Developmental Pilot Study of External Trigeminal Nerve Stimulation for ADHD

NIMH R34 MH101282

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12-Month Open Extension Study of TNS for ADHD
Clinical Trials Registration: NCT03888391

Study Protocol

05/30/2018

LAY SUMMARY

Attention-Deficit/Hyperactivity Disorder (ADHD) is estimated to affect up to 9.5% of school-aged children and 4.4% of adults. ADHD is associated with increased functional impairments, comorbid psychopathology, and overall health care costs. Although various psychosocial interventions are employed, medication remains the mainstay of ADHD treatment. It is estimated that over 2.8 million children in the United States are prescribed psychostimulants, mostly for ADHD. Although these are generally safe and effective in acute treatment, considerable concerns remain about side effects and the absence of demonstrated long-term benefit. Parents are highly ambivalent about using ADHD medications. While there is great demand for non-medication approaches to ADHD, most popular alternatives are not linked to any mechanistic understanding of brain processes and similarly lack significant scientific evidence to support their use.

External trigeminal nerve stimulation (eTNS) is a non-invasive method of brain modulation with demonstrated success in treating adults with medication-resistant epilepsy and depression. In eTNS, the trigeminal nerve receives low current electrical stimulation via an electrode applied to the forehead and worn during sleep. Preliminary adult studies revealed significant improvements in mood, sleep, and attention. PET imaging demonstrated acute eTNS-related activation in brain areas involved in attention and executive functioning. A preliminary pediatric study based on this work assessed the feasibility of eTNS for ADHD. Results demonstrated that eTNS was well tolerated and accepted, and was associated with significant improvements in ADHD symptoms and laboratory measures of response inhibition and working memory.

This R34 proposes a three-year clinical trial development project to further standardize eTNS in preparation for definitive ADHD efficacy trials and to elucidate underlying brain mechanisms that will potentially support use of eTNS in ADHD as well as other behavioral, emotional, and cognitive disorders.

The project is a four-week double-blind randomized trial of active vs. sham eTNS followed by one week follow-up after treatment discontinuation. Participants will have repeated assessments on behavioral ratings, cognitive processes, and cortical activation via electroencephalography (EEG). This study will assess differences in outcome trajectories by condition in the first randomized controlled trial of eTNS for ADHD, validity and fidelity of sham eTNS as a blinded control, time course effects regarding onset and offset of response, and underlying mechanisms of brain change that are associated with treatment outcomes.

Following completion of the 5-week double-blind trial, participants randomized to the sham condition will be offered the opportunity to receive 4 weeks open-label eTNS therapy. All participants who demonstrate positive clinical benefit to active eTNS, whether during the double-blind or open-label phase, will be offered an opportunity to receive 12 additional months of open eTNS treatment. Open-label trial and 12-month extension trial results will be listed under a separate clinicaltrials.gov registration.

The proposal is consistent with several NIMH priorities, including the development of innovative interventions and designs for intervention studies, development of an integrated understanding of brain disorder processes that provide the foundation for understanding mental disorders, and assessment of the mechanisms of action of efficacious interventions in the brain.

SPECIFIC AIMS

This application for a Clinical Trial Planning Grant (R34) seeks to develop external trigeminal nerve stimulation (eTNS), a non-invasive method of direct brain modulation previously shown to be useful in the treatment of medication-refractory epilepsy and depression, as an innovative non-medication therapy for Attention-Deficit/Hyperactivity Disorder (ADHD). The project builds on previous work that demonstrated the initial feasibility of eTNS research in youth with ADHD and its acceptability as an ADHD treatment. The proposed study will assess: 1) the behavioral, cognitive, and cortical activation effects of eTNS in a randomized double-blind active vs. sham eTNS pilot study, expanding results from our previous open trial and assessing fidelity of our proposed sham condition; 2) time to effect-onset during acute treatment and effect-offset following treatment discontinuation, and 3) proposed mechanisms of action and potential effects on cross-disorder dimensional measures of emotion and behavior consistent with Research Domain Criteria (RDoC). The overall focus is to generate additional information necessary for planning and implementation of larger randomized controlled definitive trials for ADHD and to explore potential benefits of eTNS for difficulties with mood, anxiety, and sleep which occur commonly in youth across several diagnostic categories. Our specific aims are:

Specific Aim #1: To examine ADHD symptom trajectories for active vs. sham eTNS and test the fidelity of study blinding in a double blind randomized trial spanning four weeks of acute treatment and one-week follow-up after treatment discontinuation.

Specific hypotheses to be tested include: 1) that participant receiving active eTNS will exhibit improved scores on the investigator completed ADHD IV Rating Scale (ADHD-RS) compared to those assigned to the sham condition; 2) that ADHD-RS symptoms in the active group will decrease over time during acute treatment, 3) that differences on ADHD-RS ratings between active vs. sham conditions will lose significance over time following treatment discontinuation, and 4) that treatment fidelity will be demonstrated such that participants and their parents will not be able to guess assigned treatment at a rate significantly higher than chance.

Specific Aim #2: To assess the underlying mechanisms of eTNS response by examining *condition* and time course effects on measures of executive functioning (response inhibition and working memory), reaction time, reaction time variability, and cortical activation.

Specific hypotheses to be tested include: 1) that score trajectories on the parent completed Behavior Rating Inventory of Executive Functioning (BRIEF) will differ in active vs. sham groups; 2) that trajectories on measures of response inhibition (Attention Network Test) and working memory (Spatial Working Memory Task) reaction time and reaction time variability will differ in active vs. sham groups, and 3) that specific EEG changes with active vs. sham eTNS will reflect increased activation of the anterior cingulate cortex and other frontal regions. Specifically, EEG changes with active eTNS treatment will be: a) lower theta-band (4-7 Hertz (Hz)) and higher gamma-band (30-50 Hz) spectral power in fronto-central regions during working memory and inhibition tasks; and b) higher amplitude error-related negativity (ERN) as reflected by the P50 event-related potential; and c) stronger connectivity between frontal and central sources of theta- and gamma-band spectral power.

