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Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder: Cognitive and Electroencephalographic Predictors of Treatment Response

Sandra K. Loo, PhD, Giulia C. Salgari, MSc, Alissa Ellis, PhD, Jennifer Cowen, PhD, Andrea Dillon, PsyD, James J. McGough, MD

Objective: The current study applies a precision medicine approach to trigeminal nerve simulation (TNS), a Food and Drug Administration–approved neuromodulation treatment for attention-deficit/hyperactivity disorder (ADHD), by testing secondary outcomes of cognitive and electroencephalographic [EEG] predictors of treatment response among subjects from the original randomized controlled trial.

Method: Children aged 8 to 12 years with ADHD, were randomized to 4 weeks of active or sham TNS treatment, after which the sham group crossed over into 4 weeks of open-label treatment. TNS treatment responders (RESP) had an ADHD Rating Scale (ADHD-RS) Total score reduction of ≥25%, whereas nonresponders (NR) had <25% reduction posttreatment. Assessments included weekly behavioral ratings and pre-/posttreatment cognitive EEG measures.

Results: The final sample was 25 RESP and 26 NR comprising 34 male and 17 female children, with a mean (SD) age of 10.3 (1.4) years. Baseline measures that significantly differentiated RESP from NR included: lower working memory, lower spelling and mathematics achievement, deficits on behavioral ratings of executive function (BRIEF), and lower resting state EEG power in the right frontal (F4) region (all p values <.05). Compared to NRs, responders showed significantly increased right frontal EEG power with TNS treatment, which was predictive of improved executive functions and ADHD symptomatology ($\beta = 0.65$, $p < .001$). When EEG findings and behavior were modeled together, the area under the curve (AUC) for BRIEF Working Memory scale was 0.83 ($p = .003$), indicating moderate prediction of treatment response.

Conclusion: Children with ADHD who have executive dysfunction are more likely to be TNS responders and show modulation of right frontal brain activity, improved/normalized executive functions, and ADHD symptom reduction.

Clinical trial registration information: Developmental Pilot Study of External Trigeminal Nerve Stimulation for ADHD; http://clinicaltrials.gov; NCT02155608

Key words: neuromodulation, electroencephalography, executive functions, BRIEF

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Attention-deficit/hyperactivity disorder (ADHD) is highly prevalent (present in 5–11% of children 4–17 years of age),[1] bears significant cost to the economy (eg, $143 to $266 billion per year),[2] and has a negative impact on the quality of life of affected individuals.[3,4] The consequences of ADHD are lifelong, with ADHD-related impairment persisting in 65% or more cases, regardless of whether formal diagnostic criteria for the disorder are met.[5] As many as 50% of individuals with ADHD have deficits in higher-order problem-solving and self-regulation skills,[6-8] also known as executive functions (EFs), which underlie functional impairments in academic and occupational settings.[9]

Although psychostimulant medications are the gold standard of treatment for ADHD, there has been increasing interest in nonmedication approaches to symptom management because of noncompliance, negative side effects, and nonresponse in a significant minority of patients. Trigeminal nerve stimulation (TNS) is a nonpharmacological, noninvasive, minimal-risk neuromodulation treatment that has demonstrated efficacy for reducing ADHD symptoms in open-label[10] and double-blind, sham-controlled studies, with an estimated effect size (Cohen d) of 0.5,[11] comparable

to that of nonstimulant medications.[12] In the blinded randomized controlled trial (RCT), approximately 52% of participants in the active group showed clinically meaningful improvement, as determined by the Clinical Global Impression—Improvement (CGI-I) scale, compared to 14% with sham by the end of the 4-week trial. Importantly, study analyses confirmed the fidelity of study blinding, further strengthening the integrity of study results. Based on this clinical trial, the US Food and Drug Administration (FDA) issued its first approval of a nonpharmacological, device-based treatment for ADHD among children aged 8 to 12 years in April 2019.

TNS stimulates the V1 branch of the trigeminal nerve and activates several brain regions implicated in ADHD and executive function, including the anterior cingulate cortex and the inferior and middle frontal gyri.[13] In the double-blind study,[11] the active treatment group displayed significantly increased electroencephalographic (EEG) power in the mid- and right-frontal electrodes compared to sham, which was consistent with "bottom-up" effects of subcortical trigeminal nerve activation rather than direct stimulation of frontal cortices by electrodes placed on the forehead.[14] EEG changes were associated with lower ADHD-RS scores, particularly hyperactive—impulsive and total scores at trial end.

Previous EEG studies have reported higher power in the right frontal electrodes with successful stopping within a stop signal task,[15] suggesting an association between the right frontal cortex and inhibitory control. The right inferior frontal cortex, pre-supplemental motor area, and subthalamic nuclei are believed to be part of a fronto-basal ganglia network used in suppression of motor behavior.[16] Thus, it is hypothesized that TNS treatment should also be associated with improvement in executive functions such as inhibitory control. In the open-label TNS study, a significant decrease in flanker task incongruent reaction time was reported after 8 weeks of treatment,[10] whereas secondary outcomes such as cognitive measures have not yet been reported for the blinded trial.[11] The current article will now provide analyses of these secondary outcomes to address potential mechanisms of TNS-associated ADHD treatment response.

