MHSRS 2026

Military Health System Research Symposium

Non-Invasive Deep Brain Neuromodulation to Enhance REM Sleep for Performance

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SWORD LAB

GENEVA Foundation

Uniformed Services University

Attune Neurosciences

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Disclosures

- The project was funded by DARPA REM REST Program.
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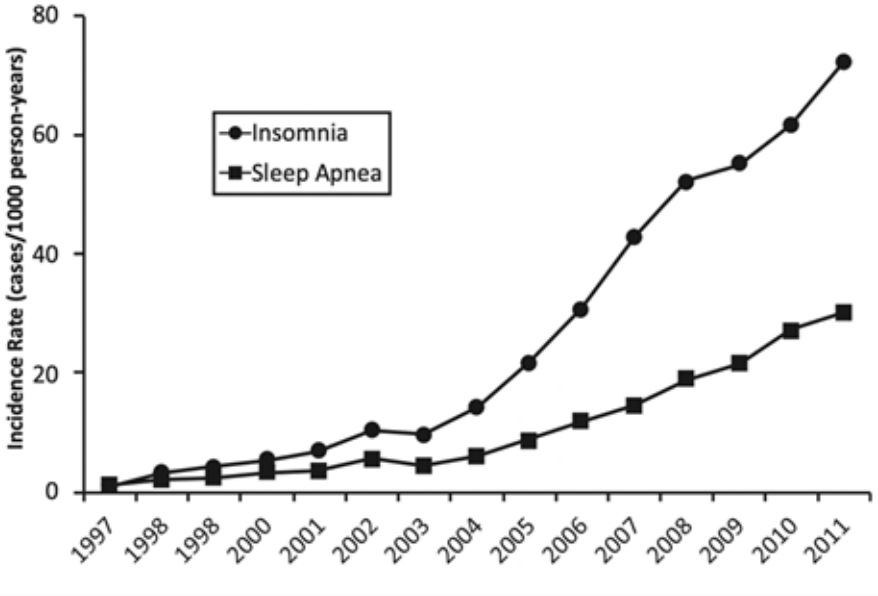
Sleep in the Military

- Insufficient Sleep Syndrome (>2/3 of military)
- Insomnia
- Obstructive Sleep Apnea
  - Urgent threats to Warfighter wellbeing (cognitive, mood, motor, immune)
    - ↓ reaction times
    - ↓ memory, attention, verbal fluency
    - ↑ anxiety , impulsivity, suicidality
    - ↑ cardio/metabolic, cancer, & dementia

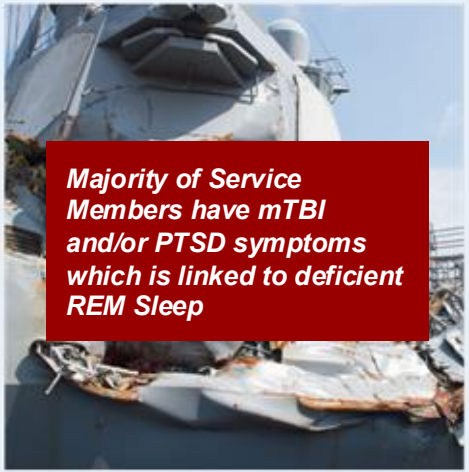


Caldwell J. et al. SLEEP. May 2019, 1-10

Targeting REM Sleep to Improve Warfighter Readiness

PROBLEM – WHY?

>2/3 Service Members insufficient sleep
↓ cognition, ↑ suicidality, chronic disease
Operational accidents (USS Fitzgerald, McCain)

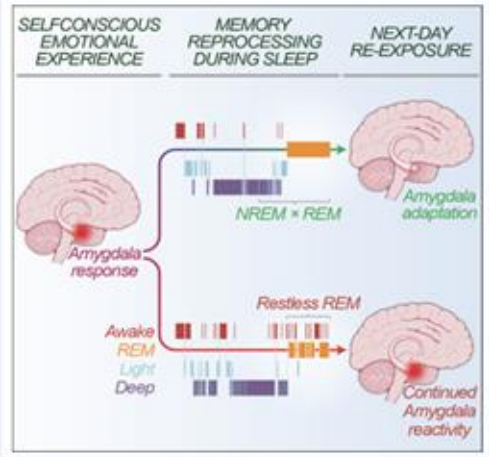


Majority of Service Members have mTBI and/or PTSD symptoms which is linked to deficient REM Sleep

USS Fitzgerald, June, 2017

MECHANISM – WHAT?

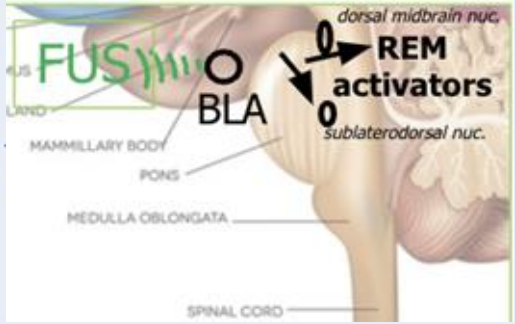
REM theta → memory & emotional regulation
Gatekeepers: BLA & CMT nuclei



Wassing et al 2019

SOLUTION – HOW?

Low-Intensity Focused Ultrasound (LIFU)
Targets REM generator nuclei safely
ATTN201: EEG + movement + ultrasound



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Scientific Rationale for the Work

Why REM – why BLA and CMT

Rodent studies with optogenetic stimulation of BLA and CMT showed

- ↑ REM onset maintenance (Machida et al., 2021; Wellman et al., 2017).
- ↑ REM, theta (Hasegawa et al., 2022)
- ↑ NREM-REM sleep stage transitions (Hasegawa et al., 2022)

Why LIFU

LIFU is capable of targeting deep brain nuclei non-invasively. Promising results in prior studies

- Depression (Tsuchiyagaito et. al 2026; Tan et.al 2026; Fan et al. 2024)
- Addiction (Mahoney et. al 2023; Meads et. al 2024)
- Disorders of consciousness (Cain et. al 2021)

No prior study has used LIFU to engage BLA or CMT to augment sleep in human***. This work is the first non-invasive test of this approach***

REM SLEEP MODULATION – In Humans

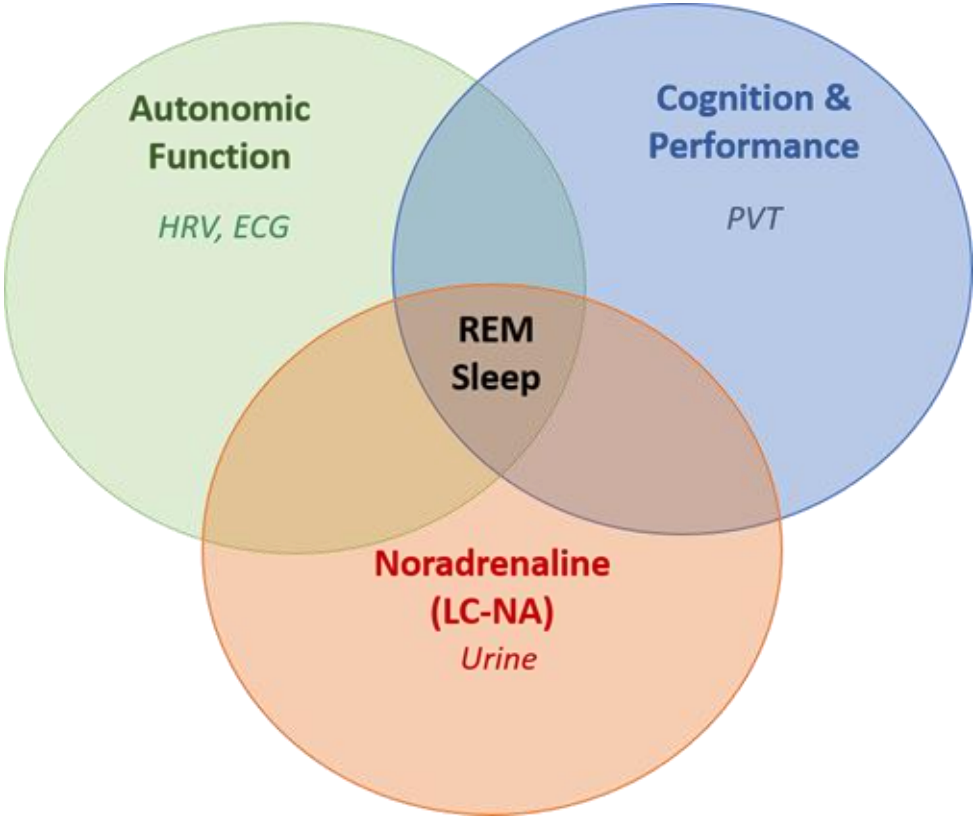
PREVIOUS ATTEMPTS IN REM AUGMENTATION – In Humans