Specific Aim #3: To examine the effects of eTNS on secondary measures that include parent and teacher Conners ADHD rating scales, a side effects rating scale, adverse event inquiry, height, weight, cardiovascular effects, sleep, anxiety, and mood.

Specific hypotheses to be tested include: 1) that score trajectories on parent and teacher Conners ratings will differ by condition; 2) that side effect and adverse event frequencies are minimal and do not differ by condition; 3) that height and weight are functions of time without effects from assigned condition; 4*)* that improved dimensions of sleep as measured by the parent completed Children's Sleep Habits Questionnaire (CSHQ) are seen in the active condition, 5) that anxiety dimensions as measured by the parent and child completed Manifest Anxiety Scale for Children (MASC) and mood dimensions measured by the CDI, and 6) that irritability measured by the parent and child completed ARI will improve in the active vs. sham eTNS groups.

Specific Aim #4:   To assess long tern trajectories of clinical response, cognitive outcomes, safety, and compliance in participants who demonstrate acute positive benefits from eTNS therapy during a 12-month open extension.

Specific hypotheses to be tested include: 1) that score trajectories on the ADHD-RS, BRIEF, MASC, CDI, ARI, and CSHQ will remain unchanged from the beginning to end of the open-label extension; 2) that trajectories on measures of working memory and response inhibition will remain unchanged from the beginning to end of the open-label extension; 3) that measurements of height and weight have age-appropriate increases over the open-label extension; 4) that side-effects remain minimal and expected; 5) that compliance remains high.

RESEARCH STRATEGY

A.   Significance

1.   Importance of the problem to be addressed.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder estimated in the United States to affect up to 9.5% of school age children [1] and 4.4% of adults [2]. ADHD is defined by clinically significant and developmentally inappropriate levels of inattentive and/or hyperactive/impulsive symptoms [3]. ADHD is associated with significant functional impairments, including educational underachievement, occupational difficulties, impaired social relationships, increased motor vehicle accidents, and overall increased health care costs, and risk for lifetime comorbid psychopathology, particularly disruptive behavior, antisocial, mood, anxiety, and substance use disorders [4, 5, 6]. A recent review of 19 studies estimates the national annual incremental cost of ADHD to be between $143 and $266 billion (B), with the cost of adult ADHD at $105 to $194B and childhood ADHD at $38 to $72B [85]. The largest costs associated with childhood ADHD were for healthcare ($21 to 44B) and education ($15-25B). ADHD has significant impact on the lives of affected individuals and their families and remains an issue of major public health importance [1].

Neuropsychological deficits are associated with ADHD throughout the lifespan, particularly in those abilities grouped as "executive control" or "executive functions" [8]. Although all children with ADHD do not exhibit full deficits in executive function [9], multiple studies reveal that ADHD-affected youth exhibit deviations in reaction time variability and the acquisition of cortical, top-down processes of executive control and attention regulation [10-12]. These differences are reflected in both structural and functional brain imaging studies that implicate prefrontal-striatal circuits and the frontoparietal control circuit among others [13]. The frontoparietal control circuit, which includes the lateral frontal pole, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, anterior PFC, lateral cerebellum, anterior insula, caudate and inferior parietal lobe, is thought to relate directly to executive function and cognitive control [14, 15]. Several studies revealed hypoactivation in frontostriatal and frontoparietal circuits during inhibitory tasks performed by ADHD children [16, 17]. Others describe hypoactivation specifically in the dorsal ACC during go/no-go, response inhibition, and attention tasks [18-22]. While not specific to ADHD, recognition of dysfunction in these regions provides a basis for targeted interventions with potential implication for treatment of ADHD and other disorders.

Although various psychosocial interventions are employed in ADHD management, pharmacotherapy remains at present the mainstay of treatment [23]. While there is increased availability of non-stimulant medications approved for ADHD, stimulants remain the most widely used class for this disorder with large clinical effect sizes demonstrated in several hundred well-controlled trials [6, 24, 25]. An estimated 2.8 million children in the U.S. receive psychostimulant medication, primarily for ADHD. The robust short-term reduction in ADHD symptoms with acute psychostimulant treatment is one of the best-replicated effects in pediatric psychopharmacology. Numerous studies demonstrate response rates of 65-75% of school-age children during acute treatment [24].

Several small recent studies have suggested that medication use is associated with brain plasticity effects in the direction of typically developing children without ADHD. For example, fMRI studies demonstrate how "typical" attentional circuits are brought on-line with acute stimulant administration [26], and in some cases

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function more efficiently [27, 28]. Stimulant use has been associated with changes in brain structure, particularly in frontal and parietal regions, such as increased white matter volumes, decreased gray matter thinning, and increased cerebellar size that more closely resemble developmental patterns seen in typically developing youth [29-31]. Although these findings are tentative and do not demonstrate causal effects, the potential for administration of medication or other interventions, particularly during critical periods of brain development, that could effect positive and possibly persistent changes in brain networks remains an intriguing area for future research.

Nonetheless, medications for ADHD have notable drawbacks. While usually manageable, stimulants are commonly associated with significant side effects, particularly appetite loss, sleep disturbance, irritability, stomachaches, headaches, and possible growth delays [25, 32]. In contrast with robust short-term improvements in ADHD symptoms, longer-term treatment studies suggest that response rates decrease over time [33, 34]. Finally, although it is necessary to stay on ADHD medication to maintain treatment effects, long-term adherence is poor, with a majority of patients leaving treatment within a year [35, 36]. Several hypotheses have been offered to explain the high rates of medication discontinuation that persist in spite of clearly evident therapy associated improvement. Some evidence suggests that problems with adverse events and tolerability substantially contribute to treatment discontinuation [36]. Others have noted the trend for discontinuation and noncompliance that is seen in management of most chronic conditions, particularly those affecting children [37]. A less discussed, but perhaps more salient reason for discontinuation, is the substantial ambivalence that most parents have about placing their child on ADHD medication and their clear preference for employment of behavioral approaches to manage the condition [38]. Of particular note, disparities in utilization of established pharmacotherapies for ADHD are particularly evident in some African American and Hispanic communities where serious concerns about medication use and safety persist [86]. In spite of this high public support for non-medication based ADHD therapies, traditional psychosocial interventions such as parent management and social skills training are now viewed as generally inferior to medication-only and multimodal approaches [39], and preliminary investigations of alternative therapies, such as EEG neurofeedback, have as yet failed to demonstrate significant benefits [40-42, 87].