Although the ~50% response rate of TNS is promising, principles based on precision medicine suggest that higher response rates might result from targeting the treatment to particular pathophysiological mechanisms underlying an individual patient's symptomatic presentation.[17] Consistent with this approach, this study tests whether baseline cognitive or EEG characteristics are predictors of positive TNS response and associated with ADHD symptom reduction within the original TNS RCT sample.[11] Given prior findings of frontal EEG power modulation with treatment, we hypothesized that (1) lower right frontal EEG power and poor executive functions at baseline would be predictive of positive TNS treatment response; and (2) improvements in these measures would be associated with lower ADHD symptoms among responders. Successful prediction of positive response would aid clinicians and families in the identification of more personalized treatment interventions and economic allocation of treatment costs.

METHOD

Participants

Children aged 8 to 12 years with clinically diagnosed *DSM-5* ADHD, based on semi-structured diagnostic (Kiddie Schedule for Affective Disorders and Schizophrenia [KSADS-PL][18] and clinical interview, clinician-administered ADHD-IV Rating Scale [ADHD-RS)] $\geq$24,[19] baseline CGI—Severity [CGI-S] score $\geq$4,[20] estimated Full Scale IQ $\geq$85 based on Wechsler Abbreviated Scales of Intelligence (WASI)[21] subtests, and the ability to cooperate with EEG and other study procedures were enrolled. Exclusion criteria were current major depression, autism spectrum disorder, lifetime psychosis, mania, seizure disorder, head injury with loss of consciousness, or baseline suicidality. Participants were recruited through community advertisements and Internet postings. Children were medication free for at least 1 month prior to participation and remained off medication throughout the trial. Prior to screening and initiation of any study procedures, parents and children received thorough verbal and written descriptions of study requirements and provided written permission/assent. The UCLA Institutional Review Board approved all study procedures.

Procedures

Detailed methods and procedures for the randomized clinical trial are provided by McGough *et al.*[11] In brief, the study was a 4-week, double-blind, sham-controlled investigation. Participants were randomized 1:1 to active TNS or sham, which was administered nightly during sleep for 4 weeks, after which treatment was discontinued. After a 1-week discontinuation, participants assigned to sham were given the option to cross over into 4 weeks of open-label TNS treatment. Methods pertaining to the sham, including blinding and demonstrating the effectiveness of study blinding, are described in detail by McGough *et al.*[11] A CONSORT diagram for the trial is also available (see Figure S1, available online).

Outcomes

In addition to the screening measures for study inclusion (ie, KSADS-PL, ADHD-RS, CGI-S, and WASI), study

participants were assessed with (1) additional parent-completed behavioral measures of executive function (Child Behavior Checklist [CBCL][22] and Behavior Ratings of Individual Executive Functions [BRIEF])[23]; (2) cognitive tasks (Wechsler Intelligence Scale for Children [WISC-4][24] Digit Span subtest and Wide Range Achievement Test [WRAT-3]);[25] and (3) computerized tests of executive function (Spatial Working Memory [SWM] and Flanker Task)[26,27]; and (4) resting-state electroencephalography. Blinded clinician (ADHD-RS and CGI-I) and parent (BRIEF) ratings occurred weekly throughout the active phase, and (unblinded) bi-weekly during the sham crossover phase of the trial. Cognitive and EEG measures were administered at baseline and the end of week 4 of the active blinded trial, but were not administered at the end of the sham-crossover trial.

TNS Intervention. Stimulation was via a CE-mark−approved neurostimulator, the Monarch eTNS System (NeuroSigma, Inc, Los Angeles, CA). Parents applied self-adhesive patch electrodes centered on their child's forehead, which were worn for 7 to 9 hours nightly and removed each morning. The active condition used a 120-Hz repetition frequency, with 250-μs pulse width, a duty cycle of 30 seconds on/30 seconds off, and stimulator current settings between 2 and 4 milli-amperes (mA) (range, 0−10 mA). Power was provided by 9-volt lithium medical-grade batteries (Energizer L522, Eveready Battery Co, St. Louis, MO), which were recharged and replaced every other day.

Electroencephalography. EEG acquisition followed procedures used in previous studies.[28] Participants underwent EEG recording during a 5-minute, eyes-open resting condition. EEG recording was carried out using Electrical Geodesics (EGI, Eugene, Oregon) GES300 system with 128-electrode sensor nets. Data were referenced to Cz, impedance threshold was set at 50 kOhms (per manufacturer standard), and sampling rate was 1000 Hertz (Hz). Eye movements were monitored by electrodes placed on the outer canthus of each eye for horizontal movements (REOG, LEOG) and by electrodes above the eyes for vertical eye movements.

