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Original Research

An Eight-week, Open-trial, Pilot Feasibility Study of Trigeminal Nerve Stimulation in Youth With Attention-deficit/Hyperactivity Disorder

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ABSTRACT

Background: This study examined the potential feasibility and utility of trigeminal nerve stimulation (TNS) for attention-deficit/hyperactivity disorder (ADHD) in youth.

Methods: Twenty-four participants ages 7–14 with ADHD enrolled in an 8-week open trial of TNS administered nightly during sleep, and were assessed weekly with parent- and physician-completed measures of ADHD symptoms and executive functioning as well as measures of treatment compliance, adverse events, and side effects. Computerized tests of cognitive functioning were administered at baseline and weeks 4 and 8.

Results: Significant improvements were seen on the ADHD-IV Rating Scale ($P < .0001$) and parent-completed Conners Global Index ($P < .0001$), as well as the majority of scales on the parent-completed Behavior Rating Inventory of Executive Functioning (BRIEF). Improvements were also noted on the computerized Attention Network Task (ANT) Incongruent Reaction Time ($P = .006$), suggesting that TNS has positive effects on response inhibition.

Conclusions: TNS therapy for youth with ADHD appears to be both feasible and without significant risk. Subjective improvements on rating scales and laboratory measures of cognition suggest a potential role for TNS in treating ADHD that merits further investigation. Future research in anticipation of designing definitive controlled efficacy trials should evaluate time to onset of TNS response and durability of treatment effects following TNS discontinuation, as well as validate an effective active sham comparator suitable for blinded studies.

Introduction

Trigeminal nerve stimulation (TNS) is a minimal risk, non-invasive method of neuromodulation currently under investigation for treatment of medication-resistant epilepsy and Major Depression Disorder (MDD) [1]. Preliminary studies suggest that TNS is useful for relief of symptoms not only in epilepsy and MDD, but also Post Traumatic Stress Disorder (PTSD) [2–9]. In TNS, a small stimulating device worn on the patient's clothing, typically during sleep, emits a low-level current generated by a 9-V lithium battery under microprocessor control. Thin wires extend from the stimulator to adhesive electrode pads worn externally on the forehead over the trigeminal nerve. The trigeminal nerve conveys sensory inputs from the skin, muscles, and joints of the head to extensive connections in the brainstem and cortex [10]. As with the vagus nerve, the trigeminal has connections with the locus coeruleus, reticular activating system, and nucleus tractus solitarious [10–13]. These brain regions are involved in a variety of affective and cognitive functions, including selective maintenance of attention during cognitive tasks [14].

Attention-deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder estimated in the United States to affect up to 9.5% of school age children [15] and 4.4% of adults [16]. ADHD is defined by clinically significant and developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity [17]. Neuropsychological deficits commonly associated with ADHD include

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those associated with executive functioning, particularly in reaction time variability and the acquisition of cortical, top-down processes of attention regulation and executive control [18–20]. Several findings from studies of TNS for depression suggest a potential role in ADHD treatment. First, item-analysis of mood disorder rating scales indicated that TNS is associated with selective improvements in concentration and attention (Ian Cook, personal communication). Second, positron emission tomography (PET) revealed that acute administration of TNS activates several brain regions implicated in ADHD and executive function, notably the anterior cingulate cortex (ACC), inferior frontal gyrus, medial and middle frontal gyri, and the parietotemporal cortex [21]. Third, TNS had been extremely well tolerated in adult studies with virtually no associated adverse events, suggesting that the modality is suitable for pediatric testing [1].

The current report represents the first clinical trial of TNS in children and adolescents and the first to assess potential effects of TNS on ADHD. The study was primarily initiated to determine if ADHD-affected youth would successfully comply with TNS procedures and to evaluate the preliminary feasibility of conducting TNS research in this population. The primary study aim was to assess TNS compliance rates in ADHD-diagnosed youth over an 8-week open trial. Secondary aims were to estimate 1) the potential effects of TNS on ADHD behavioral symptoms, 2) the potential effects of TNS on cognition and executive functioning, 3) potential effects of TNS on sleep, and 4) initial side effect and adverse event frequencies in this pilot sample.