Figure 1: Neuroanatomy of the Trigeminal Nerve and Placement of Stimulating Electrodes. Image courtesy of NeuroSigma
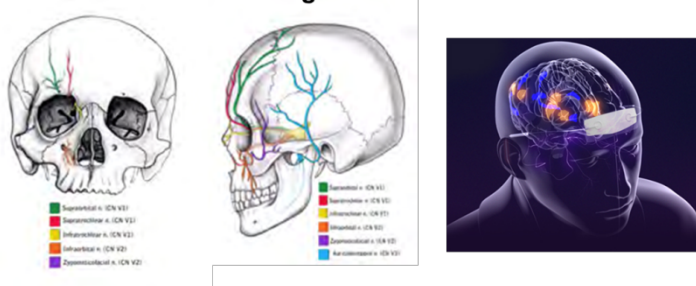
External trigeminal nerve stimulation (eTNS) is a non-invasive method of brain modulation under development at UCLA for treatment of medication-resistant epilepsy and major depression (Fig. 1). In eTNS, adhesive electrode pads are placed externally on the forehead over the trigeminal nerve and connected by thin wires to an external stimulator (approximately the size of an iPod) that is worn on the patient's clothing. The stimulator uses a nine-volt lithium battery to emit a low-grade current, which subsequently stimulates the trigeminal nerve. eTNS was developed as a substitute for two invasive methods of direct brain stimulation, vagus nerve stimulation and deep brain stimulation, which have proven useful in the treatment of epilepsy and depression, but which require surgery, with associated costs and risks, to implant electrodes directly into the vagus nerve or the brain itself. The rational for development of eTNS rests in part on anatomical similarities between the trigeminal and vagus nerves. The trigeminal nerve conveys sensory information from the skin, muscles, and joints of the head [43] and projects extensively with several brainstem structures including the thalamus, cerebellum, and cortex [43-46]. Also like the vagus nerve, the trigeminal has connections with the locus coeruleus, reticular activating system, and nucleus tractus solitarious. Based on the assumption that the therapeutic effects of vagus nerve stimulation rely in part on these connections, it was hypothesized that eTNS would have similar effects. An anti-seizure effect of eTNS was demonstrated in one animal study [47]. Preliminary studies in humans provide initial support for the efficacy of eTNS in treatment-refractory epilepsy [48-50]. Several patients in these epilepsy trials reported significant improvement in mood symptoms, prompting additional investigations for unipolar depression. Small trials in adults with major depression and post-traumatic stress disorder have since been conducted, and suggest that eTNS leads to clinical improvement in patients refractory to standard pharmacotherapies [51-53].

Emerging data on eTNS supports claims of increased utility compared with other methods of neuromodulation, for which enthusiasm has waned. The vagus nerve contains outflow fibers that project to the heart and modulate cardiac activity with potential to slow or even stop it [88]). In response, the U.S. FDA has limited VNS to maximum stimulation frequencies of 30 Hz and to unilateral stimulation. In contrast, the trigeminal nerve does not have any projections to the heart, and the V1 and V2 branches are entirely afferent fibers. Preclinical work with a rodent seizure model demonstrated that the antiepileptic effects of eTNS were far greater at frequencies ≥100 Hz than at 30Hz and significantly greater with bilateral stimulation [89, 90], suggesting that central neuromodulation effects are dependent upon frequency of stimulation and are enhanced by stimulating both hemispheres [91]. These differences likely explain the improved outcomes seen with eTNS vs. TNS and support ongoing research efforts in eTNS. eTNS is non-invasive, administered at home, requires no clinical intervention beyond assessment and monitoring. The FDA has deemed eTNS to be a non-significant risk device based on safety data from our preliminary pediatric study in ADHD (preliminary data). Pivotal Phase II trials are now ongoing for adult treatment refractory depression, post-traumatic stress disorder in veterans, and treatment refractory epilepsy in children. Since 2013, eTNS is available as an approved treatment in Europe and Canada, with treatment costs comparable to costs of brand-name ADHD medications [92]. There is no patient burden using eTNS that exceeds routine outpatient care.

Based on these findings, we conducted a preliminary feasibility study of open eTNS in children with ADHD to assess its potential acceptability as a treatment in the pediatric population and its effects on ADHD symptoms and related measures of cognition (see Preliminary Data). The outcome of this pilot suggests that: 1) eTNS is readily accepted by children aged 7-14 and their families with no practical impediments for treatment compliance; 2) open treatment with eTNS is associated with very substantial reductions in parent and clinician ratings of ADHD symptoms; 3) eTNS is associated with significant improvements on multiple indices of parent-reported executive functioning; 4) eTNS is associated with dramatic improvements in laboratory measures of response inhibition previously reported to rely on ACC function; 5) positive effects of eTNS were seen after 4 weeks of treatment – the first interval measured after baseline, and 6) eTNS is very well tolerated and does not appear to be associated with clinically meaningful adverse events.