Continuous EEG data were imported into the EEGLAB[29] environment for processing. The EEG data were preprocessed (high pass filtered (>1 Hz), re-referenced to the common average, noisy electrodes excluded) and decomposed using independent components analysis (ICA), which separates brain from nonbrain (eg, muscle artifact) activities. ICs reflecting nonbrain sources of signal (eg, eye blinks, muscle, artifacts, etc) were excluded from further analyses. Cleaned ICs were back-projected into channel space for resting state analyses. Fourier transform was used to estimate spectral power, which was averaged across all cleaned data and extracted for the following channels: F3/4, Fz, C3/4, Cz, P3/4, PZ in standard frequency bands: delta (1−3 Hz), theta (4−7 Hz), alpha (8−12 Hz), and beta (13−25 hz).

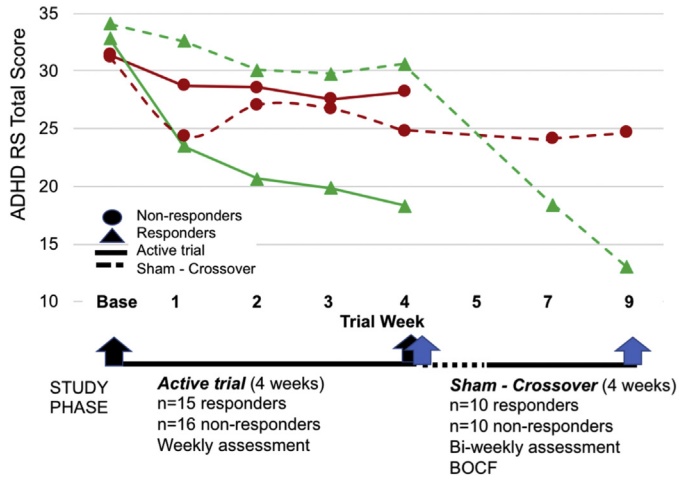
Responder Status. Past studies of ADHD medication treatments have accepted score reductions $\geq$ 25% on the ADHD-RS in designating responder status.[30,31] TNS treatment response for the current study was determined by ADHD-RS Total score using a threshold of $\geq$25% reduction to identify responders (RESP), whereas participants with score reductions <25% were considered nonresponders (NR). To determine responder status, changes between baseline and week 4 ADHD-RS Total score were used for the active blinded trial and changes between week 4 and week 9 ADHD-RS Total score were used for the sham crossover group. Analyses to establish the equivalency of the RESP and NR groups for each phase of the trial were conducted before any subsequent analyses began.

Statistical Analysis

All analyses were conducted in the Statistical Package for the Social Sciences (SPSS v23). To determine whether there is a baseline profile of treatment responders, group differences (RESP/NR) in baseline behavioral and cognitive measures of executive function and right frontal EEG measures were tested using analyses of variance (ANOVAs). Prediction by baseline measures was tested in 2 ways: (1) linear regression analyses were used for prediction of post-treatment ADHD-RS Total scores; and (2) receiver operating characteristic (ROC) curve analysis was used to determine the area under the curve (AUC) for prediction of responder status. The ROC analysis was conducted solely on active trial participants who were blinded during the trial.

Significant baseline predictors of ADHD symptoms were then tested for TNS treatment-related change by responder status and time (pre-/post-TNS) using repeated-measures ANOVAs. Here, the group by time interaction was of most interest, as this would indicate different trajectories of change according to TNS treatment response. For sham crossover subjects, the baseline observation was carried forward so that the week 4 rating was used as pretreatment and the week 9 rating was the posttreatment measurement (Figure 1). This was done to control for any placebo symptom improvement that occurred due to being in the sham condition for the first 4 weeks of the study. Finally, Pearson correlations between baseline predictors and ADHD symptoms were

FIGURE 1 Attention-Deficit/Hyperactivity Disorder (ADHD) Symptom Scores by Study Phase



Note: Blinded treatment was discontinued between weeks 4 and 5 (indicated by dotted line). Sham crossover treatment began week 5. Black and blue arrows indicate pre- and posttreatment measurements for the Active Trial and Sham Crossover groups, respectively. BOCF = baseline observation carried forward; RS = rating scale. Please note color figures are available online.

used to characterize the degree of change occurring in both variables with TNS treatment. Because of the strong age effects, age was used as a covariate of no interest in all EEG analyses. Partial eta squared (partial η^2) was used as the measure of effect size and was interpreted as follows: small, 0.01; medium, 0.06; large, 0.14.[32] To balance hypothesis generation with type 1 error, we used 2 procedures: (1) to reduce the number of contrasts, only variables that were significant at $p \leq .05$ in the baseline profile were further tested for prediction of treatment outcomes and treatment-related change; and (2) a conservative p value of $\leq .01$ was used as the threshold for significance in subsequent analyses.