Methods

Participants

Male and female youth ages 7–14 years with DSM-IV ADHD as assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) [22] and confirmed by clinical interview were eligible for participation. Additional inclusion criteria were 1) minimum baseline scores of 12 on both the inattentive and hyperactive/impulsive subscales of the investigator completed Parent ADHD-IV Rating Scale (ADHD-RS) [23], 2) a baseline Clinical Global Impression–Severity (CGI-S) rating ≥ 4 [24]; 3) no current use of medication with CNS effects, and 4) a parent able and willing to complete all required ratings and monitor proper use of the TNS device. Exclusion criteria were: 1) levels of ADHD-related impairment that required immediate medication management, 2) current diagnoses of pervasive developmental or depressive disorders, 3) current suicidality, and 4) lifetime histories of psychosis, mania, or seizure disorder. Prior to initiation of study procedures, potential participants and at least one parent received thorough verbal and written descriptions of study requirements and provided written permission and assent as approved by the UCLA Institutional Review Board (IRB). This trial was registered with ClinicalTrials.gov (NCT01388530).

Trial design

The study was an 8-week, open, pilot investigation of TNS for ADHD-affected youth. After eligibility determination, participants completed baseline measures of behavioral symptoms, executive functioning, and cognition. Participants and parents received instruction on proper electrode placement and stimulator operation, so that TNS could be correctly provided at home. TNS was administered nightly during sleep for the 8-week trial. Participants and parents completed weekly ratings of compliance, side effects, and behavioral symptoms. Visits at weeks 4 and 8 included repeated laboratory assessments of executive functioning and cognition. Study staff were free to provide parents and participants with supportive counseling as indicated, but evidence-based psychosocial treatments for ADHD, such as behavioral parent management and social skills treatment, were not allowed for the duration of the 8-week trial.

TNS intervention

TNS procedures were based on previous work in epilepsy [3–6] and adult depression [7–9]. The EMS7500 Stimulator (TENS Products, Inc. Granby, CO) generated an electrical current set by established parameters based on these previous investigations: 120-Hz repetition frequency, with 250-μs pulse width, and a duty cycle of 30 s on/30 s off. The stimulator was worn on the child's pajamas or t-shirt and attached with thin wires to disposable, silver-gel, self-adhesive electrodes (NeuroSigma, Inc., Los Angeles, CA). Parents applied electrodes to their child's forehead to provide bilateral stimulation of the V_1 branches of the trigeminal nerve for 7–9 h each night. Stimulator current settings between 2 and 4 (range: 0–10 units) were based on initial titration at the baseline visit, which identified a perceptible stimulation level that was below the participant's subjective level of discomfort. Power was provided by 9-V lithium medical-grade batteries (Everyready Energizer L522, Energizer, St. Louis, MO), which were recharged and replaced every other day.

Study outcomes

Treatment adherence was measured daily with a parent-completed TNS compliance diary and weekly by clinical interviews conducted at study visits. The primary ADHD behavioral symptom outcome established *a priori* was the Investigator Completed Parent ADHD-RS [23], completed at baseline, week 4, and week 8. Other weekly behavioral ratings obtained included an investigator-completed Clinical Global Impression-Improvement (GCI-I) Scale [24], and the parent-completed Conners Global Index [25] and Children's Sleep Habits Questionnaire (CSHQ) [26]. Computer-based cognitive measures conducted at baseline, week 4, and week 8 included the Attentional Network Task (ANT) [27] to assess cued reaction time, and Spatial Working Memory [27], the spatial version of the Sternberg delayed match to sample task, to assess working memory [28]. Other measures collected at baseline, week 4, and week 8 included the parent-competed Behavior Rating of Executive Functioning (BRIEF) [29] and Multidimensional Anxiety Scale for Children (MASC) [30], and participant-completed Children's Depression Inventory (CDI) [31]. Potential side effects and adverse events were assessed with weekly parent-completed Side Effect Ratings Scales and open-ended Adverse Event Inquiries with parents conducted by study investigators.