- ❑ PRAZOSIN – Limited success with REM augmentation (Raskind et al., 2018)
- ❑ TRANSCRANIAL ELECTRICAL STIMULATION (TES) – Not as successful as Prazosin (Johnson & Durrant, 2018)
- ❑ CLOSED LOOP ACOUSTIC STIMULATION – Did not demonstrate improvements in REM (Guerrien et al., 1989; Harrington et al., 2021; Mouze-Amady et al., 1986)

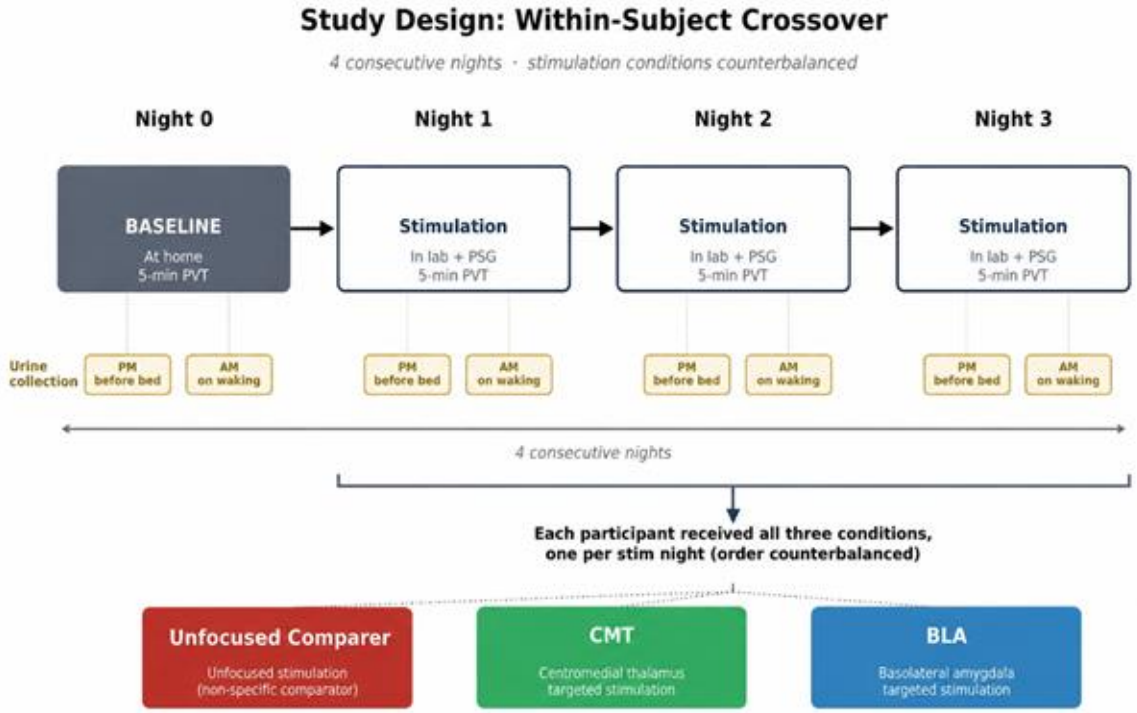
OUR HYPOTHESIS:

- ❑ Nontargeted electrical and acoustic stimulation theta targeting may have failed due to LACK OF TARGET ENGAGEMENT.
- ❑ Slow wave sleep success → cortical networks and brain-wide effects.
- ❑ REM cortical theta activity (complex) → may best respond to activation of Deep Nuclei (e.g. BLA and CMT).

REM SLEEP□ performance □ Autonomic Functions □ Noradrenaline



Experiment Protocol



Condition	Night 1	Night 2	Night 3
Unfocused Comparator	4	5	5
CMT	4	5	4
BLA	5	4	2

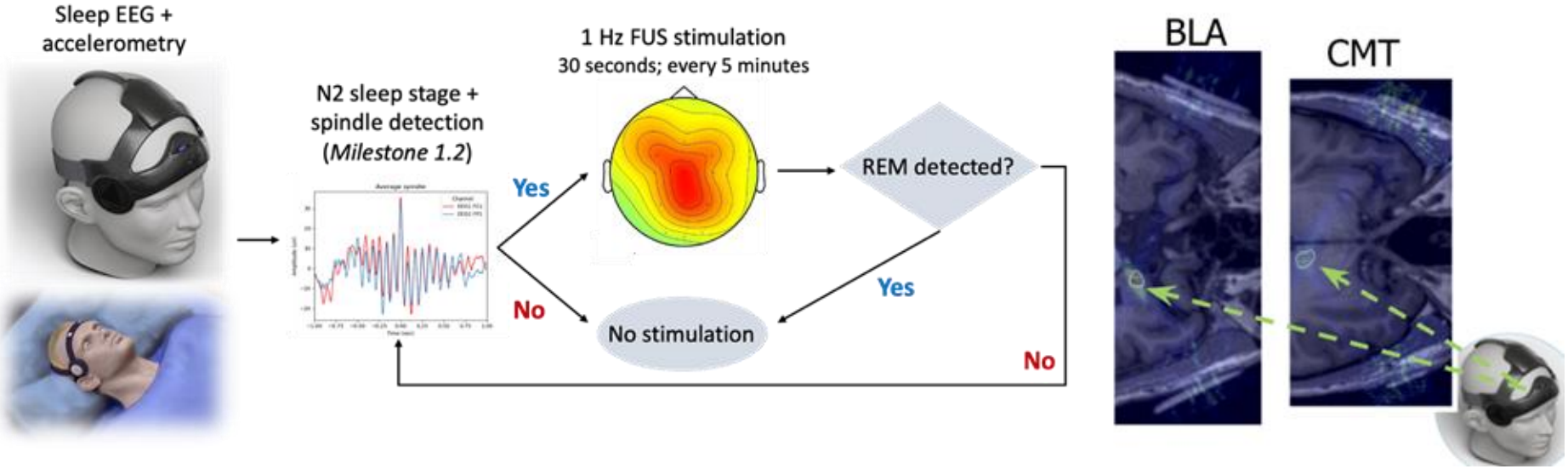
A chi-square, $\chi^2(4) = 1.27$, $p = .866$

Participant Demographics

Characteristic	Value
Age (years)	
Mean ± SD	38.1 ± 8.1
Median	38
Range	27–52
Sex (n%)	
Male	9 (64.2%)
Female	5 (35.7%)
Race (n%)	
African American	6 (42.8%)
Caucasian	7 (50%)
Asian	1 (7.1%)