RESULTS

TNS Responders' Demographic and Clinical Characteristics

Using ADHD-RS Total Score reduction ≥25% as the criteria for response, the active trial had 15 responders and 16 nonresponders. Of the 30 participants originally randomized to the sham group, 20 crossed over and completed 4 weeks of active treatment, of whom 10 (50%) were responders (Figure 1). There were no serious adverse events, and no participant withdrew because of adverse events. As seen in Table 1, the RESP and NR groups in active trial and sham crossover phases did not differ on any demographic or baseline clinical variables, including age, sex, IQ, or SES. The degree of treatment change on the ADHD-RS Total Score was not significantly different between the active trial and sham crossover groups for responders ($F_{1,23} = 1.3$, $p = .26$) and nonresponders ($F_{1,19} = 2.4$, $p = .14$); therefore they were combined together across phases.

TNS Treatment Responder Baseline Profile

Responders were lower on baseline WRAT Spelling ($F_{1,49} = 4.6$, $p = .04$) and Math ($F_{1,49} = 4.1$, $p = .05$), with trends toward lower WRAT Reading ($F_{1,49} = 3.8$, $p = .06$) and WISC Digit Span ($F_{1,49} = 3.3$, $p = .08$) than were nonresponders, but there were no significant differences on flanker task performance (Accuracy, RT, RTSD, all p values >.2) or SWM accuracy ($p > .3$). On the behaviorally rated measures of executive function, the RESP group had significantly worse cognitive functioning (ie, higher t scores) relative to the NR group on the parent-

TABLE 1 Demographic Information for Trigeminal Nerve Stimulation (TNS) Treatment Responders and Nonresponders

	Combined		Active trial		Sham crossover	
	Resp	NR	Resp	NR	Resp	NR
Characteristic	**(n = 25)**	**(n = 26)**	**(n = 15)**	**(n = 16)**	**(n = 10)**	**(n = 10)**
Age, y	10.5 (1.5)	10.1 (1.3)	10.4 (1.4)	10 (1.5)	10.7 (1.8)	10.2 (1.2)
Sex, male, n (%)	11 (44)	23 (88)	5 (33)	14 (88)	6 (60)	9 (90)
SES rank	2 (0.7)	1.8 (0.8)	1.9 (0.9)	1.9 (0.8)	2.1 (0.6)	1.7 (0.5)
IQ	108.1 (13.6)	112.5 (13.3)	108 (12)	113.3 (14)	109.6 (14)	110.6 (18)
CGIS	4.7 (0.5)	4.6 (0.5)	4.7 (0.5)	4.7 (0.5)	4.7 (0.5)	4.6 (0.5)
Baseline ADHDRS Total	31.9 (6.7)	28.9 (7.2)	32.8 (6.4)	31.4 (6.5)	30.6 (7.2)	24.8 (6.5)
ADHDRS tx chg	15.8 (6.6)	2.2 (4.1)	14.5 (6)	3.3 (4.2)	17.6 (7.2)	0.3 (3.3)

Note: Responders and nonresponders within active trial and sham crossover study phases did not differ significantly from each other in demographic or ADHD symptom treatment change. Combined includes both active trial, which was double-blind, and sham crossover, which was open label. All data presented as means and standard deviations unless noted. ADHDRS = ADHD Rating Scale; CGIS = Clinical Global Impression, Severity; IQ = estimated intelligence; NR = nonresponders; Resp = responders; SES = socioeconomic status; tx chg = treatment change after 4 weeks of TNS.

TABLE 2 Trigeminal Nerve Stimulation Treatment Responder Status: Baseline Differences and Prediction of Treatment Response