Statistical analyses

Descriptive statistics were derived for participant characteristics. Participation rates and treatment compliance were determined based on all participants deemed eligible at screening. The safety population included all participants with at least one night's exposure to TNS. The treatment population included all participants with outcomes data at week 4, the first post-baseline point at which primary behavioral and cognitive outcomes were obtained. Behavioral and cognitive measures were assessed for change over time with the general linear mixed model using PROC MIXED (SAS Version 9.2), which automatically handles missing observations. All tests were two-tailed, with an *a priori* significance level of $P < .05$. Due to the exploratory nature of this pilot investigation, no corrections were made for multiple testing.

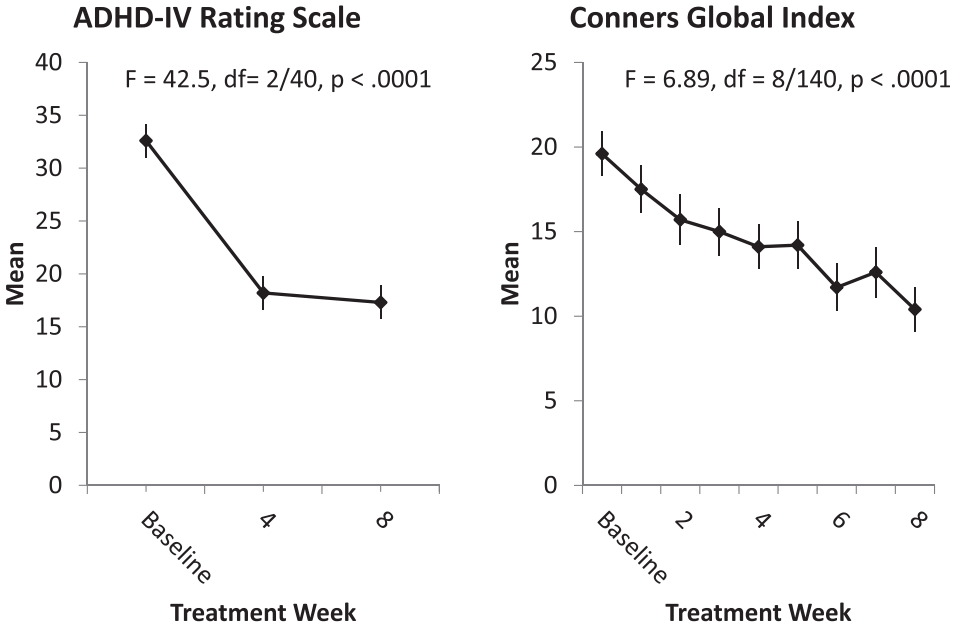

Figure 1. ADHD behavioral rating scales.

Results

Of 29 individuals screened, $N = 25$ were eligible for participation. One participant withdrew consent for personal reasons prior to beginning TNS. $N = 24$ initiated TNS and were included in our assessment of treatment compliance and protocol adherence. Two participants were lost to follow-up prior to Visit 4 outcome assessments, one each at Visits 2 and 3. Reasons for these dropouts are not known. Visit 4 outcomes data were available in $N = 22$ participants. One participant was lost to follow-up for unknown reasons after Visit 6, leaving a final study sample size of $N = 21$ participants who completed 8 weeks treatment.

Participants were 92% male. Mean (SD) age was 10.3 (2.1), range 7–14 years; mean (SD) full scale IQ was 100.7 (12.7), range 75–127. The sample was 75% white, 13% African American, 13% Asian, and 46% Hispanic. ADHD subtypes were 88% combined, 8% inattentive, and 4% hyperactive/impulsive. Comorbid oppositional defiant disorder was present in 46%.

There was 100% nightly treatment compliance for participants who remained in the study, based on daily treatment diaries. There were no reported difficulties with acceptance or implementation of TNS therapy. Participants showed small but significant increases in height ($F = 2.52$, df = 8/81, $P = .02$), weight ($F = 2.74$, df = 8/81, $P = .01$), and pulse ($F = 2.67$, df = 8/81, $P = .01$), but no changes in blood pressure ($F = 1.1$ systolic and diastolic, df = 8/81, $P = .4$) over the 8-week treatment course.