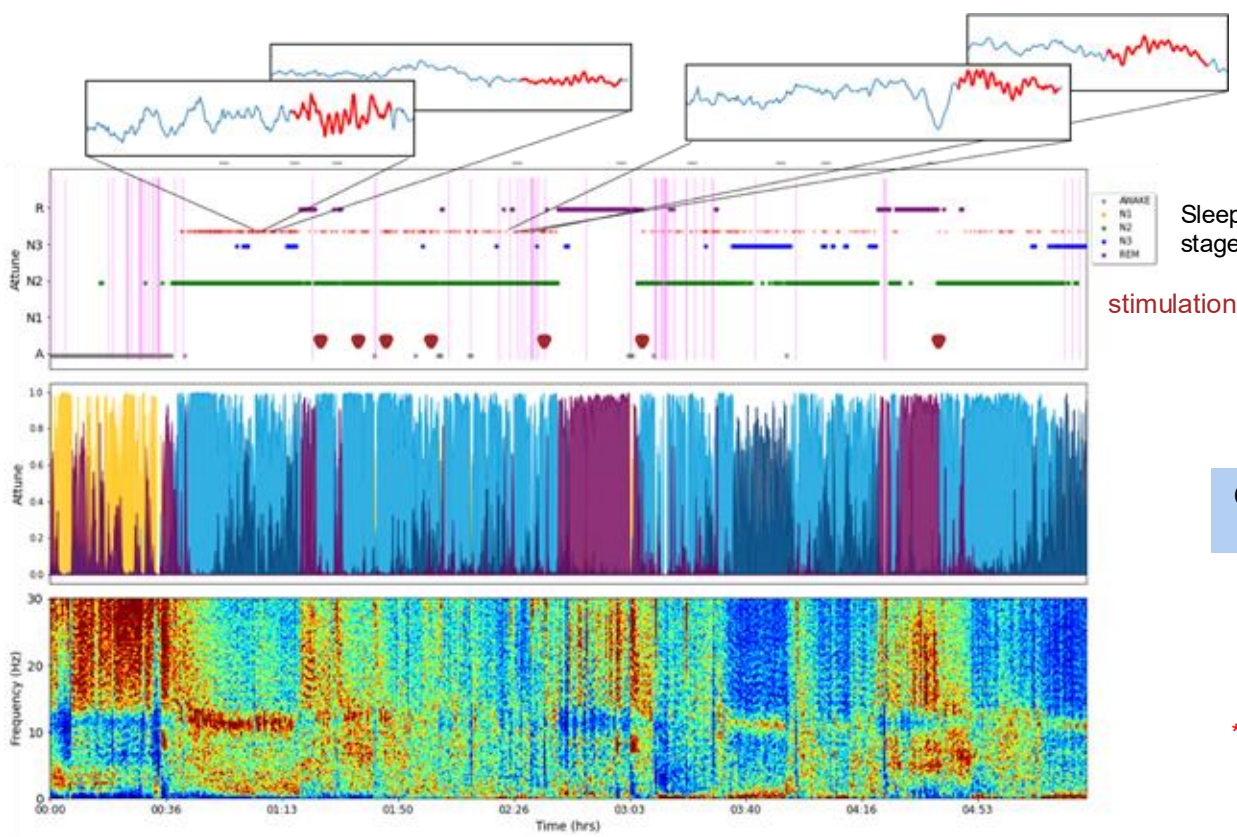
*All statistical analysis was performed using **linear mixed effects model with stimulation as the fixed effect and participant as the random intercept***

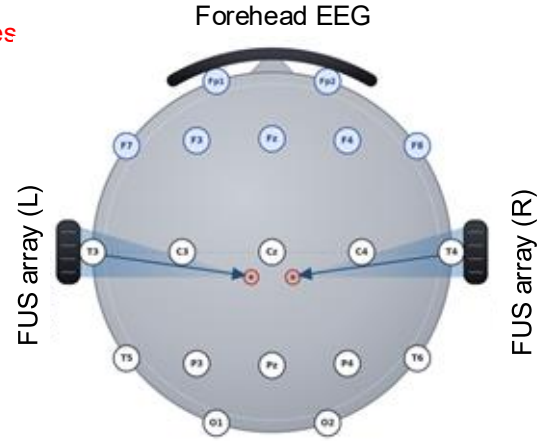
LIFU Closed Loop Stimulation



- Wearable Fus Headset (W/ Human Prelim Data) Stimulate a 1cm X 0.3cm X 0.3cm Brain Region and Activate REM Targets (BLA vs CMT) - Trial In Military Participants
- Used MRI, prior to stimulation, to localize the brain targets spatial coordinates.
- Targeting with FUS was hypothesized to see ↑ NREM to Rem Transitions with ↓ Noradrenergic Hyperactivity - core features deficient in mTBI and PTSD service members.

Closed-Loop Algorithm for Real-Time Sleep Staging, Spindle Detection, and LIFU Device Triggering





Closed-loop stimulation logic based on real-time EEG analysis

- N1/N2 has exceeded 5 minutes (cumulative) &
- N3 has exceeded 5 minutes (cumulative) &
- Total sleep time has exceeded 45 minutes &
- Must be within N2 and spindles detected &
- At least 5 minutes since last stimulation ended

*Never exceed 10 stimulation events

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RESULTS – EEG Architecture

Sleep Architecture

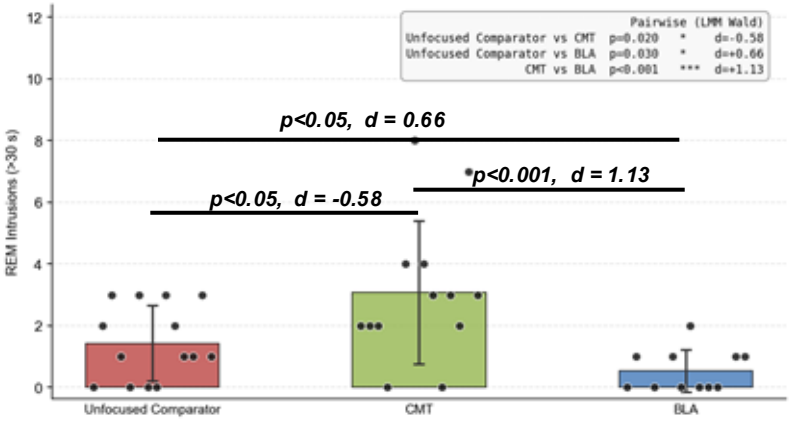
Sleep Metric	Comparison	LMM overall *p*	Pairwise *p*	Cohen's *d*
TST (mins)	Unfocused comparator vs CMT	0.3291	0.7452	-0.0980
	Unfocused comparator vs BLA		0.3838	0.2597
	CMT vs BLA		0.0747	0.5374
N1 (mins)	Unfocused comparator vs CMT	0.6719	0.4425	0.2316
	Unfocused comparator vs BLA		0.5522	0.1792
	CMT vs BLA		0.9227	-0.0293
N2 (mins)	Unfocused comparator vs CMT	0.4929	0.3178	-0.3012
	Unfocused comparator vs BLA		0.6970	-0.1174
	CMT vs BLA		0.2628	0.3376
N3 (mins)	Unfocused comparator vs CMT	0.2309	0.5747	0.1692
	Unfocused comparator vs BLA		0.1428	0.4419
	CMT vs BLA		0.1914	0.3939
WASO (mins)	Unfocused comparator vs CMT	0.2127	0.3589	0.2766
	Unfocused comparator vs BLA		0.4324	-0.2367
	CMT vs BLA		0.0614	-0.5640
N1 (%)	Unfocused comparator vs CMT	0.7371	0.4995	0.2036
	Unfocused comparator vs BLA		0.9124	0.0332
	CMT vs BLA		0.4244	-0.2408
N2 (%)	Unfocused comparator vs CMT	0.2226	0.3137	-0.3038
	Unfocused comparator vs BLA		0.0694	-0.5474
	CMT vs BLA		0.6911	-0.1198
N3 (%)	Unfocused comparator vs CMT	0.4611	0.6164	0.1510
	Unfocused comparator vs BLA		0.2459	0.3499