	Baseline measures			Prediction		
	Responder	Nonresponder		ADHD sxs		Responder status
	Mean (SD)	Mean (SD)	*F*	β [CI]	*t*	AUC (SE)
Child Behavior Checklist						
Sluggish cognitive tempo	66.0 (8.2)	60.3 (8.9)	7.3**	−0.41 [−0.7, −0.1]	−3.1†	0.69 (0.1)
BRIEF Rating Scale						
Initiate	69.8 (10.6)	62.6 (8.7)	7.2**	−0.13 [−0.3, 0.1]	−0.9	
Working memory	76.4 (6.5)	68.0 (6.5)	20.7†	−0.41 [−0.7, −0.1]	−2.9†	0.83 (0.1)**
Planning	73.1 (9.0)	62.7 (8.5)	17.8†	−0.36 [−0.5, −0.1]	−2.6**	0.75 (0.1)*
Organization	61.2 (9.6)	55.5 (6.7)	5.9*	−0.21 [−0.5, 0.1]	−1.4	
Metacognition	73.2 (8.6)	64.9 (6.5)	14.9†	−0.32 [−0.6, −0.03]	−2.2*	0.74 (0.1)*
General executive composite	72.2 (10.3)	66.0 (7.4)	5.8*	−0.79 [−0.3, 0.18]	−0.6	
Wide Range Achievement Test						
Spelling	102.5 (17)	112 (14.1)	4.6*	0.24 [−0.03, 0.3]	1.7‡	
Reading	102.5 (16.3)	111.1 (14.4)	3.9‡			
Math	98.9 (12.4)	108.1 (18.7)	4.1*	0.21 [−0.04, 0.24]	1.5	
Flanker task						
Accuracy	0.66 (0.2)	0.62 (0.2)	<1			
Reaction time	658 (121)	621 (106)	1.2			
Reation time variability	191 (54)	190 (68)	<1			
Working memory						
WISC digit span	9.6 (2.3)	10.8 (2.6)	3.3‡			
SWM accuracy	0.73 (0.1)	0.71 (0.1)	<1			
EEG						
F4 theta (4−7 Hz) power	51.7 (6)	54.7 (4.3)	7.7**	0.43 [0.2, 1.1]	3.0†	0.23 (0.1)
F4 alpha (8−12 Hz) power	49.6 (5.8)	52.9 (3.9)	8.3**	0.44 [0.3, 1.2]	3.2†	0.21 (0.1)

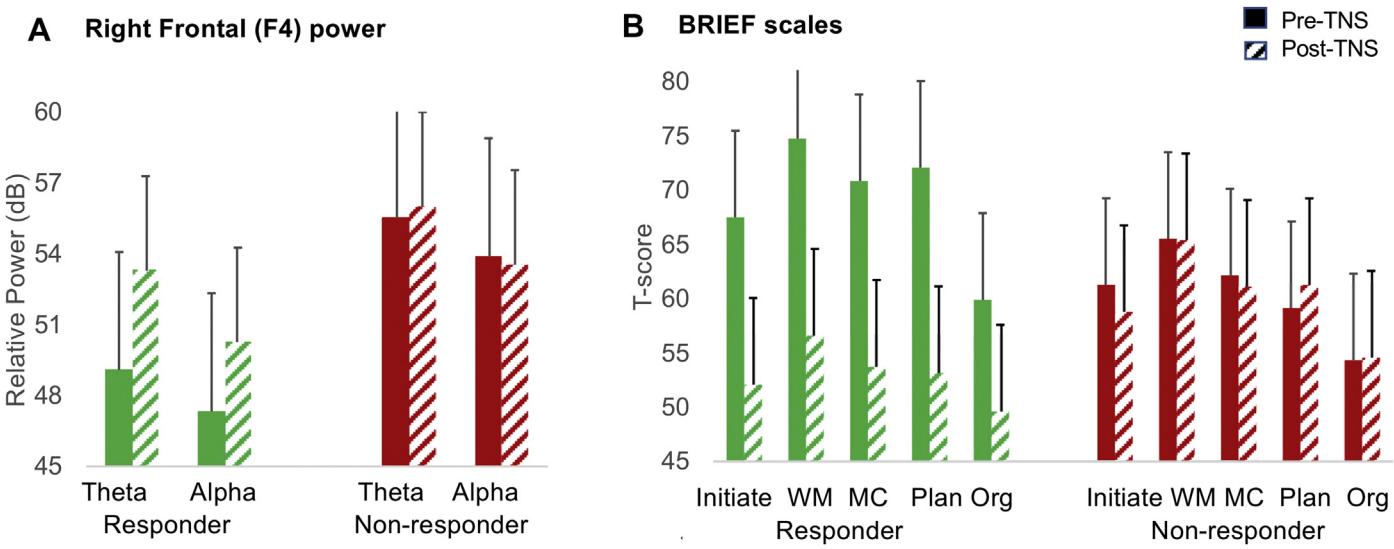
Note: *Responders had poorer cognitive performance and lower EEG power at baseline. BRIEF Working Memory score was the strongest predictor of treatment response and posttreatment attention-deficit/hyperactivity disorder (ADHD) symptoms treatment. ADHD sxs = attention-deficit/hyperactivity disorder symptoms after TNS treatment; AUC = area under curve; β = standardized beta coefficient; BRIEF = Behavioral Ratings of Individual Executive Functions; EEG = electroencephalogram; Hz = Hertz; SWM = spatial working memory; SE = standard error; WISC = Wechsler Intelligence Scale for Children.*
*p <.05; ** p < .01; †p <.005; ‡p <.1.

completed CBCL Sluggish Cognitive Tempo index ($F_{1,49}$=7.3, p = .009) and BRIEF Initiate ($F_{1,49}$ = 7.2, p = .01), Working Memory ($F_{1,49}$ = 20.7, p < .001), Planning ($F_{1,49}$ = 17.8, p < .001), Organization ($F_{1,49}$ = 5.9, p = .02), and Metacognition ($F_{1,49}$ = 14.9, p < .001) scores and the General Executive Composite (GEC) ($F_{1,49}$ = 5.8, p = .02). On EEG measures, right frontal (F4 electrode) spectral power in the theta (4−7 Hertz [Hz]; $F_{1,45}$ = 9.2, p = .004) and alpha (8−12 Hz; $F_{1,45}$ = 9.2, p = .004]) bands was significantly lower among treatment responders relative to the nonresponders (Table 2).