Robust improvements were seen on both the investigator completed ADHD-RS and parent-completed Conners Global Index (Fig. 1). Improvements on the ADHD-RS were evident for both the Inattentive ($F = 30.25$, df = 2/40, $P < .0001$) and Hyperactive/Impulsive ($F = 30.31$, df = 2/40, $P < .0001$) subscales. On the CGI-I, 64% met response criteria (improved or very much improved) at Week 4, and 71% met these criteria at Week 8. Although participants did not meet categorical diagnoses of depressive diagnoses, significant improvements over the 8-week study were noted on dimensional CDI scores ($F = 3.40$, df = 2/38, $P = .04$). There were no apparent changes in self-reported anxiety as indicated by changes in MASC scores ($P = .82$).

Robust improvements in parent-reported executive functioning were found in 7 of 11 BRIEF subscales (Table 1). On cognitive outcomes, there was a significant decrease in ANT Incongruent Reaction Time ($P = .006$), while changes on SDRT Block 2 Accuracy approached significance (Table 2). Significant improvements were detected on the CSHQ for Sleep Anxiety, Total Bedtime Problems, and Total Sleep Problems, while other subscales remained unchanged (Table 3).

Table 1
Behavior rating inventory of executive functioning (BRIEF) – parent report ($N = 22$).

Scale (T score)	Study week least square means					
	Baseline	Week 4	Week 8	F	df	P value
Inhibit	69.4	64.9	62.4	6.52	2/40	.004
Shift	62.1	60.0	56.8	1.68	2/40	.20
Emotional control	59.0	55.6	53.7	1.94	2/40	.16
BRI index	65.5	61.8	59.0	3.83	2/40	.03
Initiate	64.7	61.9	59.6	2.60	2/40	.09
Working memory	70.0	65.8	63.0	9.67	2/40	.0004
Plan/organize	69.3	64.2	64.0	6.25	2/40	.004
Organization materials	57.7	55.5	54.1	2.46	2/40	.10
Monitor	67.2	62.4	60.1	6.94	2/40	.003
MI index	69.0	64.2	61.7	8.57	2/40	.0008
Global exec composite	69.2	64.2	61.5	7.31	2/40	.002

Table 2
Cognitive outcomes ($N = 22$).

Measure	Least square means					
	Baseline	Week 4	Week 8	F	df	P value
ANT neutral reaction time	745.6	733.8	751.5	.32	2/37	NS
ANT neutral accuracy	87.6	86.6	88.7	.53	2/37	NS
ANT congruent reaction time	786.3	745.8	773.8	2.14	2/37	NS
ANT congruent accuracy	89.3	86.6	89.0	1.49	2/37	NS
ANT incongruent reaction time	902.0	835.0	823.4	5.93	2/37	.006
ANT incongruent accuracy	82.1	79.7	84.8	1.96	2/37	NS
SDRT block 1 accuracy	71.8	70.9	71.0	.12	2/37	NS
SDRT block 1 reaction time	1300	1308	1255	.33	2/35	NS
SDRT block 2 accuracy	72.2	67.2	69.8	2.70	2/37	.08
SDRT block 2 reaction time	1409	1301	1321	1.57	2/35	NS

ANT – Attentional Network Task; SDRT – Spatial Working Memory.

Table 3
Children's Sleep Habits Questionnaire (CSHQ) ($N = 22$).

Subscale		F	df	P value
1	Bedtime resistance	1.35	9/81	.23
2	Sleep onset delay	.41	9/81	.93
3	Sleep duration	1.06	9/81	.40
4	Sleep anxiety	2.27	9/81	.03
5	Night wakings	.71	9/81	.70
6	Parasomnias	.92	9/81	.51
7	Disordered breathing	.91	9/81	.91
8	Daytime sleepiness	.53	9/81	.85
	Total bedtime problems	7.38	9/81	<.0001
	Total sleep behavior problems	1.98	9/79	.05
	Total problems daytime sleepiness	1.48	9/79	.17
	Total sleep problems	4.58	9/79	<.0001

TNS was well tolerated. No participants left the study due to adverse events (AEs) or other side effects. A total of 13 AEs were spontaneously elicited over the 8 weeks (Table 4). Of these, only two (eye twitching and headache) were deemed potentially related to treatment. Eye twitching, which occurred during active stimulation, resolved with alternative placement of forehead electrodes. Headaches were reported by two subjects on one occasion each, and resolved without further intervention. Side effects rated "moderate" or "severe" on the Side Effects Rating Scale and reported at least once by at least 5% of participants are summarized in Table 5.