Although encouraging, findings suggesting the potential utility of eTNS as an intervention for ADHD require confirmation in blinded controlled trials. Several impediments must be resolved prior to initiation of pivotal studies. Consistent with the stated intent of the R34 mechanism, this application seeks to establish the additional information required for the optimal design and implementation of controlled clinical trials of eTNS for ADHD. Of primary importance is the development of sham or placebo eTNS to serve as comparator with active treatment. Since our initial application, technological developments have enabled creation of an effective inactive sham eTNS treatment, which is identical in appearance and operation to both participants and staff. Use of the sham in blinded trials has now been implemented in studies for other disorders, but the sham has not been validated in ADHD trials nor has any assessment been done in this study group of participants' ability to see through the study blind. The randomized active vs. inactive sham eTNS trial proposed in this application is designed to address this question. Second, differences in outcomes across active and sham conditions would provide an additional signal of potential benefit that would provide additional justification for larger studies beyond that suggested in our initial open trial. Third, although our preliminary work demonstrated behavioral and cognitive changes after four weeks of treatment, more information pertaining to the onset of treatment effects is required as a prerequisite for the appropriate design of definitive clinical trials. Fourth, a similarly unknown and critical issue is the time to offset of clinical effect after cessation of active therapy, which would also influence future trial design and approaches to clinical use of eTNS. Fifth, this preliminary study will allow estimation of treatment effect sizes, which will be critical for future trial design. Finally, additional information regarding the mechanistic effects of eTNS will inform on its clinical application in ADHD as well as its potential for use in other brain-based behavioral disorders.

B.   Approach

1. Project Overview

This three-year developmental study is a double-blind randomized trial of active vs. inactive sham eTNS for ADHD, with four weeks acute treatment followed by an additional week of clinical observation and

testing after treatment cessation. The study will enroll 85-90 participants aged 8-12 years to achieve a completion target of N=36 for each study condition (total final N = 72). Participants will be recruited from UCLA clinical programs and through public advertising and will meet DSM-*5* criteria for ADHD, any current presentation, as established by the Behavior Disorders Module of the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-PL) [55] and clinical interview. Other screening procedures include measures of ADHD symptom severity, other behavioral ratings, and cognitive assessments. Once inclusion/exclusion criteria (see Protection of Human Subjects) have been reviewed and verified, participants will have a pre-treatment visit to establish behavioral and cognitive baseline ratings and to obtain an EEG. Participants and parents will be instructed in the use of eTNS, and participants will begin use of the eTNS as directed during sleep each night. Participants will be randomized 1:1 to active or inactive sham eTNS. Participants, families, and most of the study team will remain blind to treatment assignment. Participants will have weekly assessments over the five week study to assess behavioral, cognitive, and brain activation change and to monitor safety, tolerability, and compliance. Weekly ratings will be obtained from a parent, teacher, and clinician investigator. EEG will occur at baseline and end of treatment (week 4).

2. Preliminary Studies

The Co-PI's and study team have conducted over 13 years of collaborative research on clinical phenomenology, genetics, neurocognitive correlates, EEG profiles, and clinical interventions of behavioral disorders. Several lines of current and past research provide the foundation for the current proposal:

a) Studies of eTNS in Adult Mood and Anxiety Disorders: UCLA investigators remain at the forefront for developing eTNS for epilepsy and behavioral disorders. Dr. Leuchter, project study co-investigator, is currently PI on several current studies examining potential roles for eTNS in treatment of adult major depression (MDD) and post-traumatic stress disorder (PTSD). Recently published studies demonstrate significant improvement in mood symptoms in an open-label study of MDD [56] and in a sham-controlled treatment study in epilepsy [*91*]. Item-analysis of mood disorder rating scales in these studies suggests selective improvements in concentration and attention. Another sham-controlled study in MDD is ongoing and the blind has not yet been broken. According to a functional neuroimaging study using [O-15] positron emission tomography (PET) scans of adults with MDD with and without eTNS, underlying neural mechanisms of action appear to be increased activation of frontal and parietal regions [92] (see Fig. 2). Exposure to TNS resulted in significant increases in regional cerebral blood flow in anterior cingulate gyrus (bilateral BA 32,24) and medial/middle frontal gyri of the DLPFC (right BA 6,8, 45, 46), as

Fig. 2. Areas showing significant activation during TNS

well as the inferior frontal gyrus (left BA 44,6,22) and parietotemporal cortex (bilateral BA 39,40). All regions had peak voxels showing highly significant differences ($p<0.0005$) and significant cluster size ($p_{pcluster\ corr}<0.05$). Results from these studies suggest efficacy of eTNS in placebo-controlled efficacy studies as well as a mechanism of action that may target areas (i.e., frontal and ACC regions) found to be under activated in ADHD [93].
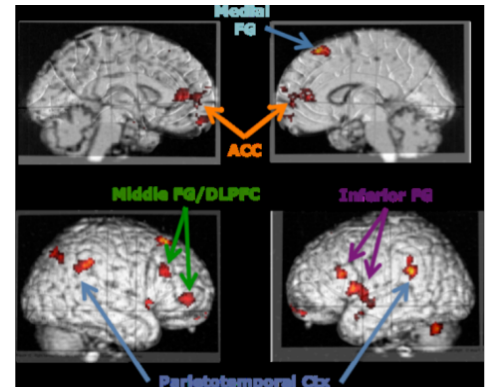
b) Translational Treatment Studies: The investigators have had long-standing involvement in clinical trials for over 15 years. Our recently completed CIDAR Center (P50 MH077248) exceeded its original recruitment goal of 180 and randomized 202 children and adolescents with ADHD over a 37-month recruitment period, supporting the feasibility of our current recruitment targets. We have a cadre of trained experienced research staff able to carry out large-scale, complex, intervention and cognitive assessment protocols involving children, adolescents, and adults with developmental psychopathologies. In CIDAR, we utilized the Attention Network Task (ANT), Go/NoGo and Sternberg spatial working memory (SWM) task to assess cognitive response in a three-arm trial of guanfacine, d-methylphenidate, and the combination. SWM accuracy was significantly improved in the combination group relative to the monotherapies ($p < .05$) and was no longer significantly different from controls ($p>.10$). Similarly, errors of commission were significantly reduced in the combined group when compared with the other medication groups ($p < .05$), but remained marginally different from controls ($p=.08$). In contrast, reaction time (RT) variability was significantly
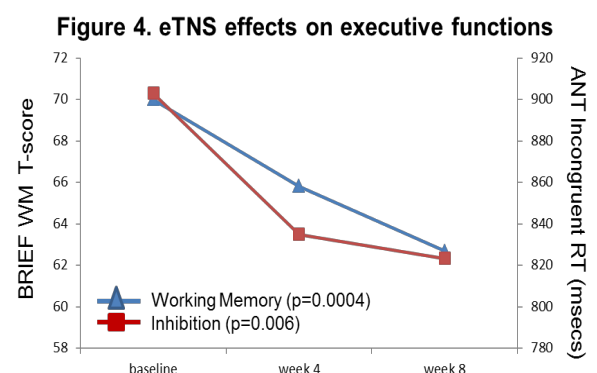
improved in the combined and d-methylphenidate groups compared with guanfacine alone (p < .05) and also normalized relative to controls (p=.89). Results from this work also demonstrate that there are virtually no practice effects on the ANT and SWM tasks, which support their use as repeated measures in the currently proposed study. These studies demonstrate that the cognitive measures we plan to use are sensitive to ADHD medication treatment effects as well as our ability to measure and differentiate cognitive treatment effects in blinded clinical trials.

