TITLE: Adjunctive non-invasive vagus nerve stimulation supports significant improvement in persistent mood and cognition dysfunction in patients with mTBI with comorbid PTSD: a retrospective cohort.

INTRODUCTION: Mild traumatic brain injury (mTBI), also known as concussion, is a leading cause of sustained physical, cognitive, emotional, and behavioral deficits.[1,2] Non-invasive vagus nerve stimulation (nVNS) has recently been reported as a potential adjunctive therapy for mTBI since nVNS has been shown to improve cognitive function, reduce inflammation, reduce breakdown of the blood-brain barrier, has neuroprotective effects and balances the autonomic system.[3-7]

OBJECTIVE: The objective of these retrospective analyses was to determine if adjunctive nVNS combined with standard of care (SoC) supports improvement in patients with persistent symptoms due to mTBI with comorbid PTSD (mTBI+PTSD).

METHODS: Data from a previously reported cohort of 102 patients with clinically diagnosed mTBI was collected at Cherry Creek Neurology from October 2020 to September 2024. These patients were assessed with Neurobehavioral Symptom Inventory (NSI) at intake and approximately 3-4 months after starting nVNS (2 consecutive stimulations, twice daily) to evaluate symptom improvement. Of those, 42 patients were administered the PTSD Checklist for DSM-5 (PCL-5) and 35 of those scored a 31 indicating a high likelihood of PTSD. Baseline and follow-up NSI scores were compared using the Wilcoxon signed-rank tests. Any effects of injury date on symptom severity and treatment efficacy were tested with ANOVA. Principle component analysis (PCA) was performed to evaluate whether there was a unique constellation of symptoms associated with the mTBI+PTSD vs mTBI without PTSD.

RESULTS: Analyses showed that adjunctive nVNS significantly reduced 15 out of 22 NSI scores from baseline in mTBI+PTSD patients($p<0.05$). The average NSI score across all 22 parameters decreased from 2.50 ± 0.60 to 2.03 ± 0.46. NSI components with the most significant improvements were being *easily overwhelmed* (-0.71, p = 0.0014), *poor coordination* (-0.60, p = 0.0024), *loss of balance* (-0.69, p = 0.0033), and *post-traumatic headache* (-0.71, p = 0.0037). The NSI composite score for 'affective symptoms (*anxiety, depression, irritability, overwhelm*)' were initially the most severe (mean: 2.97) and subsequently most improved (mean: -0.67 per symptom, p = 0.0025); the cognitive composite score was similarly severe at intake (mean: 2.94) and improved (mean: -0.65; p = 0.0076).The time elapsed since injury did not affect the initial NSI severity (p = 0.075 to 0.966) nor treatment efficacy (p = 0.142 to 0.987) for any symptoms. PCA analyses showed that individuals with mTBI+PTSD presented with more severe symptoms than those without PTSD (means: 2.50 vs 1.81), but 40% of patients in both groups experienced clinically meaningful improvement in their total NSI score.

CONCLUSION: While patients in this mTBI+PTSD cohort presented with 38% more severe symptomatology, adjunctive nVNS+SoC was effective in reducing the persistent symptom burden at rates similar their counterparts without PTSD. Affective and

cognitive symptoms were especially prevalent in the mTBI+PTSD patient subset and were also the most improved.

REFERENCES

[1.] Amorim, R.L.O., Brunoni, A.R., Oliveira, M.A.F. et al. Transcranial Direct Current Stimulation for Post-Concussion Syndrome: Study Protocol for a Randomized Crossover Trial. Front Neurol 2017. 8:164.

[2.] Korupolu, R., Miller, A., Park, A., Yozbatiran, N. Neurorehabilitation with vagus nerve stimulation: a systematic review. Front Neurol 2024. 15:1390217.

[3.] Morais, A., Chung, J.Y., Wu, L., et al. Non-Invasive Vagal Nerve Stimulation Pre-Treatment Reduces Neurological Dysfunction After Closed Head Injury in Mice. Neurotrauma Rep 2024. 5:150-158.