REM Architecture

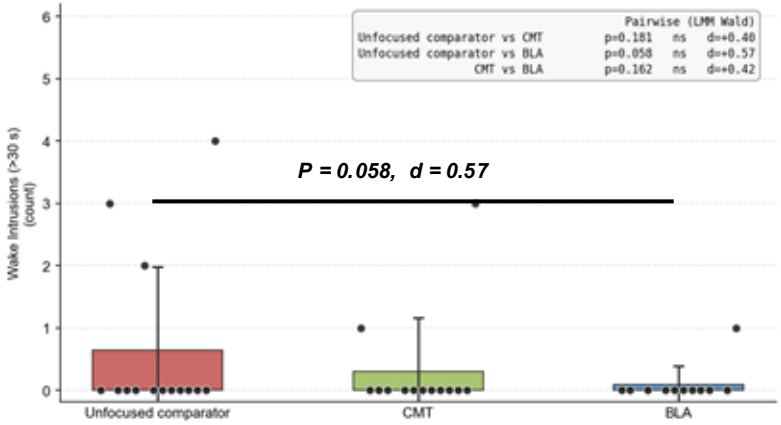
Sleep Metric	Comparison	LMM overall *p*	Pairwise *p*	Cohen's *d*
REM (mins)	Unfocused comparator vs CMT	0.5830	0.8708	0.0490
	Unfocused comparator vs BLA		0.3677	0.2716
	CMT vs BLA		0.4522	0.2267
REM (%)	Unfocused comparator vs CMT	0.8076	0.5893	0.1628
	Unfocused comparator vs BLA		0.5808	0.1665
	CMT vs BLA		0.8954	0.0396
REM onset latency (mins)	Unfocused comparator vs CMT	0.3103	0.2146	-0.3742
	Unfocused comparator vs BLA		0.4723	-0.2167
	CMT vs BLA		0.3217	0.2988
REM bouts (n)	Unfocused comparator vs CMT	0.8172	0.7385	-0.1006
	Unfocused comparator vs BLA		0.8217	0.0679
	CMT vs BLA		0.5023	0.2023
REM bouts (average length)	Unfocused comparator vs CMT	0.6913	0.3966	0.2467
	Unfocused comparator vs BLA		0.8441	-0.0593
	CMT vs BLA		0.4043	-0.2514
REM bouts (longest)	Unfocused comparator vs CMT	0.8753	0.3961	0.2559
	Unfocused comparator vs BLA		0.7929	0.0772
	CMT vs BLA		0.8715	-0.0488
REM fragmentation (events)	Unfocused comparator vs CMT	0.1248	0.2350	-0.3581
	Unfocused comparator vs BLA		0.3377	0.2891
	CMT vs BLA		0.0736	0.5394
REM fragmentation index	Unfocused comparator vs CMT	0.1844	0.1815	-0.3822
	Unfocused comparator vs BLA		0.9643	0.0135
	CMT vs BLA		0.0791	0.5294
REM intrusions	Unfocused comparator vs CMT	0.0010	0.0297	-0.6525
	Unfocused comparator vs BLA		0.0283	0.6611
	CMT vs BLA		0.0002	1.1307

RESULTS – REM Continuity

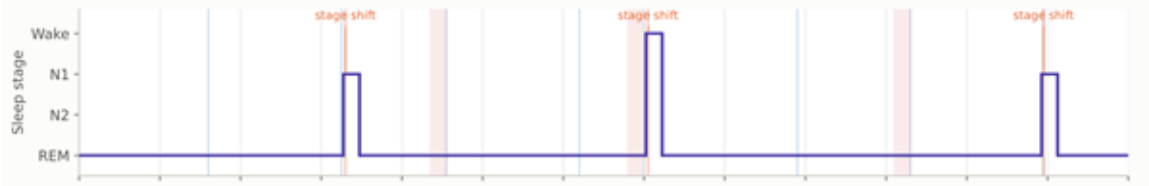
NREM+Wake Intrusions in REM



Only Wake Intrusions in REM



CMT stimulation shows the significant REM intrusions, however majority of them were NREM intrusions, *BLA stimulation shows most consolidated REM* **



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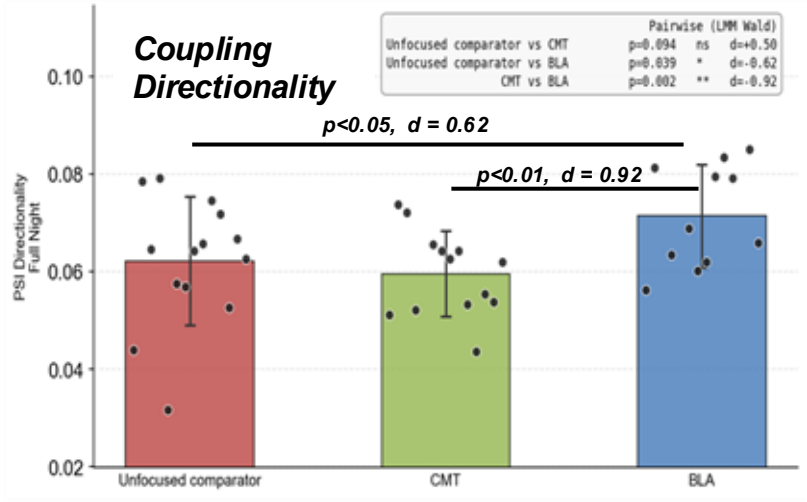
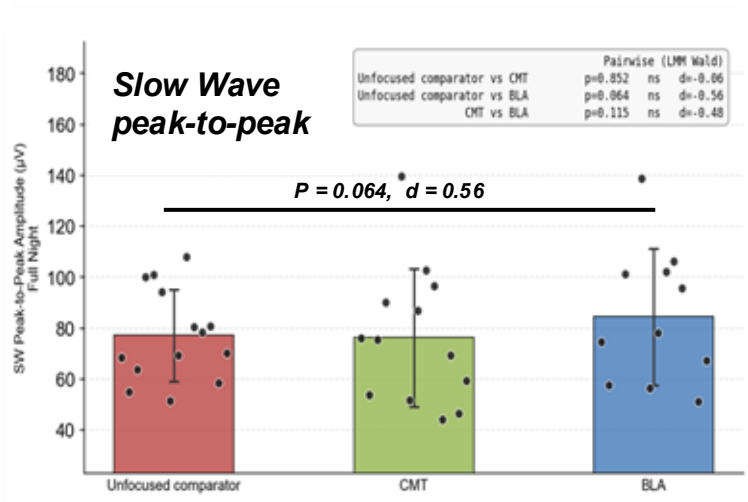
RESULTS – NREM Slow Oscillation and their Coupling with Spindles

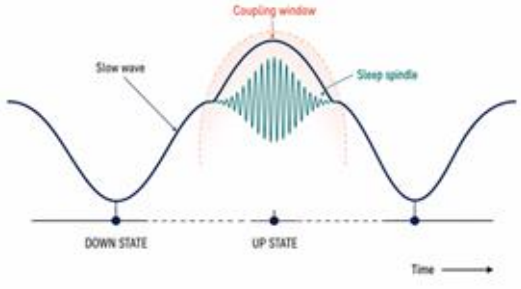
(A)



(B)



BLA stimulation shows more coupling directionality (PSI) and Slow Wave peak-to-peak amplitude compared to unfocussed (close to significance)



