Sleep Effects of Trigeminal Nerve Stimulation for ADHD

Sandra K. Loo, PhD
Kelsey Stiles, PhD; J. McGough, MD
UCLA Semel Institute for Neuroscience and Human Behavior

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Outline

- Brief overview of sleep problems in ADHD and need for non-pharmacological treatments
- Overview of trigeminal nerve stimulation (TNS)
- TNS for ADHD Trial
- Secondary outcomes of TNS treatment response
- Sleep effects of TNS treatment response
- Future directions

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Sleep disorders and ADHD

''Generally, the parents of hyperkinetic children are so desperate over the night problems that the daytime ones pale in significance." Laufer & Denhoff, 1957

- Sleep disorders and sleep problems are often comorbid with ADHD (Cortese et al., 2009)
- Research on management of sleep problems in youth with ADHD is limited (Cortese et al., 2024)
- Sleep onset delays are common with stimulant medications (Heijden et al., 2007), particularly for children and adolescents with ADHD (Stein et al., 2012)
- Somnolence is common with non-stimulant medications (Daviss et al., 2008; Yildiz et al., 2011)

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Non-Pharmacological Interventions for ADHD

- Response to interventions is highly variable
- Challenges with stimulant medications
  - Suboptimal response
  - Adverse side effects
  - Treatment non-compliance
- Need for empirically supported non-pharmacological interventions, especially those that also address comorbid sleep problems.

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External Trigeminal Nerve Stimulation (TNS)

- Developed to mimic vagal nerve stimulation
- TNS = stimulator and electrode worn on the forehead during sleep nightly
- Stimulation is mild and can be adjusted according to comfort level
- Commercially available by prescription in the US

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TNS Trial: Sample characteristics

- 62 children aged 8-12 years
- full-scale IQ > 85
- Diagnostic Interview for ADHD and other diagnoses
- TNS trial: 4 weeks of nightly active or sham TNS treatment.
- Battery of assessments including behavioral, cognitive, and EEG at baseline and post-tx

- No differences between Active (n=32) and Sham (n=30) in age, gender, race/ethnicity, ADHD subtype, psychiatric co-morbidity, CGIS, height, weight, BP, pulse or resting EEG spectral power.
- Treatment blind fidelity maintained.
- Excellent compliance, well tolerated, minimal side effects

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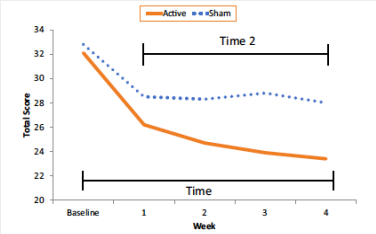
TNS Trial: Clinical Improvements



Significant effect of TNS on core ADHD symptoms in the active versus sham groups

1. Sig improvements in ADHD symptoms and symptom severity
2. No clinically meaningful adverse events, treatment was well tolerated
3. FDA issued clearance in 2019
4. Follow-up study – ongoing

McGough et al., 2019

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TNS Trial: Clinical Improvements

Week	1	2	3	4
Active TNS	25%	34%	47%	52%
Sham TNS	13%	15%	12%	14%

- Blinded clinician-rated global improvement (p=.003)
- Estimated treatment effect size (Cohen *d*) was .5, suggesting a medium-size treatment effect
- Treatment effect size similar to non-stimulants (atomoxetine, guanfacine Cohen *d* ~ 0.57)

McGough et al., 2019

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Correlates of TNS Response

- Goal: identify improvements in secondary outcomes that occur with TNS treatment response
- Examine TNS Responders vs non-responders
  - Includes sham cross-over
  - Responder: CGI-I 1 or 2, non-responder: CGI-I 3+
  - n = 28 responders, n = 23 non-responders

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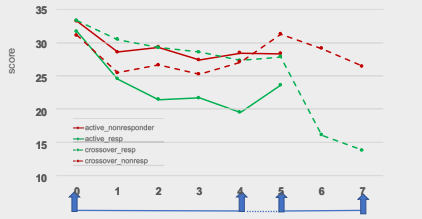
ADHD-RS Total Score across treatment



Active trial (4 weeks)
n=16 responders
n=15 non-responders

Sham Crossover (4 weeks)
n=12 responders
n=8 non-responders
Week 4 = pre-tx baseline

N=28 responders
N=23 non-responders

Responder Status:
Responder=CGII 1 or 2
Non-responder= CGII 3+

Weekly measures:
ADHD-RS
Conners' Global
BRIEF-P

Loo et al., 2021, *JAACAP*

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Correlates of TNS Response

- Secondary outcomes associated with TNS response
  - More executive function impairment predictive of TNS response (Loo et al., 2020)
  - Treatment change in executive function highly correlated (r=.75) with treatment change in inattentive symptoms (Loo et al., 2020)
  - TNS responders exhibited less emotion dysregulation at baseline but also exhibited greater improvements with treatment (Loo & McGough, 2023)
  - What about sleep problems?