c) <u>EEG Studies of ADHD and Treatment Correlates</u>: In two studies [61, 62] we have demonstrated possible associations with EEG change and treatment responder status during an inhibition task (Go/NoGo). Additionally, we have examined EEG correlates of acute medication administration on performance on the SWM task with the CIDAR ADHD treatment sample. Shown in Fig. 3 are the EEG effects for the Combined medication group, which improved significantly in SWM accuracy. Independent components analysis of event-related EEG during the maintenance (M) phase suggests that there is a frontal component (see inset Fig. 3), which corresponds with previous findings of frontal midline activation during working memory tasks [63]. In neuroimaging studies, frontal midline theta power has been linked to activation of the anterior cingulate [94]. As shown in the event-related spectra plots (Fig. 3), significant theta band (4-8 Hz) synchronization and gamma (30-50 Hz) desynchronization are apparent during the maintenance interval among ADHD children at baseline relative to controls (p<.05, corrected). With acute medication administration in the ADHD group, theta synchronization and gamma desynchronization are normalized such that they are not significantly different from controls. Further, theta power is significantly associated with SWM accuracy (r=-0.23, p<.05) and number of hyperactive/impulsive symptoms (r=0.21, p<.05). These studies support our EEG hypotheses of decreased frontal midline theta power with eTNS treatment and our ability to assess treatment-associated changes in cortical activation in clinical intervention trials.

Fig. 3 Medication-related normalization of frontal theta power during SWM task
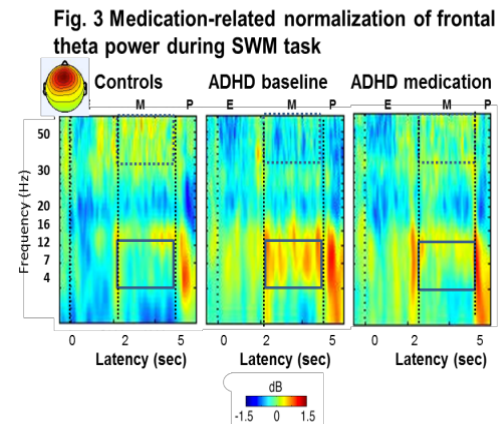
d) <u>Feasibility study of eTNS in pediatric ADHD</u>: Project investigators (McGough, Loo, Leuchter) conducted an 8 week open treatment study in **24** youth with ADHD aged 7-14 to obtain preliminary data on: 1) potential effects of eTNS on ADHD behavioral symptoms; 2) potential effects of eTNS on cognition and executive functioning, and 3) potential tolerability, acceptability, and feasibility of eTNS treatment and eTNS research in children diagnosed with ADHD **[95, 96]** Once inclusion/exclusion criteria were met, participants had a pre-treatment baseline visit to assess ADHD symptom severity and several measures of executive functioning and cognition. Subsequently, participants began eTNS therapy during sleep each night. Participants returned for 8 weekly clinic visits for repeated assessment of behavioral response, tolerability, and compliance. Visits at weeks 4 and 8 also included repeated measurements of cognitive outcomes. The primary outcome variable established *a priori* was the Investigator Completed ADHD-IV Rating Scale (ADHD-RS), which along with CGI scores were completed at baseline, week 4, and week 8. Parents also completed weekly Conners and side effects rating scales.

Sample was 92% male, 75% White, 13% African American, 13% Asian, and 46% Hispanic. Mean age was 10.3 years and mean Full Scale IQ was 100.7. Almost one-half had comorbid oppositional defiant disorder. Strong improvements were noted on the Investigator Completed ADHD-RS (p < .0001) and Conners Parent Index (p < .0001). On the CGI-Improvement Scale, 64 % met response criteria (improved or very much improved) at Week 4, and 71% met criteria at Week 8. Although participants did not have depressive disorders, significant improvement was noted on the Children's Depression Inventory (p= .04) suggesting general mood improvement.   On the Children's Sleep Habits Questionnaire, improvements were detected for selected subscales including Sleep Anxiety (p=.03), Total Bedtime Problems (p < .0001), and Total Sleep Problems (p < .0001).

Figure 4. eTNS effects on executive functions

Working Memory (p=0.0004)
Inhibition (p=0.006)

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eTNS effects on cognitive outcomes. Results from the Behavior Rating Inventory of Executive Functioning (BRIEF), a parent completed measure of participants' executive functioning, demonstrated significant improvements on 7 of 11 subscales (p value range .03 to < .001). The most significant improvement on the BRIEF was on the Working Memory scale ($F_{2,37}$=9.7, p=.0004), as shown in Figure 4. Note that improvement is indicated by a decrease in t-score. On a laboratory measure of executive functioning, the ANT, eTNS had positive effects on response inhibition (see Fig. 4). Results suggest a significant decrease in the reaction time to correctly respond to the ANT incongruent flanker condition ($F_{2,37}$=5.9, p=.006). Over the course of eTNS treatment, the speed of the inhibitory process became faster and more efficient. Neuroimaging studies using the ANT have found that successful performance of this task is associated with activation of the anterior cingulate cortex [64].