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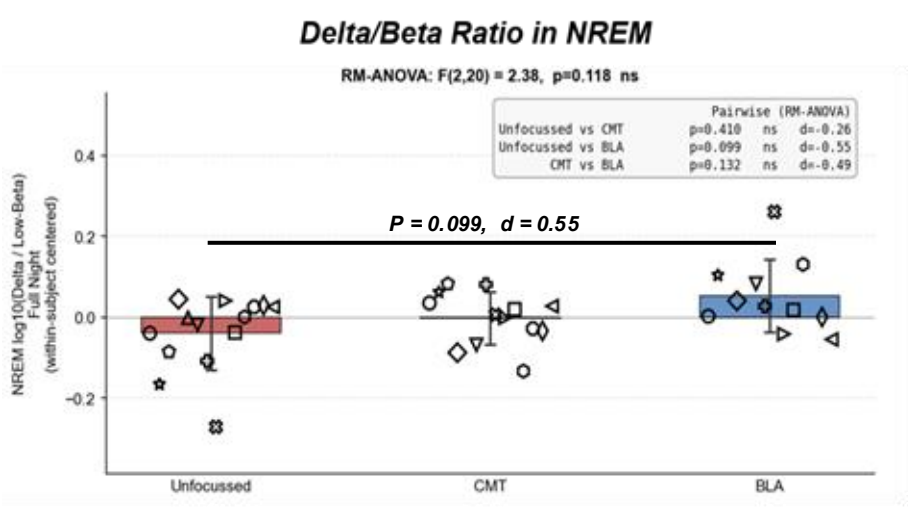
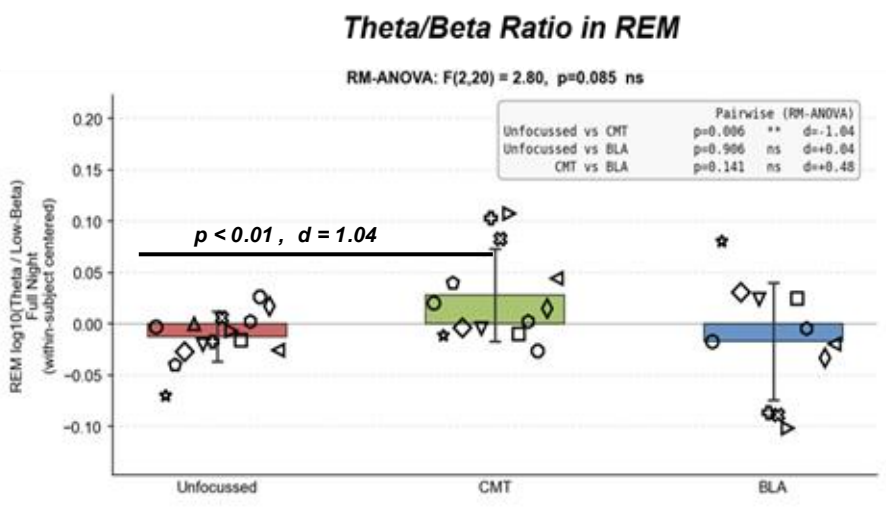
RESULTS – Spectral Powers in NREM and REM





BLA shows the more Delta dominant NREM structure, while CMT shows more Theta dominant REM structure w.r.t beta arousal

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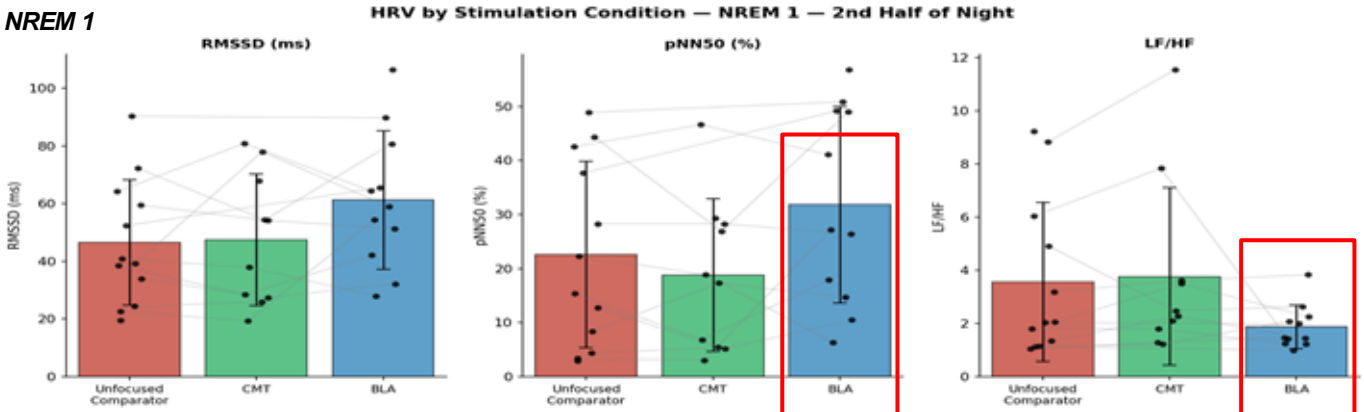
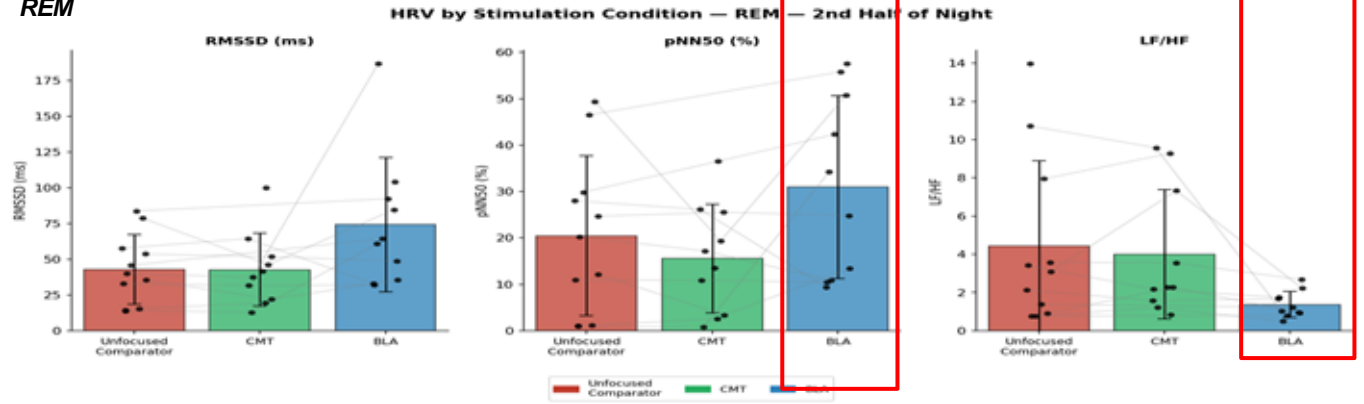
RESULTS - CHANGES IN AUTONOMIC ACTIVITY

Heart Rate Variability in NREM across Stimulation Conditions – Second Half of the Night

NREM 1



REM



Frequency domain HRV metrics
LF/HF - sympathovagal ratio
Log (LF/HF) - log transformed ratio

Time domain HRV metrics
RMSSD - beat to beat heart beat variability
pNNS50- successive difference between beats > 50ms

Healthy HRV patterns

↓ Lower LF/HF, log (LF/HF) (less sympathetic dominance)

↑ Higher RMSSD, pNNS50, HF power (strong vagal tone)