[4.] Darrow, M.J., Torres, M., Sosa, M.J., et al. Vagus Nerve Stimulation Paired with Rehabilitative Training Enhances Motor Recovery after Bilateral Spinal Cord Injury to Cervical Forelimb Motor Pools. Neurorehabil Neural Repair 2020. 34:200-209.

[5.] Lerman, I., Hauger, R., Sorkin, L., et al. Noninvasive Transcutaneous Vagus Nerve Stimulation Decreases Whole Blood Culture-Derived Cytokines and Chemokines: A Randomized, Blinded, Healthy Control Pilot Trial. Neuromodulation 2016. 19:283-291.

[6.] Zhou, L., Lin, J.H., Lin, J.M., et al. Neuroprotective effects of vagus nerve stimulation on traumatic brain injury. Neural Regen Res 2014. 9:1585-1591.

[7.] Meneses, G., Bautista, M., Florentino, A., et al. Electric stimulation of the vagus nerve reduced mouse neuroinflammation induced by lipopolysaccharide. J Inflamm 2016. 13:33.

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Contributions to Research:

Michael Ament: Principal Investigator

Emily Leonard: Co-Investigator and Study Coordinator

Norianne Ingram: Data Analysis, Figure Creation, Writer

Peter Staats: Co-Investigator, Senior Researcher

Adjunctive non-invasive vagus nerve stimulation supports significant improvement in persistent mood and cognition dysfunction in patients with mTBI with comorbid PTSD: a retrospective cohort

If you would like to discuss this work, please email.

Michael Ament, MD; Emily Leonard; Norianne T. Ingram, PhD; Peter Staats, MD

CHERRY CREEK NEUROLOGY

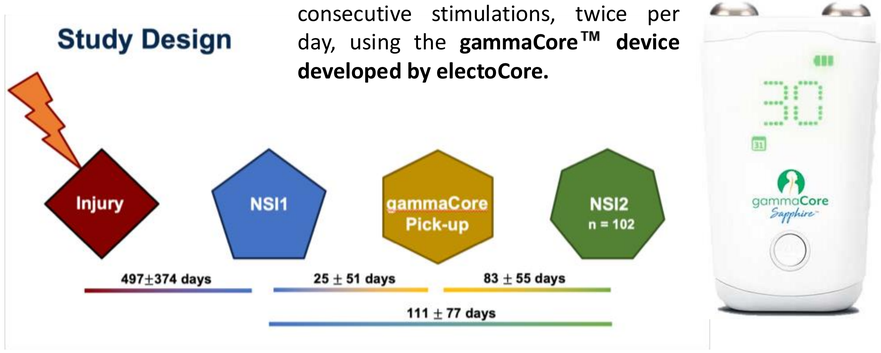
Introduction

Mild traumatic brain injury (mTBI), commonly referred to as concussion, is a major source of prolonged cognitive, emotional, and somatic dysfunction. This burden is often exacerbated in patients with comorbid post-traumatic stress disorder (PTSD), where neuropsychiatric symptoms are more severe and resistant to standard interventions. Non-invasive vagus nerve stimulation (nVNS) has emerged as a promising adjunctive therapy for mTBI, with evidence of neuroprotective effects including modulation of autonomic tone, reduction of neuroinflammation, preservation of the blood–brain barrier, and enhancement of cognitive resilience. Recent preclinical and clinical findings suggest that nVNS may be particularly beneficial in complex mTBI phenotypes such as those involving PTSD.

Methods

This retrospective analysis was conducted at Cherry Creek Neurology between October 2020 and September 2024. Patients were included based on clinical diagnosis of mild traumatic brain injury (mTBI), elevated symptom burden as assessed by the Neurobehavioral Symptom Inventory (NSI), and willingness to initiate adjunctive non-invasive vagus nerve stimulation (nVNS) therapy. A subset of patients also completed validated surveys for PTSD (PCL-5), depression, and anxiety at intake.

