Brain Stimulation 8 (2015) 299–304

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

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

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ARTICLE INFO

Article history:
Received 2 June 2014
Received in revised form
21 November 2014
Accepted 21 November 2014
Available online 19 December 2014

Keywords:
Attention deficit hyperactivity disorder
ADHD
Trigeminal nerve stimulation
Brain stimulation
Neuromodulation
Clinical trial

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

This study was funded in part by an investigator initiated research grant from NeuroSigma, Inc. (to Dr. McGough). NeuroSigma had no role in project design, data collection, analyses, or conclusions, which are solely the work of study investigators.

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http://dx.doi.org/10.1016/j.brs.2014.11.013
1935-861X/

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.