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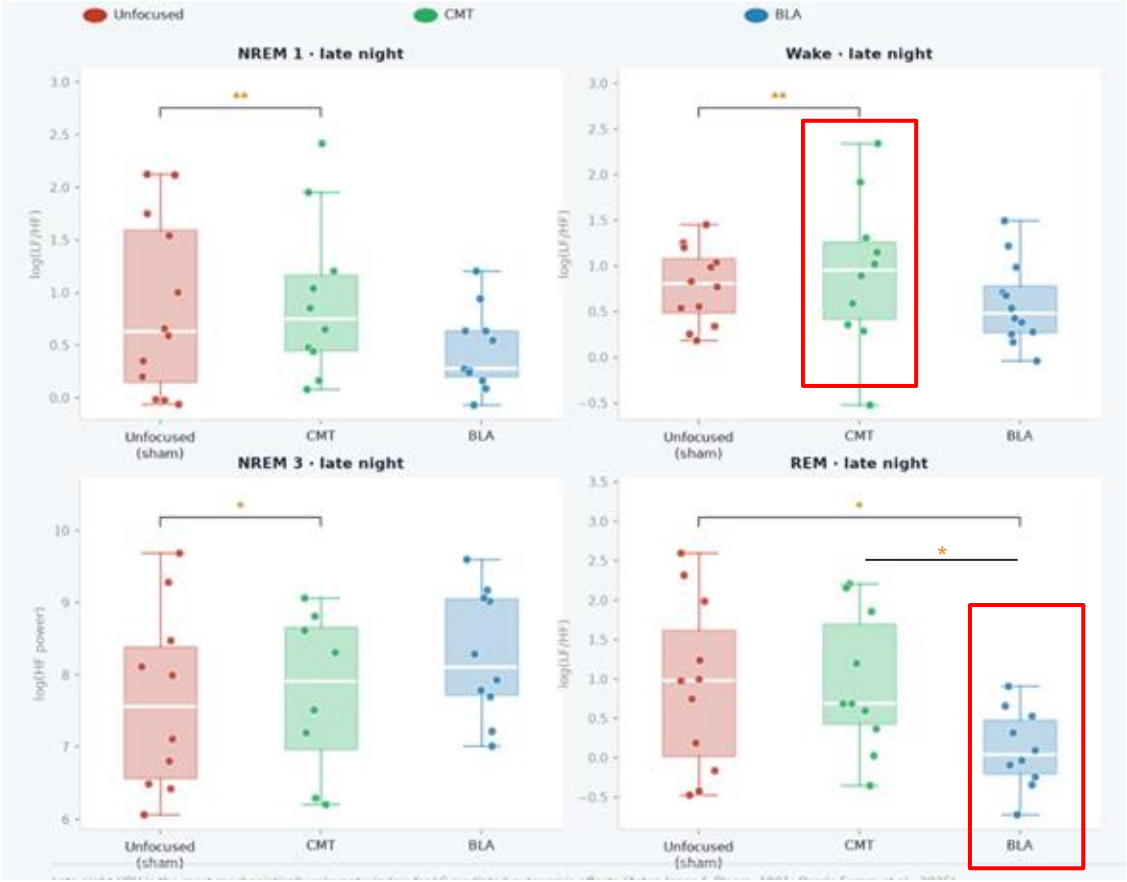
RESULTS - CHANGES IN AUTONOMIC ACTIVITY



Main Effects

Unfocused Comparator vs CMT in N1
d = -1.56, p = 0.003
Unfocused Comparator vs BLA in REM
d = 1.04, p = 0.21
CMT vs BLA in REM
d = 1.24, p = 0.029

Takeaway

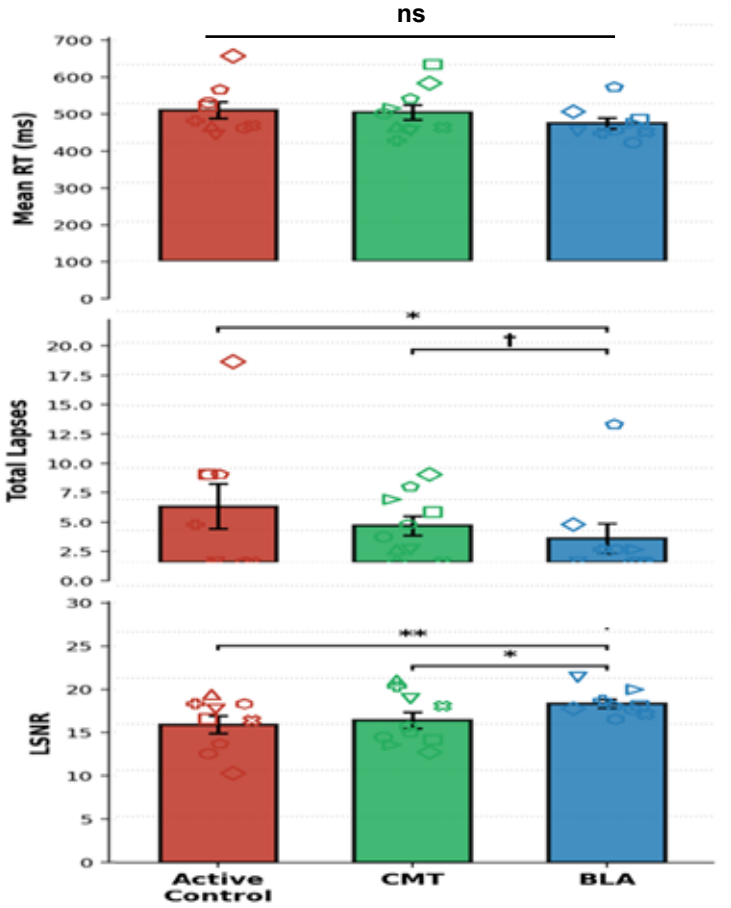
Active Stimulation reshapes the sympathovagal balance.

Direction of Shift

BLA → parasympathetic (vagal) shift
Lower LF/HF and higher RMSSD in REM

CMT → relative sympathetic shift
Higher log (LF/HF), lower HF power in wake and NREM1

RESULTS - CHANGES IN COGNITIVE PERFORMANCE



Key Findings (BLA vs Unfocussed Comparator)

- *Reaction Time not significantly reduced*
- *Lapses significantly reduced ($p < 0.05$; $d = 0.71$)*
- *LSNR improved significantly ($p < 0.01$)*

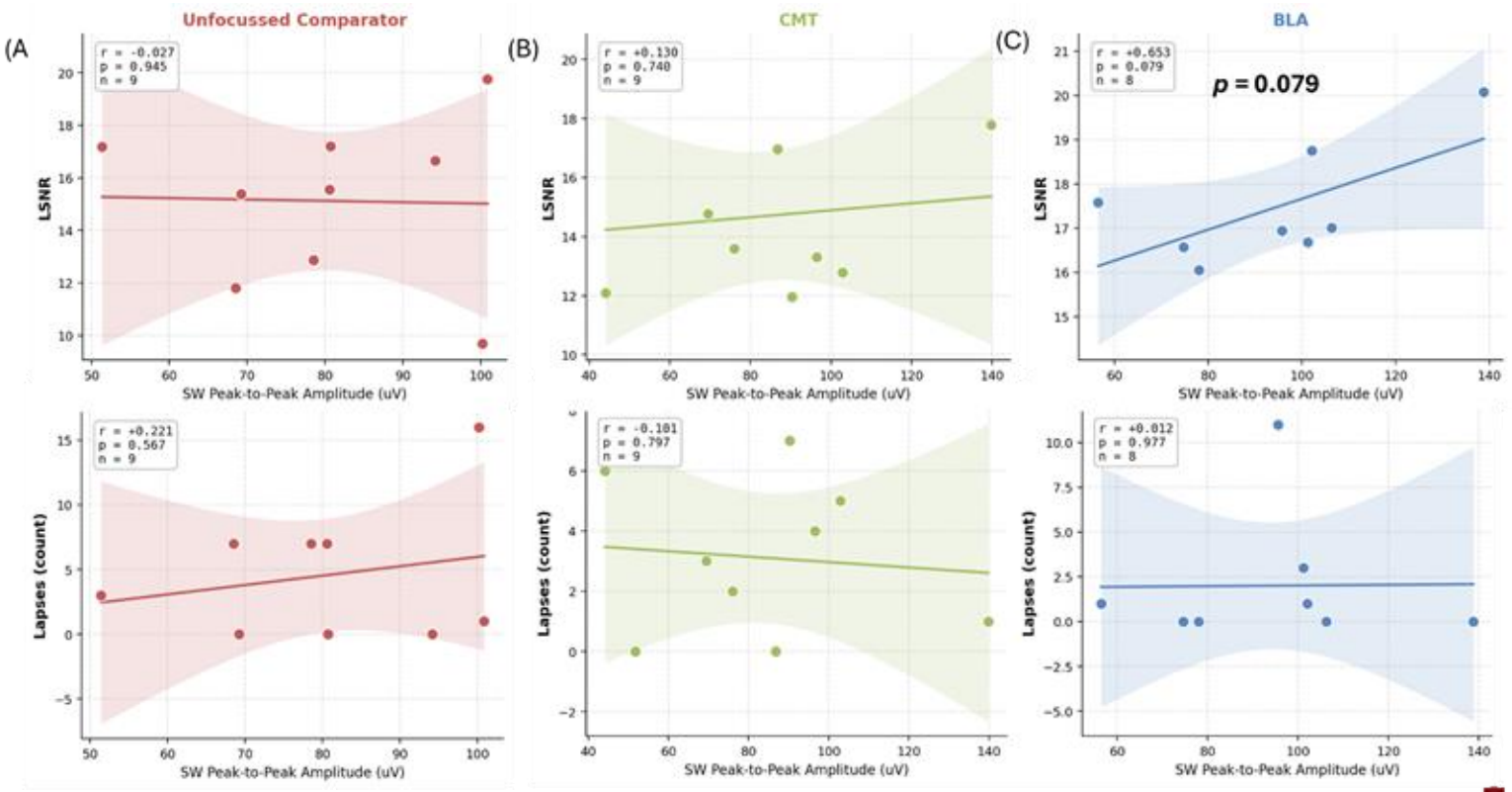
Key Findings (CMT vs Unfocussed Comparator)