These preliminary results provide objective evidence of improvement among children with ADHD due to TNS treatment. There were no clinically significant side effects or adverse events. Treatment compliance and satisfaction were high and families were generally enthusiastic in their participation. While it is acknowledged that placebo effects were not controlled for in this open trial, positive changes on several objective laboratory measures of cognition as well as robust improvements noted on some, but not all, sleep measures, provide further support to behavioral rating scales that suggest potential benefits in ADHD and other pediatric psychiatric conditions. Of particular note was the strength of response demonstrated even in such a small sample. This study demonstrated the feasibility of eTNS research for ADHD in children and points to the eventual need to conduct randomized controlled trials.

3. Summary of Project Visits.

A schedule of study visits and procedures appears in Table 2. Screening procedures may be divided over several days at the convenience of participants, and screening measures obtained in other UCLA clinical or research settings may be used if they were collected within one month of the screening visit. Study baseline visit will be scheduled within one week of study screening, unless participant circumstances necessitate a mild deviation from this timeframe. At the baseline visit, inclusion/exclusion criteria will be verified and participants and parents will be instructed on the proper use of the eTNS stimulator. Participants will be randomized to their study condition, and the eTNS stimulator will be programmed accordingly by the one research assistant privy to randomized assignment. All other study personnel will remain blinded. eTNS treatment will commence at home during sleep after the baseline visit and continue nightly for four weeks. Afterward, data collection will continue for one week following treatment cessation to ascertain offset of any treatment effects. Behavioral ratings, safety assessments, and cognitive outcomes will be collected weekly throughout the study. Participants will be asked whether they believe they are on active or sham treatment after the first week of intervention. At the conclusion of study participation, parents will be asked to complete a questionnaire designed to assess their satisfaction with treatment and their involvement in research.

At end of treatment (Visit 4) treatment will stop. Participants will have one week off treatment and then return for a final assessment visit (Visit 5). After all procedures for Visit 5 are complete, blind will be program and families advised as to which treatment (active or sham) they were assigned. Patients randomized to sham treatment will then have the option to begin 4 weeks of open active eTNS therapy. These participants will return for two subsequent visits at two-week intervals to complete safety and behavioral measures.

At Visits 2 and 3, participants who have access to the Internet can choose to complete study ratings on-line in lieu of an in-clinic weekly visit. If parents are agreeable, the study investigator will contact them by phone each week to complete the ADHD-RS, CGI ratings, concomitant medications, and adverse event inquiry. Height, weight, and vital signs ratings will be waived in weeks that assessments are done away from clinic.

Participants with clinically meaningful improvement on active eTNS treatment, during either double blind or open treatment and defined by a CGI-I score ≤ 2, will be offered 12 additional months of eTNS therapy in an open extension phase (Table 3). Data obtained at the final visit following active treatment, either Visit 4 for those randomized to active eTNS or Visit 7 for those randomized to sham that receive 4 weeks open eTNS treatment, will serve as baseline for the 12 month extension. During the extension, participants will return for

study visits every 3 months to complete behavioral, safety and compliance measures. ADHD and other medications with CNS effects will be permitted if clinically indicated and will be recorded as concomitant medications. Cognitive testing will be repeated at the final study visit, either after 12 months or at early termination.

Table 2. Double Blind Study Procedures.

Visit Number	Screen	Base	1	2	3	4	5	6	7		
Study Week	-1	0	1	2	3	4	5	7	9		
General											
Informed permission/assent	X										MD
Verify inclusion/exclusion		X									MD
Med History/Demographics	X										Parent
Height/Weight	X	X	X	X	X	X	X	X	X		RA
Pulse, Blood Pressure	X	X	X	X	X	X	X	X	X		RA
TNS Randomization		X									RA
TNS Training		X									RA
TNS Diary			X	X	X	X		X	X		Parent
TNS Compliance			X	X	X	X		X	X		RA
Early Impression Question			X								Parent
End double-blind						X					MD
Break blind							X				MD
Begin open treatment							X				MD
End open treatment									X		MD
Clinical Assessment											
KSADS-PL	X										MD
Clinical Interview	X										MD
Saliva Sampling	X										Child
Safety Assessments											
Concomitant meds	X	X	X	X	X	X	X	X	X		MD
Adverse event inquiry		X	X	X	X	X	X	X	X		MD
Side effects rating scale		X	X	X	X	X	X	X	X		Parent
C-SSRS		X	X	X	X	X	X	X	X		MD
Behavioral Ratings											
CBCL	X										Parent
ADHD-RS	X	X	X	X	X	X	X	X	X		MD
CGI-Severity	X	X				X	X		X		MD
CGI-Improvement			X	X	X	X	X	X	X		MD
BRIEF		X	X	X	X	X	X	X	X		Parent
Conners Global Index-P		X	X	X	X	X	X	X	X		Parent
Conners Global Index-T		X	X	X	X	X	X	X	X		Teacher
CSHQ		X	X	X	X	X	X	X	X		Parent
Affective Reactivity Index-C	X					X	X		X		Child
Affective Reactivity Index-P	X					X	X		X		Parent
MASC-child report		X				X	X		X		Child
MASC-parent report		X				X	X		X		Parent
Child Depression Inventory		X				X	X		X		Child

Cognitive Assessments											
WISC subtests	X										RA
WASI subtests	X										RA
WRAT quick screen	X										RA
Spatial Working Memory		X	X			X	X				RA
Attention Network Test		X	X			X	X				RA
Laboratory Assessments											
EEG		X				X					RA
HappyCaFe		X				X					RA
Affective Posner Task						X					RA

Table 3: Procedures for 12 month Extension.