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TNS and Sleep Problems: Tx group, time

- Both active and sham groups improved from baseline to week 4 on the CSHQ:
  - **Sleep onset** (p < .001)
  - **Bedtime resistance** (p < .001)
  - **Parasomnias** (p <.001)
  - **Daytime sleepiness** (p=.001)
- But no significant differences between active and sham TNS groups
  - On any CSHQ subscale
- Non-specific effect of using the TNS device: easier bedtime

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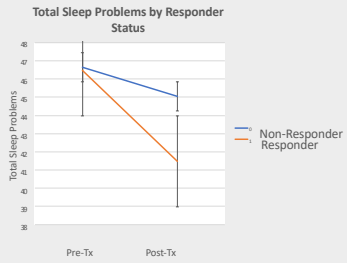
TNS Response and Sleep Problems



Total sleep problems improved more among TNS responders vs non-responders

$F(1,41) = 4.22$, $p < .05$

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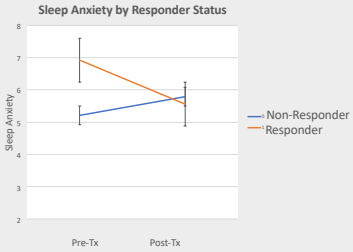
TNS Response and Sleep Problems



Sleep anxiety improved more among TNS responders vs non-responders

$F(1,42) = 6.55$, $p < .05$

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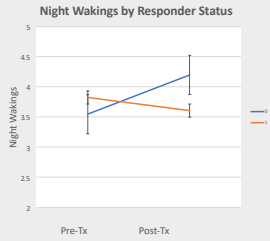
TNS Response and Sleep Problems



Nighttime waking improved marginally more among TNS responders vs non-responders

$F(1,41) = 3.65$, $p = .06$

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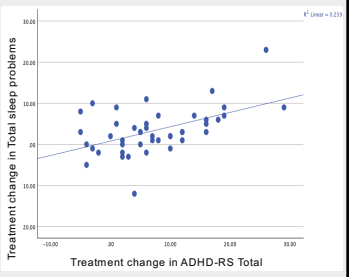
Improved sleep mediates TNS response: ADHD sxs

- Improved sleep significantly predicts change in ADHD-RS scores from pre- to post-treatment
- Significant contributors: bedtime resistance & daytime sleepiness
- Accounts for ~26% of variance
- Consistent with research finding a causal role of sleep disturbance contributing to ADHD symptoms (Becker et al., 2019)



(β= .74, t=-3.8 p<.001)

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Sleep and Emotion Dysregulation

- Poor sleep quality associated with emotion dysregulation problems (Fisher et al., 2022)
  - Across diagnoses
  - Bidirectional associations throughout adolescence (Gilchrist et al., 2023)
- Sleep related to several dimensions of emotional and behavioral dysfunction (Meltzer, 2016)

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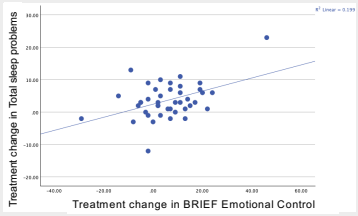
Improved sleep mediates TNS response: emotion dysregulation

- Improvements in total sleep problems also predicted better emotional control.
- Sleep duration is also associated with emotion dysregulation in adolescents with ADHD (Becker et al, 2020).



(β= .74, t=-3.8 p<.001)

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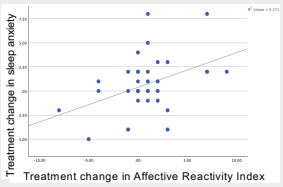
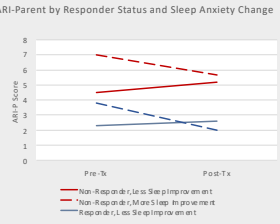
TNS Response, Sleep Problems, and Irritability

Treatment-related changes in irritability varied by responder status and change in sleep anxiety



(β= .48, t=-2.9 p=.006)



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Summary – TNS Response and Sleep Problems

- Non-specific effects of TNS device use = improvement in sleep problems (sleep resistance and sleep onset delay).
- TNS responders experienced more improvement in total sleep problems, sleep anxiety, nighttime wakings vs non-responders
-
- Improved sleep predicts treatment-related changes in ADHD symptoms and emotion dysregulation problems, accounting for some but not all of the TNS effect (~20-25% of variance).

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Ongoing Research on TNS

- Ongoing follow-up study
  - Double-blind, sham-controlled
  - Projected N = 225
  - Children aged 7-12 years
  - 4-week confirmatory efficacy trial
  - 3 and 6-month follow-up measurements
- Replicate findings in larger, more diverse sample

UCLA Research Study of Non-medication Treatment for Children With ADHD

Children are eligible to participate if they:
- Are ages 7-12 years
- Have symptoms of inattention, impulsivity, and hyperactivity
- Are not taking any ADHD medications

Participants will receive
- An evaluation for ADHD
- 4 weeks of treatment with stimulation of nerves in the forehead during sleep

For more information:
call UCLA at 310-876-2042,
email adhdandmood@ucla.edu
or visit
https://www.semel.ucla.edu/adhdandmood

Protocol ID:IRB#22-001119 UCLA IRB Approved Approval Date: 10/20/2024 Through: 10/21/2025 Committee: Medical IRB 3

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