- *Reaction Time not significantly reduced*
- *Lapses not significantly reduced*

Key Findings (CMT vs BLA)

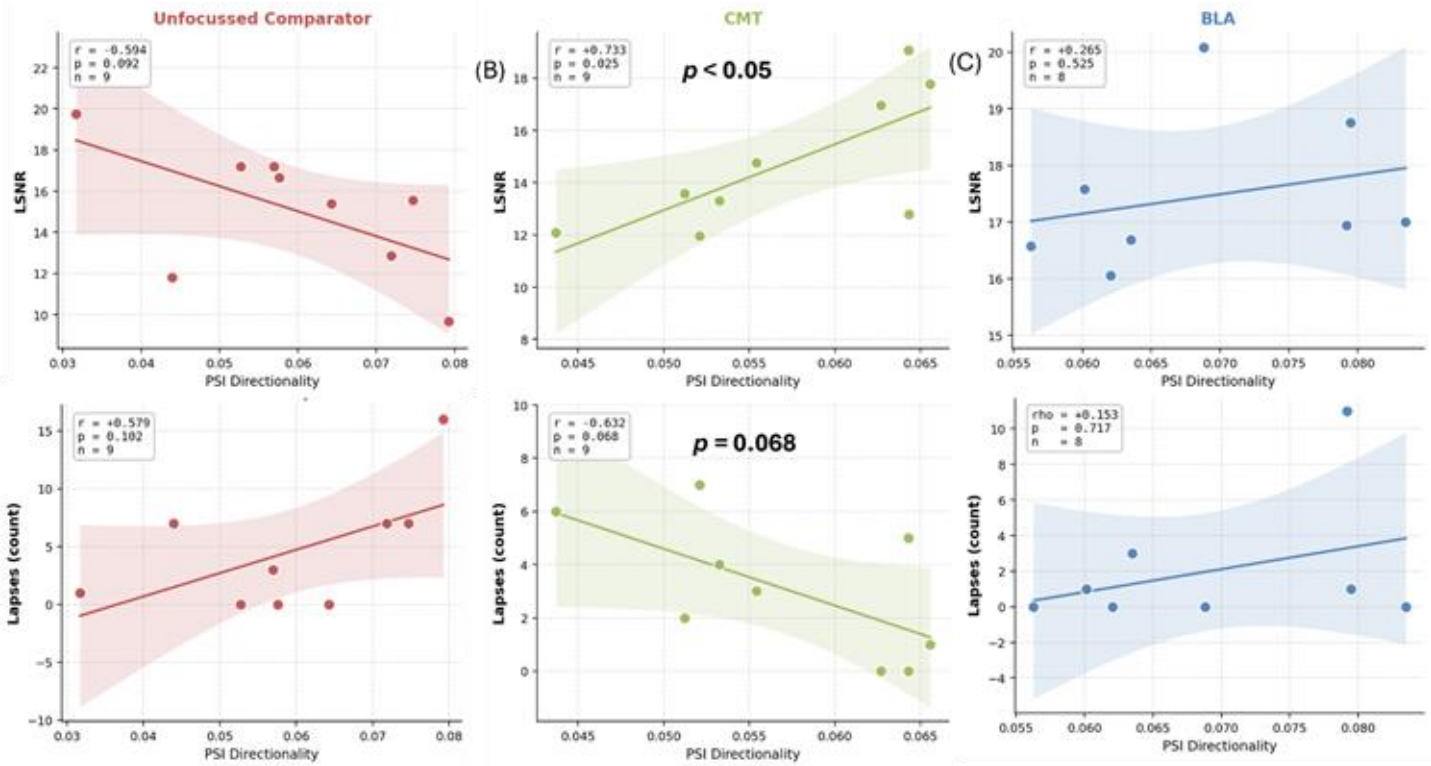
- *LSNR significantly improved in BLA ($p < 0.05$)*

RESULTS - EEG Slow Wave (SW) Amplitude and PVT correlations



Bigger slow waves trended with better PVT performance - for BLA

RESULTS - EEG SW and Spindle Coupling and PVT correlations



SW-spindle coupling associated with better PVT performance - for CMT

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Conclusion and Future Steps

Conclusion

- Sleep duration is preserved; microstructure is selectively modulated.
- BLA stimulation consolidates REM and deepens NREM.
- Sleep changes translate to vigilant-attention improvements - strongest with BLA.
- CMT stimulation reshapes the spindle/slow-wave coupling axis, distinct from BLA in associating with performance.
- Two stim targets, two complementary pathways from sleep to cognition.

Future Steps

- Preliminary data support the feasibility of LIFU during sleep.
- Early findings suggest potential performance benefits, but larger clinical trials are needed in TBI and PTSD Service members
- Stimulation parameters must be characterized and optimized.
- The goal is to identify the safest and most effective LIFU protocol for human sleep.
- Behavioral testing should be expanded to include emotional regulation and memory consolidation.
- This would clarify how LIFU-induced changes in REM sleep affect mood, emotion, and memory.

Clinical Research Team

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Thank You

Questions & Discussion!

