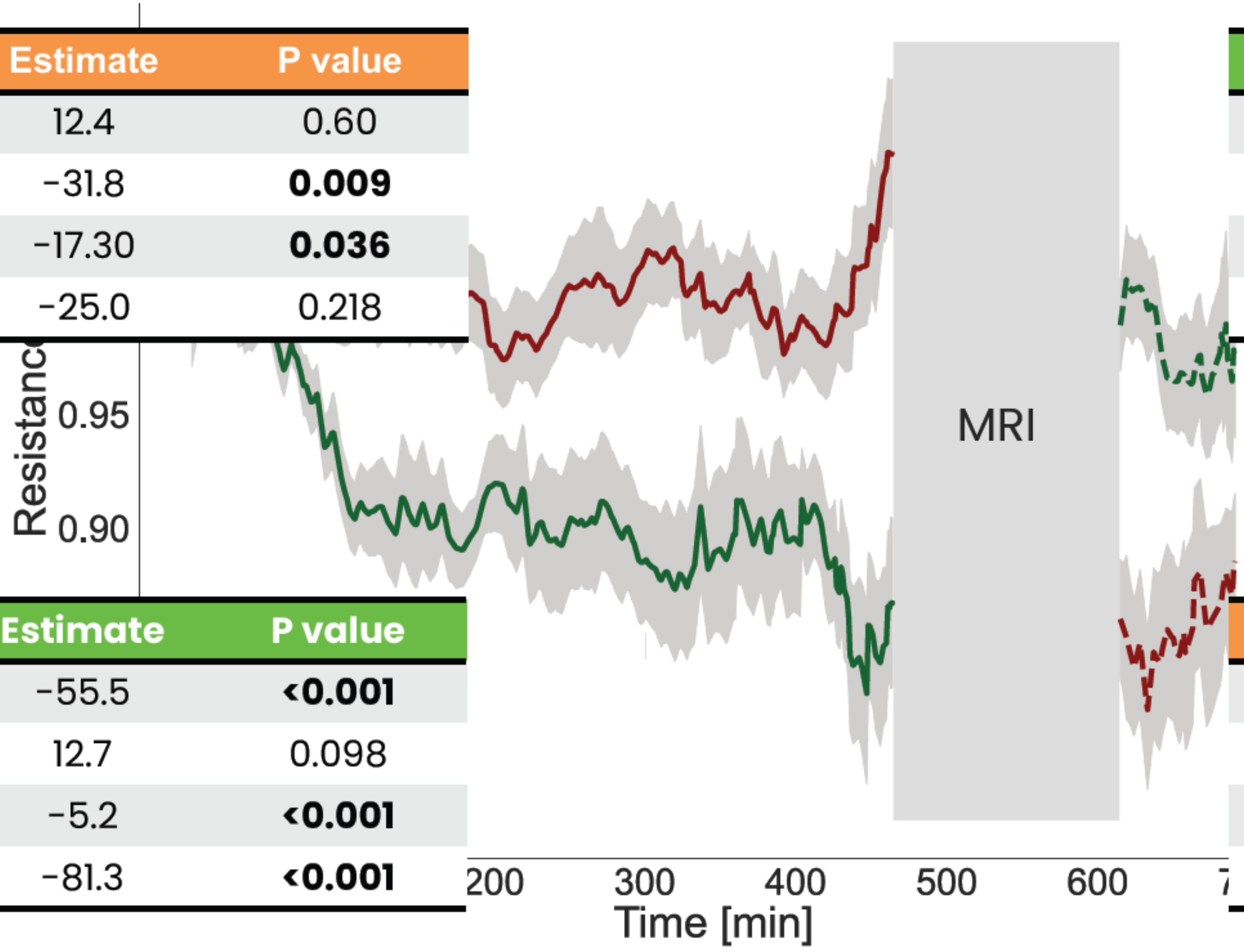

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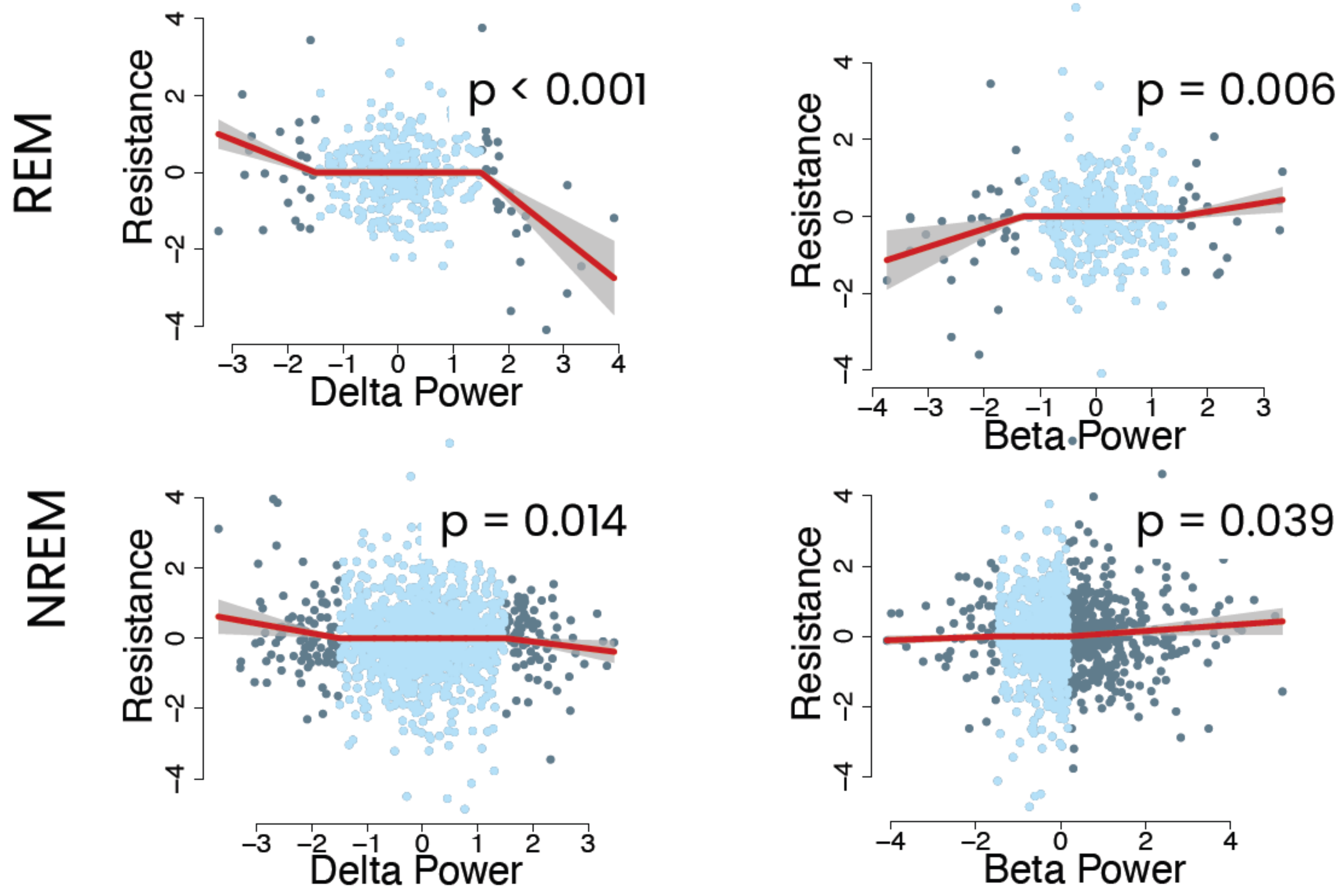
HR	230.9	**<0.001**

These large changes in resistance associate strongly with large changes in EEG power



These associations occurred with REM and NREM sleep separately and across REM-NREM transitions

Do they represent bursts of synchronized neuronal oscillations?

Conclusions

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1. Glymphatic flow resistance can be measured in humans and predicts influx and clearance of parenchymal CSF

2. Large changes in resistance associate with large changes in delta and beta power in REM and NREM sleep

3. Resistance decreases during N2, N3 and REM sleep

Thank You

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[redacted]