Prediction of Treatment Response

The measures that differed significantly at baseline were then tested for whether the baseline score was predictive of end-of-treatmentADHD-RS Total Score. Several behavioral measures of cognitive dysfunction, such as the CBCL Sluggish Cognitive Tempo (β = −0.40, 95% CI = −0.68, −0.14, p = .004), BRIEF Working Memory (β = −0.40, 95% CI = −0.70, −0.14, p = .004), Planning (β = −0.36, 95% CI = −0.51, −0.08, p = .01), and Metacognition (β = −0.32, 95% CI = −0.57, −0.04, p = .02) subscales were significantly predictive of post-TNS treatment ADHD scores (Table 2). In addition, the EEG right-frontal theta (β = 0.43, 95% CI = 0.2, 1.1, p = .005) and alpha band power (β = 0.45, 95% CI = 0.3, 1.2, p = .003) measures significantly predicted ADHD symptoms after treatment. In contrast, WRAT Spelling (β = 0.24, 95% CI = −0.02, 0.3, p = .09) and Math (β = −0.21, 95% CI = −0.04, 0.24, p = .15) and BRIEF Initiate (β = −0.14, 95% CI = −0.35, 0.11, p = .32), Organization (β = −0.22, 95% CI = −0.48, 0.06, p = .13), and

FIGURE 2 Treatment Change in Right Frontal Electroencephalogram Power and Executive Function Scores



Note: *In panel A (left), responders exhibited increased power in right frontal theta (4–7 Hertz [Hz]) and alpha (8–12 Hz) power, whereas nonresponders showed no change. In panel B (right), Responders generally had pretreatment scores in the clinically impaired range (T score ≥65) on the Behavioral Rating of Individual Executive Function (BRIEF) scales, which improved and normalized (T score <60) with treatment, whereas nonresponders show no changes and generally had a T score >60. Solid bars indicate pre–trigeminal nerve stimulation (TNS) treatment. Diagonal bars indicate post-TNS treatment. dB = decibel; MC = metacognition; Org = organization; Plan = planning; WM = working memory. Please note color figures are available online.*

GEC ($\beta = -0.07$, 95% CI = −0.3, 0.2, $p = .58$) were not predictive of ADHD symptoms posttreatment.

TNS Treatment–Related Change in Cognitive Function and EEG Power

The EEG and BRIEF measures that significantly predicted posttreatment ADHD symptoms were examined for TNS treatment related change. EEG data were collected at baseline and week 4 of the active trial and not for sham crossover participants; therefore EEG treatment changes were limited to the active trial responders. EEG data were missing (because of technical difficulties at baseline or week 4) for 3 participants, 1 from the responder group and 2 from the nonresponder group, leaving 14 participants in the RESP and NR groups for pre–post treatment analyses. Among RESP, TNS treatment resulted in right frontal theta- and alpha-band power increase, whereas the NR group did not (F4 theta: $F_{1,25} = 4.4$, $p = .05$, F4 alpha: $F_{1,25} = 4.1$, $p = .06$, partial $\eta^2 = 0.18$) (Figure 2). Finally, treatment related change in F4 theta was moderately correlated with ADHD symptom change ($r = 0.3$, $p = .14$); however, it did not reach statistical significance.

The BRIEF was collected during the crossover period, thus significant treatment responder effects were tested in the combined active trial and sham crossover groups. To account for placebo effects that may have occurred during the active trial, pretreatment observations for the sham crossover group were moved forward from baseline to week 4, and posttreatment measurement was conducted at week 9. Several BRIEF scales, such as working memory, Metacognition, Initiate, Planning, and Organization, demonstrated significant treatment-related change from pre- to post-TNS measurements (Figure 2). Significant group by time interactions indicated that TNS responders showed significant treatment-related improvement in BRIEF Metacognition ($F_{1,45} = 38.6$, $p < .001$, partial $\eta^2 = 0.47$), working memory ($F_{1,45} = 41.1$, $p < .001$, partial $\eta^2 = 0.48$), Initiate ($F_{1,45} = 18.3$, $p < .001$, partial $\eta^2 = 0.29$), Planning ($F_{1,45} = 36.7$, $p = .001$, partial $\eta^2 = 0.51$), and Organization ($F_{1,45} = 19$, $p = .001$, partial $\eta^2 = 0.30$), whereas NR did not change. Finally, treatment-related change in these BRIEF variables and ADHDRS Total scores were very strongly correlated, with Pearson r values ranging from 0.65 (Planning, $p = 6.5E\text{-}7$) to 0.79 (working memory, $p = 3.0E\text{-}11$), indicating that the BRIEF score changes are commensurate with ADHD symptoms during TNS treatment.