Discussion

This study supports the feasibility of conducting TNS research in children and adolescents, and suggests a potential role for TNS as a treatment for ADHD. TNS was well accepted by patients and families, treatment compliance was high, and there were no clinically meaningful side effects or adverse events. These safety findings are consistent with previous adult studies for depression and epilepsy. Study data suggest that TNS is safe, minimal risk, and suitable for additional testing in pediatric age groups.

Dramatic reductions in ADHD symptoms, demonstrated by the ADHD-RS and Conners Global Index, are consistent with improvements in attention and concentration previously described in studies of TNS in epilepsy and adult depression [1,7]. Inattentive and hyperactive/impulsive ADHD subscales had comparable levels of change. These improvements were evident within the initial weeks of treatment. Results on the majority of subscales from the parent-completed BRIEF, a well-validated and frequently used measure of executive functioning also suggested significant TNS benefits, with the largest effect seen for Working Memory. One limitation of this study is that open trials of non-medication ADHD therapies have been reported often to yield positive outcomes,

Table 4
Spontaneously reported adverse events ($N = 24$).

Event	Total#	Related/ possibly related	Unrelated
Asthma	1	0	1
Eye twitch	1	1	0
Gagging	1	0	1
Headache	4	2	2
Inguinal hernia	1	0	1
Congestion	1	0	1
Sore throat	2	0	2
Swallowed tack	1	0	1
Tingles in head	1	0	1

Table 5
Moderate and severe side effects occurring in >5% of participants ($N = 24$) based on side effects rating scale ($N = 24$).

Side effect	% Reporting
Trouble sleeping	29
Nightmares	21
Feeling drowsy	21
Feeling nervous	58
Weakness or fatigue	21
Irritable	42
Poor memory[a]	46
Trouble concentrating[a]	92
Feeling strange or unreal	8
Headache	13
Stuffy nose	24
Drooling	8
Muscle twitch	8
Trouble sitting still[a]	71
Poor concentration[a]	71
Slurred speech	8
Stomach discomfort	8
Excess sweating	8
Weight gain	8
Diminished mental acuity/sharpness	13
Difficulty finding words	8
Apathy/emotional indifference	13

[a] ADHD symptoms.

particularly when individual who rate symptoms are highly invested in treatment outcomes [32]. Claims for efficacy of TNS as an ADHD treatment will require well-controlled trials conducted under blinded conditions. Nonetheless, this current report supports the feasibility of additional research on TNS in youth for ADHD and provides justification for the design and implementation of definitive efficacy studies.

Although obtained in an uncontrolled trial, the positive changes detected on laboratory measures of executive functioning are apt to be less affected by participant expectations and parental or investigator bias in assessing treatment effects. Robust effects on the computer administered ANT suggest that TNS has positive effects on response inhibition, with a significant decrease in the reaction time required to respond correctly to the ANT incongruent flanker condition. Specifically, this result suggests that, over the course of TNS treatment, the speed of the inhibitory process became faster and more efficient. Prior neuroimaging studies using the ANT have found that successful performance on this task is associated with ACC activation [33]. The putative impact of TNS on the ACC seen in this study is consistent with earlier PET findings in adults with depression suggesting that TNS has functional benefits in specific brain regions [21].

As a hypothesis-generating pilot study, we chose not to adjust for multiple testing of outcome variables. Notwithstanding, the level of significance associated with changes on the ANT would survive Bonferroni correction based on 6 ANT subtests ($P < .008$) and is likely to represent a true treatment effect. ANT incongruent reaction time is a primary measure of response inhibition, whereas other ANT subtests reflect other processes related to processing speed and arousal. Significant changes on this one ANT subtest might well represent specific treatment effects on inhibitory functions that are not measured by other subtests. It is less certain that the trend finding on SDRT working memory, which would not survive statistical correction for multiple tests, similarly represents specific treatment effects on working memory or a false-positive result in a small sample.