Patients were prescribed nVNS and were instructed to deliver two consecutive stimulations, twice per day, using the **gammaCore™ device developed by electoCore.**

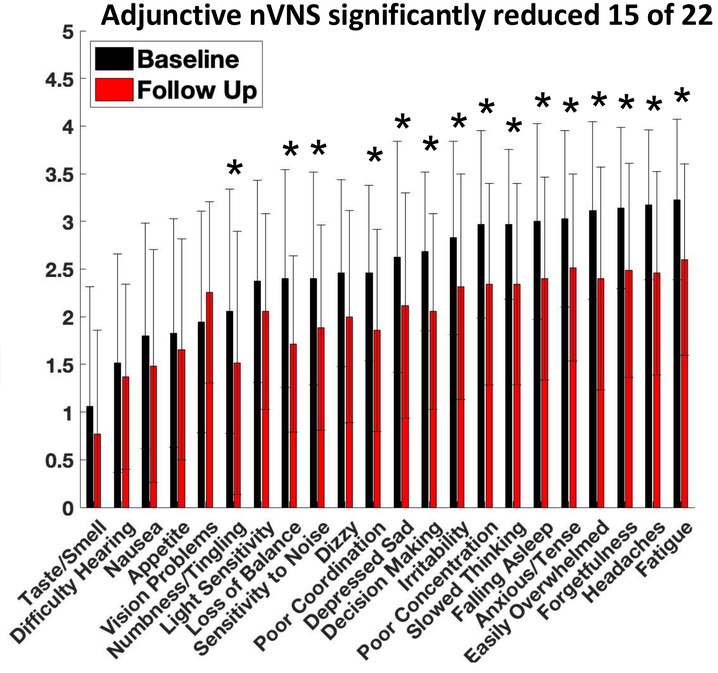


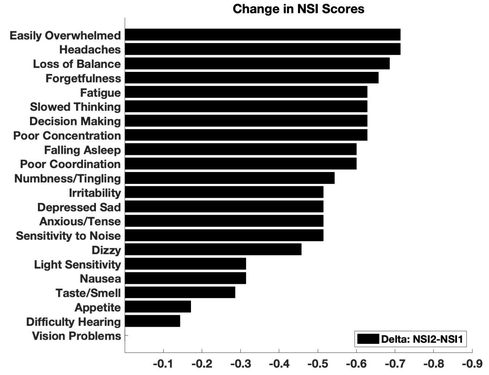
Patients self-administered nVNS (two consecutive stimulations, twice daily) in addition to standard of care (SoC), individualized per clinical discretion. NSI scores were collected at intake (NSI1) and again after approximately 3–4 months of nVNS therapy (NSI2). PTSD was identified in individuals scoring ≥31 on the PCL-5.

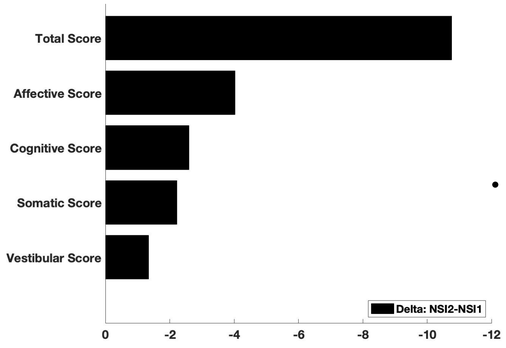
Paired NSI scores were compared using Wilcoxon signed-rank tests. Correlations between NSI and psychiatric scales were assessed, and principal component analysis (PCA) was used to explore symptom clustering by PTSD comorbidity. Effects of injury chronicity on baseline severity and treatment response were tested using ANOVA. Among 175 patients screened, 102 had complete pre/post NSI data; of these, 42 had PCL-5 data and 35 met the threshold for comorbid PTSD. Time since injury ranged from 5 days to 3.5 years.

Results

Adjunctive nVNS significantly reduced 15 of 22 NSI parameters from their baseline values in mTBI+PTSD patients.