Visit Number	Base	1	2	3	4		
Study Month	0	3	6	9	12		
General							
Height/Weight	X	X	X	X	X		RA
Pulse, Blood Pressure	X	X	X	X	X		RA
Device check	X	X	X	X	X		RA
TNS Diary	X	X	X	X	X		Parent
TNS Compliance	X	X	X	X	X		RA
Replace supplies	X	X	X	X			Parent
Begin open treatment	X						MD
End open treatment					X		MD
Safety Assessments							
Concomitant meds	X	X	X	X	X		MD
Adverse event inquiry	X	X	X	X	X		MD
Side effects rating scale	X	X	X	X	X		Parent
Behavioral Ratings							
CBCL					X		Parent
ADHD-RS	X	X	X	X	X		MD
CGI-Severity	X	X	X	X	X		MD
CGI-Improvement	X	X	X	X	X		MD
BRIEF	X	X	X	X	X		Parent
Conners Global Index-P	X	X	X	X	X		Parent
Conners Global Index-T	X	X	X	X	X		Teacher
CSHQ	X	X	X	X	X		Parent
Affective Reactivity Index-C	X	X	X	X	X		Child
Affective Reactivity Index-P	X	X	X	X	X		Parent
MASC-child report	X	X	X	X	X		Child
MASC-parent report	X	X	X	X	X		Parent
Child Depression Inventory	X	X	X	X	X		Child
Cognitive Assessments							
WISC subtests				X			RA

WASI subtests					X	RA
WRAT quick screen					X	RA
Spatial Working Memory	X				X	RA
Attention Network Test	X				X	RA

* Visit 4 cognitive assessments will be conducted at final visit in case of early termination.

4. TNS Therapy

Equipment - Stimulation is supplied using a CE-mark approved neurostimulator, the Monarch eTNS System^{TM} (NeuroSigma, Inc., Los Angeles CA); NeuroSigma is the exclusive licensee of UCLA's intellectual property around trigeminal nerve stimulation and in August 2012 received CE mark certification for use of the Monarch for adjunctive treatment in epilepsy and major depression in adults and children age 9 and older. The Monarch comprises two elements: the electrical pulse generator and the hypoallergenic, self-adhering custom electrodes for delivery of the signal to the supraorbital and supratrochlear branches of the V1 division of the trigeminal nerve. The system offers features not available in off-the-shelf transcutaneous nerve stimulators, such as limiting the applied current to known safe ranges and two levels of lock-out codes to prevent the device from being used or reprogrammed by the patient. As well, the composition and geometry of the electrodes have been engineered to provide the optimal amount of adhesion to be worn for 7-9 hours with a gel devoid of volatile compounds that are present in most surface electrodes used for nerve stimulation that lead to skin irritation.

The same devices are used for the active and sham treatment conditions. To maintain blinding, the sham system is identical in appearance and in operation: each night the participant applies a patch to the forehead, attaches the patch to the generator with lead wires, turns the device on (after putting in a new battery), presses the "up" button until the stimulation is uncomfortable and then presses "down" to reduce it, or reaches the maximum current the device is programmed to supply. In active units, current flows to the patch and is limited to a safe range. It is likely to produce some sensation, albeit not for everyone. Any sensation experienced generally fades with time. In the sham unit, no current flows, so participants adjust settings without actually controlling current. For this reason, all participants are informed: "pulses may come so fast or so slowly that the nerves in the forehead might or might not detect a sensation." The active condition will employ the same parameters previously studied in ADHD, epilepsy, and major depression: 120 Hz repetition rate, 250 µs pulse width, duty cycle of 30s on: 30s off. The sham is currently being used in a study of PTSD with no evidence that blinding is compromised.

If devices break or malfunction, they will be replaced upon return to study staff. Devices will be returned at the end of study participation.

Randomization - A web-based randomization tool will be implemented by the Semel Institute's Statistics Core (SIStat) as part of the project's centralized data system. Participants will be block-randomized in a 1:1 ratio to active or sham eTNS to maintain group balance throughout the study. A random mixture of block lengths of 4 and 6 will be employed to further ensure preservation of the blind. Randomization will be further stratified by high vs. low screening ARI scores. Access to the randomization system will be restricted via password- protected login, with privileges limited to one designated member of the study team who is responsible for adjusting device settings

Procedures- Procedures for eTNS are based on previous work in epilepsy and depression [48-54]. After collection of baseline measures, a RA will instruct participants in the use of the device, including replacing the batteries, applying the forehead electrode, and general operation of the device. The RA will conduct a brief trial of the stimulator, gradually increasing current to find a level of perceptible stimulation that remains comfortable. The RA will check the device settings and review system use at each subsequent visit. Participants use new electrodes each day. Study staff will provide adequate study supplies at each weekly visit. Parents will maintain a daily diary to quantify nightly use of eTNS, and the RA will confirm compliance at weekly at visits 1 – 4. Additionally, after the first week of treatment at Visit 1, participants and parents will be asked to complete the Early Impressions Questionnaire, a measure designed to assess ability to guess or detect treatment assignment [97] allows us to assess the fidelity of condition blinding. This is administered after

the first week of treatment to avoid judgments about treatment assignment once efficacy differences might emerge.

Participants will receive devices and supplies without cost. If devices break, they should be returned to the study staff and will be replaced. Participants will return the device and any remaining supplies to study staff at the conclusion of their involvement in the study.

5. Clinical Assessment

Determination of eligibility to participant in the project will be based on standard approaches to clinical assessment of ADHD. Diagnostic approaches proposed here are similar to those used in other NIMH funded research studies as well as in the UCLA clinical program:

a) KSADS-PL [55]: A validated, frequently used, semi-structured clinical interview to assess pediatric psychopathology. Although the current instrument was designed to assess DSM-IV defined ADHD it remains suitable for assessment of DSM-5 ADHD as symptoms in each edition are unchanged.

b) Clinical History: Standard psychiatric and medical interview used in UCLA Child and Adolescent Outpatient Clinics and the UCLA ADHD Program.

c) Saliva/DNA sampling: Participants will be asked to provide approx. 5 cc's of saliva in a standard collection tube. Saliva will be sent for DNA isolation

6. Safety Assessments

Although all available evidence suggests that eTNS is acceptable and well tolerated in patient groups, with an absence of clinically meaningful adverse events, standard approaches to safety monitoring and assessment of tolerability will employ the following:

a) Concomitant Medication Inquiry: At each study visit, participants will be asked about medications they might have used since the previous visit.

b) Adverse Event Inquiry: Open-label inquiry about any changes in medical status or behavior since the prior visit.

c) Side Effects Rating Scale: A structured, parent completed assessment of common side effects associated with eTNS.

d) Columbia-Suicide Severity Rating Scale (C-SSRS) [66]: A validated, semi-structured assessment of suicidality commonly used in clinical intervention studies.