Based on these and earlier findings, it is possible to hypothesize about the specific mechanisms of action that mediate between TNS and changes in neural circuit activity. It is well established that the trigeminal system projects into the neocortex, including the ACC,

hippocampus, amygdala, thalamus, raphe nuclei, and locus coeruleus [34]. PET data showed engagement of frontoparietal structures following 60 s of TNS exposure with significant increases in regional cerebral blood flow in the anterior cingulate gyrus (bilateral BA 32, 24) and medial/middle frontal gyri of the dorsolateral prefrontal cortex (right BA 6, 8, 45, 46), as well as the inferior frontal gyrus (left BA 44, 6, 22) and parietotemporal cortex (bilateral BA 39, 40) [21]. Results from the current study suggest that TNS exhibits a mechanism of action that might target areas (i.e. frontal and ACC regions) known to be underactive in ADHD [35]. Confirmation of this hypothesis awaits future investigation.

One of the most surprising and compelling findings from the current study was the dramatic improvement detected in several CSHQ subscales that suggests positive TNS benefits on sleep-related anxiety as well as total sleep and bedtime related problems. Improvement in some, but not all, subscales argues against a placebo-driven response, which would be more likely to yield positive changes across the entire instrument. Sleep disturbance is a common symptom that cuts across many child and adolescent psychiatric disorders. Chronic sleep difficulties are particularly problematic in individuals diagnosed with ADHD, autism spectrum disorder, anxiety, and mood disorders. This study should provide the basis for further investigations of the potential utility of TNS as a non-medication therapy for chronic sleep problems.

Also encouraging were the significant improvements in self-reported mood quantified by CDI scores, despite the absence of categorical mood disorders in study participants. The potential mood-enhancing effects of TNS seen in this trial are consistent with emerging results from studies of TNS in epilepsy [5] and adult major depression [7–9]. The possibility that TNS affects identifiable brain circuits and leads to positive changes on dimensions of attention, mood, and sleep quality provides a basis for future investigations that are consistent with research priorities consistent with National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) [36]. Emerging evidence suggests that TNS might prove to be an effective individual or adjunctive treatment for a range of psychopathology.

Several aspects of potential TNS effects on ADHD and associated changes in brain functioning merit further investigation prior to the design and implementation of large-scale efficacy trials. First, validation of an active “sham” TNS treatment is a prerequisite for definitive investigations. Many studies of non-medication ADHD treatments have provided false-positive results due to inadequate blinding of control conditions [32]. Ideally, a “sham” intervention should be identical in all ways to the active intervention with the exception that the device emits no level of stimulation. Attempts to validate a sham intervention in anticipation of definitive controlled trials should include some mechanism to assess whether or not participants are able to guess their correct study assignment. Second, additional work should determine precisely the time-to-onset of treatment effects after initiation of nightly TNS therapy, as well as the durability of treatment effects once TNS is discontinued. Given the current study design, in which the primary behavioral and cognitive outcomes were not collected until the fourth week of treatment, we are unable to assess the duration of TNS required before treatment benefits are evident. This information is critical for determining of the optimal length of larger studies. Finally, further studies that utilize expanded neurocognitive test batteries and brain imaging methods such as electroencephalography are warranted to better characterize the nature of TNS effects on neural circuits and related dimensions of behavior and executive functioning. A mechanistic understanding of these effects is likely not only to inform on the potential of TNS for ADHD, but might also lead to the application of TNS for other brain-based behavioral conditions.

This study has several additional limitations. The small sample size increases the chance of Type II error due to insufficient power to detect real but small treatment effects. This difficulty would be addressed in a properly controlled and powered trial. Similarly, while it is critical to understand if TNS exerts direct effects on ADHD symptoms or indirect effects through potential treatment moderators, such as the presence of comorbid conditions, changes in sleep, mood symptoms, etc., the small sample size precludes this level of analysis. Finally, although all existing evidence suggests that TNS carries minimal risk, identification of significant but infrequent risks will require long-term courses of treatment in much larger patient samples.

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