Among mTBI+PTSD patients, the most significantly improved NSI components were:

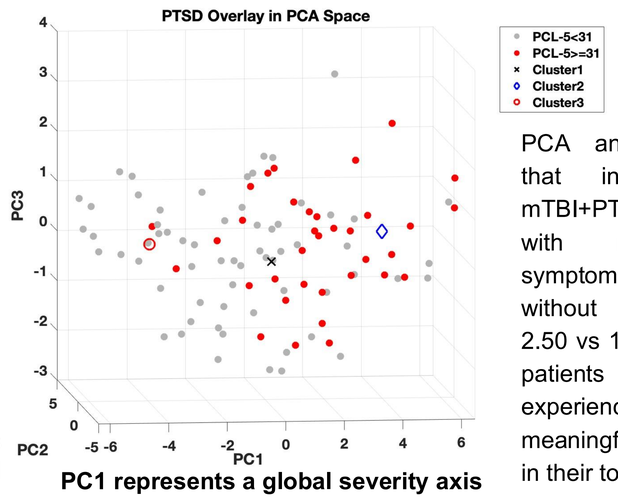
- **Easily overwhelmed** (mean change: −0.71; $p = 0.0014$)
- **Poor coordination** (−0.60; $p = 0.0024$)
- **Loss of balance** (−0.69; $p = 0.0033$)
- **Post-traumatic headache** (−0.71; $p = 0.0037$)

- The time elapsed since injury did not affect the initial NSI severity (p = 0.075 to 0.966) nor treatment efficacy (p = 0.142 to 0.987) for all symptoms.

The average NSI score across all 22 symptoms decreased from **2.50 ± 0.60** at baseline to **2.03 ± 0.46** post-treatment.

Differential improvement was seen in Composite symptom domains:

- **Affective symptoms** (anxiety, depression, irritability, and overwhelm) were the most severe at baseline (**mean: 2.97**) and demonstrated the largest average reduction (**−0.67 per symptom**; $p = 0.0025$).
- **Cognitive symptoms** (e.g. poor concentration, slowed thinking) were also elevated at intake (**mean: 2.94**) and improved significantly following treatment (**−0.65 per symptom**; $p = 0.0076$).



PC1 represents a global severity axis

PCA analyses showed that individuals with mTBI+PTSD presented with more severe symptoms than those without PTSD (means: 2.50 vs 1.81), but 40% of patients in both groups experienced clinically meaningful improvement in their total NSI score.

Conclusions

Although patients with comorbid PTSD presented with 38% greater symptom severity compared to those with mTBI alone, adjunctive nVNS combined with SoC produced comparable therapeutic benefit across groups. Significant reductions were observed in affective and cognitive symptom domains. Notably improvements were seen in symptoms of overwhelm, coordination, balance, and post-traumatic headache. Importantly, the duration since injury did not impact baseline severity or treatment efficacy. These findings support the use of adjunctive nVNS in managing persistent neurobehavioral symptoms in complex mTBI phenotypes, including those with comorbid PTSD.

- This mTBI+PTSD cohort presented with 38% more severe symptomatology and nVNS+SoC was effective in reducing the persistent symptom burden at rates similar their counterparts without PTSD
- 40% of patients mTBI+PTSD experienced clinically meaningful improvement in their total NSI score

References

Improve cognitive function

1. Klaming, R., et al., (2022). Effects of noninvasive cervical vagal nerve stimulation on cognitive performance but not brain activation in healthy adults. *Neuromodulation: Technology at the Neural Interface*, *25*(3), 424-432.

Reduce breakdown of the blood-brain barrier

2. Yang, Y et al., (2018). Non-invasive vagus nerve stimulation reduces blood-brain barrier disruption in a rat model of ischemic stroke. *Brain stimulation*, *11*(4), 689-698.

Neuroprotective effects

3. Divani, A. et al., (2023). Non-invasive Vagus nerve stimulation improves brain lesion volume and neurobehavioral outcomes in a rat model of traumatic brain injury. *Journal of neurotrauma*, *40*(13-14), 1481-1494.
4. Morais, A., et al., (2024). Non-Invasive Vagal Nerve Stimulation Pre-Treatment Reduces Neurological Dysfunction After Closed Head Injury in Mice. *Neurotrauma Reports*, *5*(1), 150-158.
5. Cáceres, E., et al., (2025). Noninvasive Vagus Nerve Stimulation Protects Neurons in the Perihematomal Region and Improves the Outcomes in a Rat Model of Intracerebral Hemorrhage. *Neurocritical Care*, 1-13.
6. Schindler, A., et al.,(2019). Non-invasive vagus nerve stimulation for the prevention/treatment of comorbid mild traumatic brain injury and PTSD. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *12*(2), 418-419.