Using the measures that predicted posttreatment ADHD symptoms and the treatment-related change in right frontal EEG power, an ROC curve analysis to predict posttreatment responder status indicated that baseline BRIEF WM score was the strongest predictor (AUC = 0.83, $p = .003$), followed by treatment-related change in F4

theta power (AUC = 0.81, p = .03), BRIEF Planning (AUC = 0.75, p = .02), and BRIEF Metacognition (AUC = 0.74, p = .03); baseline F4 theta and alpha EEG power measures were not significant predictors of responder status (AUC = 0.2, p = .13) (Table 2). Collectively, these results indicate that the BRIEF WM score was the strongest predictor of TNS responder status and modulation of right frontal EEG power was the neural mechanism underlying TNS response.

DISCUSSION

The current study tests secondary outcomes of cognitive and EEG predictors of treatment response from the first successful double-blind, sham-controlled investigation of external trigeminal nerve stimulation treatment, which provided the basis for the first FDA approval of a nonpharmacological, device-based therapy for ADHD.[10] Our current analyses provide analysis of secondary outcomes for a mechanistic basis in understanding TNS effects in ADHD, and suggest that baseline executive function and EEG treatment change might serve as biomarkers predictive of positive treatment outcomes, consistent with the aims of personalized medicine.[17] If confirmed, these findings would represent a successful application of precision medicine in ADHD and potentially provide a simple and cost-effective method to identify patients more likely to respond to TNS therapy.

The data thus far indicate that the best candidates for TNS treatment are children with ADHD who have executive functioning weakness or deficits. Across studies, approximately 50% of children with ADHD show executive dysfunction[6-8], which reflects difficulties with top-down control of attention and response inhibition; this maps well onto the TNS treatment response rate of ~50%.[11] The BRIEF WM scale was a significant predictor of treatment response (AUC = 0.83) and post-TNS ADHD symptoms. In addition, responders were clinically impaired (t score >70) on several BRIEF subscales at baseline, which were subsequently normalized (t score <60) over the course of treatment. Nonresponders, on the other hand showed, virtually no change on BRIEF subscales after 4 weeks of TNS treatment.

Notably, performance on cognitive measures (SWM and flanker task) were not predictive of treatment response, and the pattern of scores differed significantly from the behaviorally rated measures of cognitive function. Low correlation between measures has been widely reported,[33,34] suggesting that they represent different aspects of cognitive functioning. Although performance-based measures such as the SWM or flanker task are thought to measure specific cognitive processes within the context of a controlled environment, behavioral ratings of executive functions encompass a broader set of cognitive skills that are used while functioning in everyday environments. Given our hypothesis of the fronto-basal ganglia network involvement, cognitive tasks that involve motor inhibition may show more treatment-related change in future studies. Pretreatment screening with the parent-rated BRIEF might prove to be a simple and cost-effective measure of identifying patients more likely to respond positively to TNS. This requires confirmation in prospective study.

The neural mechanism underlying TNS treatment effects was increased cortical activity in right frontal regions, which makes sense with the hypothesized TNS neural effects of activation of anterior cingulate, inferior frontal gyrus, and medial and middle frontal gyri including DLPFC.[13] These changes in frontal brain activity are predictive of treatment-related improvement in executive functioning, which in turn drove ADHD symptom reduction. Right frontal brain regions have been implicated by numerous studies in the pathophysiology of ADHD,[35-37] particularly during response inhibition tasks. The data presented here support our hypothesis regarding activation of the fronto-basal ganglia network, as reflected by TNS-related increase in EEG right frontal spectral power, resulting in normalization of executive dysfunction and improved top-down control of ADHD symptoms.

Limitations of this first report of baseline predictors of TNS response include that the current study derives from the original RCT, and all results should be considered exploratory until confirmed via independent replication. Both type 1 and type 2 error rates may be of concern because of the limited sample size. The type 1 error rate was addressed using stepwise analyses and a conservative p value (.01) threshold for significance. Several BRIEF subscales, particularly working memory, survived this correction; nonetheless, the possibility of false-positive findings exists, which should be addressed via replication. Use of sham crossover subjects in the analysis may be a limitation, as they are technically in open-label treatment. However, the baseline observation was carried forward for the sham crossover group, which likely accounted for placebo effects that occurred during the active, double-blind trial. In addition, responders and nonresponders in both the active double-blind trial and sham crossover groups were not significantly different in terms of demographics, ADHD symptoms, or amount of treatment-related change in ADHD symptoms, suggesting that it was appropriate to combine the groups.