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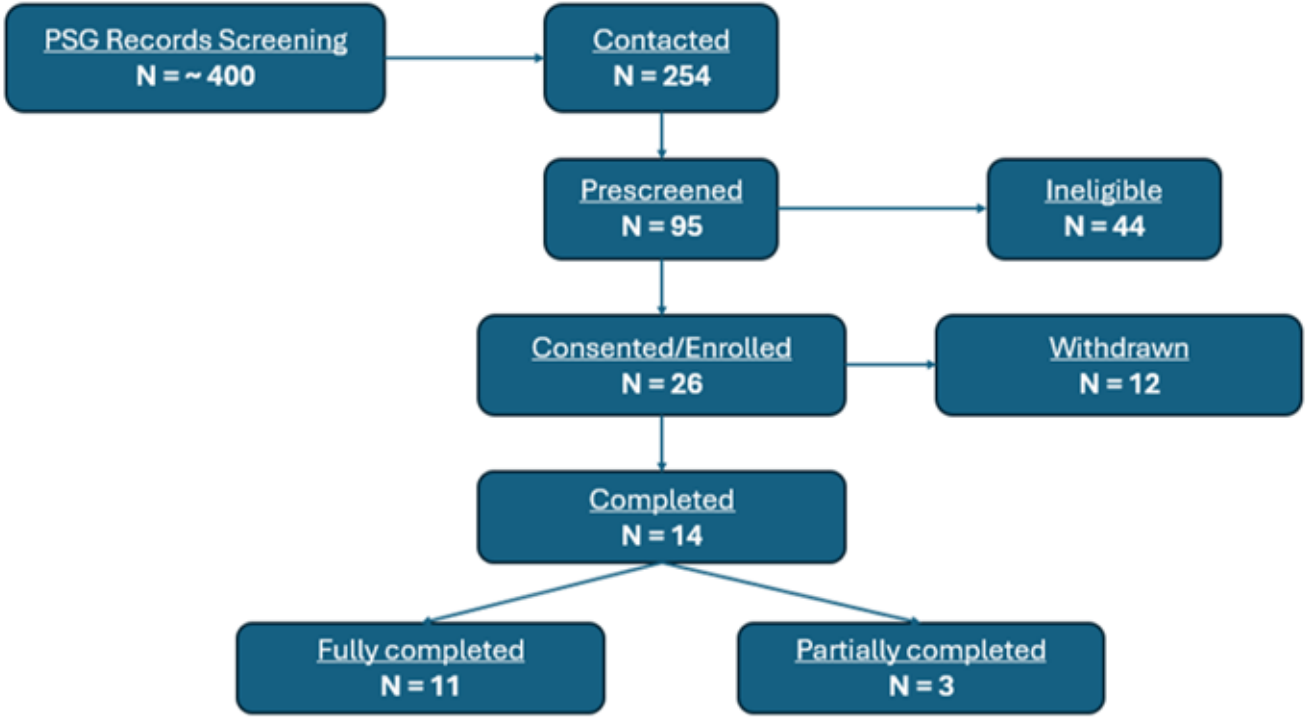
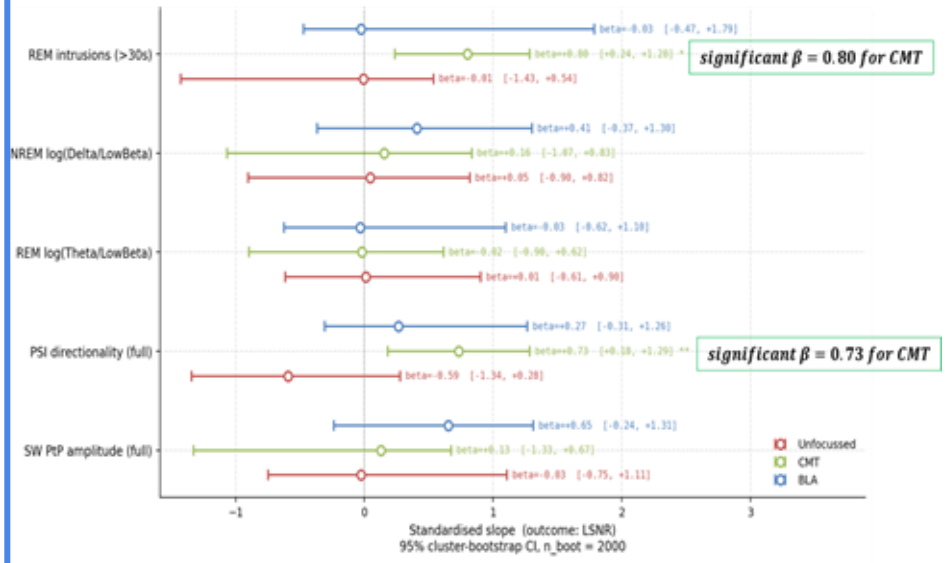
Appendix

Participant Recruitment

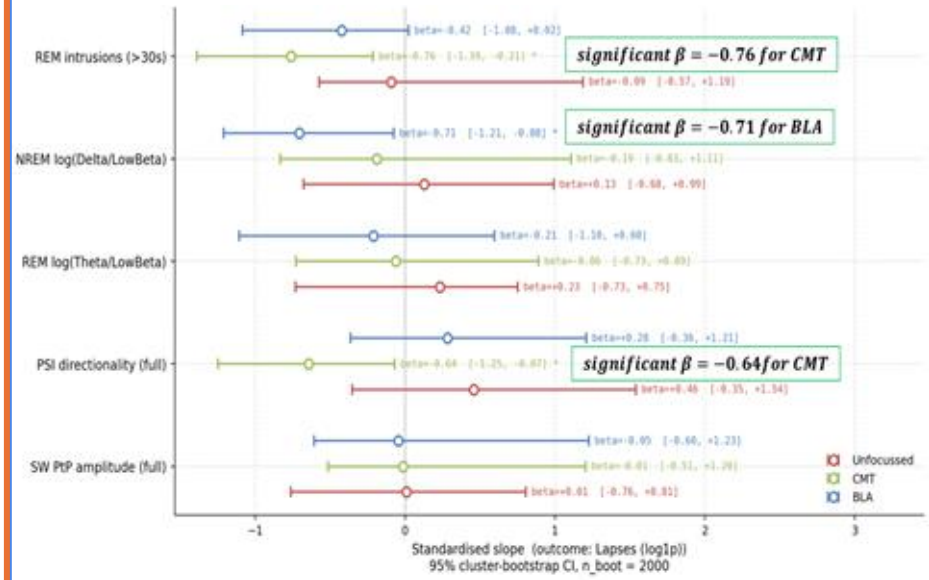


Supplemental Results - Statistical Modeling

Mixed Effects Model - LSNR



Mixed Effects Model - Lapses



$$\underbrace{y_{ij}}_{\text{outcome}} = \beta_0 + \beta_1 \underbrace{x_{ij}}_{\text{sleep driver}} + \beta_2\,\text{Cond}_j + \underbrace{u_i}_{\text{participant}} + \varepsilon_{ij}$$

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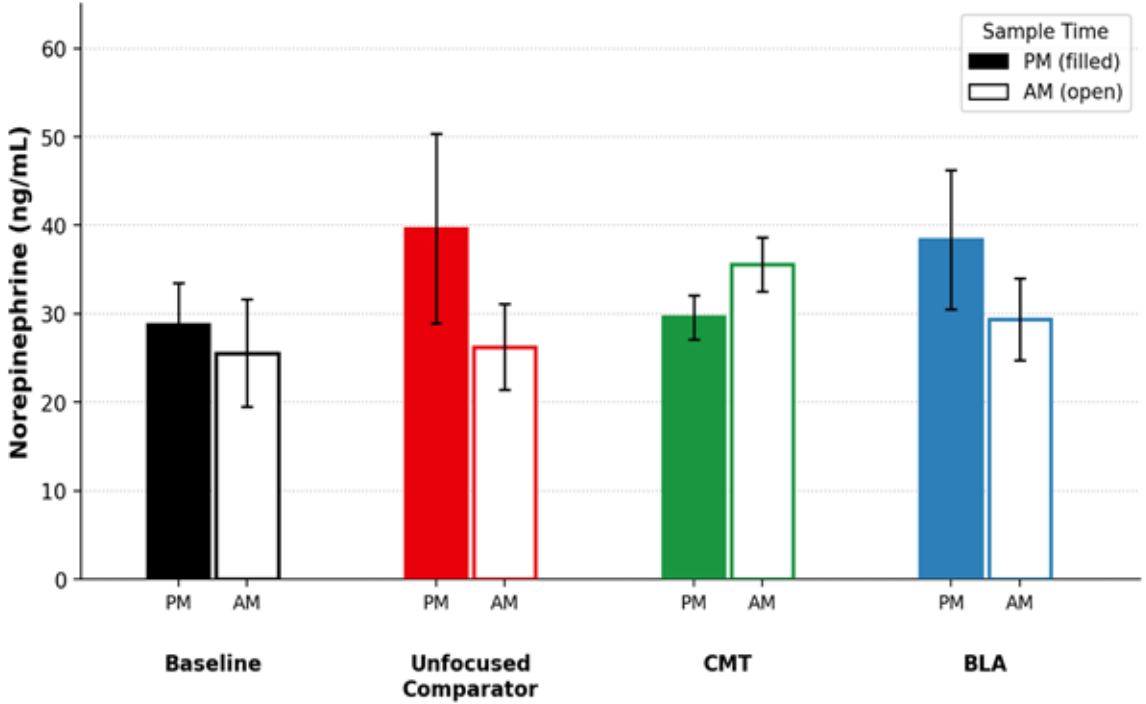
Supplementary Results - Changes in Noradrenaline

Urine noradrenaline differed sharply between PM and AM collections, exceeding any effect of stimulation



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