In conclusion, TNS is an FDA approved, non-pharmacological, minimal risk treatment that improved ADHD symptomatology and day-to-day executive

functioning via increased cortical activity in the right frontal regions for approximately half of the children who received this therapy. The BRIEF rating scale is commonly used clinically and is easily deployed in community settings, which should facilitate better screening of children who are most appropriate for TNS treatment. Future work on precision medicine approaches for treatment interventions, pharmacological and nonpharmacological alike, is highly feasible and should be ussed more commonly across psychiatric populations. More research is needed on TNS, including but not limited to durability of effects, efficacy for individuals outside of the 8- to 12-year-old range, and additive or interaction effects with other empirically supported ADHD treatments.

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Dr. Loo served as the statistical expert for this research.

Author Contributions
Conceptualization: Loo, McGough
Data curation: Loo, Salgari, Ellis, Dillon
Formal analysis: Loo, Ellis
Funding acquisition: Loo, McGough
Investigation: Salgari, Cowen, McGough
Methodology: Loo, Cowen, McGough
Project administration: Cowen, Dillon, McGough
Supervision: Loo
Writing — original draft: Loo
Writing — review and editing: Loo, Salgari, Ellis, Dillon, McGough

ORCID
Sandra K. Loo, PhD: https://orcid.org/0000-0002-9108-0565
Giulia C. Salgari, MSc: https://orcid.org/0000-0002-9533-303X
Jennifer Cowen, PhD: https://orcid.org/0000-0003-0404-6930
Andrea Dillon, PsyD: https://orcid.org/0000-0002-2151-7776
James J. McGough, MD: https://orcid.org/0000-0001-8007-9086

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Correspondence to Sandra K. Loo, PhD, 760 Westwood Plaza, A7-456, Los Angeles, CA 90095; e-mail: sloo@mednet.ucla.edu

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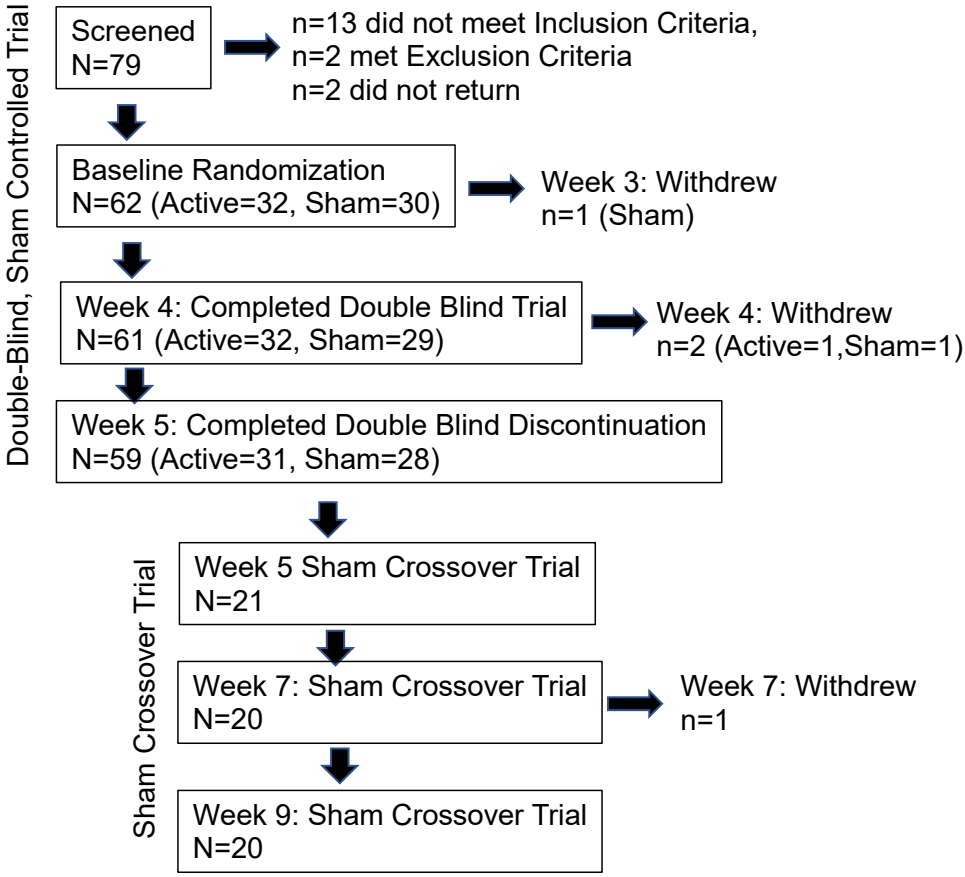
FIGURE S1 CONSORT Diagram for Trigeminal Nerve Simulation (TNS) Active Trial and Sham Crossover Study Phases



Note: Primary outcomes for the Active Trial were presented in McGough et al., *2019.*[11] *Data for the current study represent responders and non-responders during the Active Trial and Sham Crossover study phases.*