7. Behavioral Ratings

Selected measures include either a commonly used instrument to better characterize patients with ADHD (CBCL) or ratings that are commonly used in clinical medication trials of ADHD. Behavioral ratings to be used in this study are:

a) Achenbach Child Behavior Checklist (CBCL) [67]: A well-normed self-report measure assessing a broad range of behavioral problems.

b) ADHD IV Rating Scale (ADHD-RS) [68]: A DSM-IV based rating scale of ADHD symptoms used frequently in clinical trials.

c) Clinical Global Impression-Severity (CGI-S) [69]: A clinician rating of overall illness severity.

d) Clinical Global Impression-Improvement (CGI-I)[69]: A clinician rating of overall improvement from baseline [67].

e) Behavior Rating Inventory of Executive Functioning (BRIEF) [70]: An often-used parental completed questionnaire that assesses a child's executive functioning in home settings.

f) Conners Global Index- parent [71]: A 10-item parent completed rating scale of ADHD-related behaviors with a particular emphasis on externalizing symptoms.

g) Conners Global Index-teacher [71]: A 10-item teacher completed rating scale of ADHD-related behaviors with a particular emphasis on externalizing symptoms.

h) Children's Sleep Habits Questionnaire (Abbreviated) (CSHQ) [72]: A validated parent-report measure that has proved useful in quantifying sleep problems in school-aged children with ADHD

i) Multidimensional Anxiety Scale for Children (MASC) [73]: A self-report scale of pediatric anxiety, both parent and child version will be used.

j) Children's Depression Inventory (CDI) [74]: Standard self-report ratings of depressive symptoms.

k) Affective Reactivity Index (ARI): A recently validated measure of irritability based on parent and child self-report [98].

8. Cognitive Measures

Cognitive measures were selected to assess potential treatment-related changes in brain regions associated with executive functioning and identified in PET studies of adults receiving eTNS for mood disorders. Test of response inhibition and working memory were also selected based on their lack of practice effects and their suitability for repeated testing. A description of these cognitive tests is as follows:

a) Wechsler Intelligence Scale for Children (WISC-IV), Digit Span, Coding [75]: Standardized measure of verbal working memory and processing speed.

b) Wechsler Abbreviated Scale of Intelligence (WASI), Matrix Reasoning and Vocabulary [76]: A brief and reliable assessment of overall intellectual ability, validated with respect to the WISC-IV.

c) Wide Range Achievement Test (WRAT III) [77]: Brief test of reading recognition, spelling, and arithmetic.

d) Spatial Working Memory [79]: The spatial version of the Sternberg delayed match to sample task that provides a measure of working memory.

e) Attention Network Test (ANT) [80]: A test of cued reaction time and response inhibition (conflict resolution).

f) HappyCaFe (Happy-Calm-Fearful) Task, a measure designed for and currently in use in the IRB approved high-risk bipolar disorder study in which participants view photographs of young adults with calm, happy, fearful, and neutral facial expressions and indicate the sex of each by pressing one of two buttons. The measure activates brain regions associated with emotional processing

9. Laboratory Assessments

EEG Acquisition- We will follow procedures used by our laboratory in previous studies. Participants will undergo EEG recording for ~2 hours, which includes baseline (eyes open and eyes closed) and cognitive activation (SWT, ANT) conditions. A head cap fitted with 84 active electrodes positioned according to the International 5%-system [81] will be used, and eye movement detected at the outer canthus of each eye (REOG and LEOG). Recording electrodes are connected to an isolation amplifier that is part of the MANSCAN EEG system (SAM Technology). Stimuli and responses are marked on the EEG record to allow for event-related analyses by stimulus type and response (correct/incorrect). All EEGs will be digitized, which is a process of recording key landmarks (nasion, inion, preauricular notches) and electrode locations to allow 3-dimensional reconstruction of electrode positions on the scalp.

EEG Data Processing- continuous EEG data will be exported from MANSCAN into MATLAB [82] where we will use the independent components (IC) analysis tool in EEGLAB [83] to assess for super-Gaussian (e.g. vertical eye movement) and sub-Gaussian (e.g. EKG) noise and remove it from the data, while maintaining the dataset in its entirety.

IC analyses of event-related spectra- Trials are then sorted according to event type. The data are segmented based on conditions of interest (e.g. SWM: encoding, maintenance, retrieval). Group IC clusters will be found by applying "Measure Product Method" (as implemented in EEGLAB) to the full set of ICs across all subjects. This method finds similarity measures for each pair of components based on scalp maps, ERSP (event-related spectra plots) and ERPs of each component. The similarity measures are then used to identify clusters of components via a clustering algorithm. Treatment-group differences in event-related potentials (i.e., ERN), synchronization (increased gamma power) and desynchronization (decreased theta power) in the frontal component will be tested using permutation tests with multiple-comparison correction.

EEG connectivity analyses in EEGLAB using the SIFT toolbox- The SIFT functions use time-varying (adaptive) multivariate autoregressive modeling to detect and measure fluctuations in event-related effective connectivity between sources of neural activity. This general approach allows for implementation of a number of popular multivariate measures of information flow, such as Granger Causality Modeling and Directed Transfer Function Modeling. To test the present model, sift functions will be constrained to examine effective connectivity between fronto-central theta/gamma band sources, and the time courses of particular connections will be tested between experimental conditions (i.e., active vs. sham treatment) using Bootstrap/resampling techniques to correct for multiple comparisons.

Affective Posner Task -This paradigm allows measurement of brain circuits dealing with frustration and reward, and has previously shown effects in studies of youth with chronic irritability. The task will be performed once at Visit 4, while undergoing EEG and following administration of the SWM and ANT tasks. The paradigm involves 3 individual tasks. For each of these three tasks, a fixation cross will appear in the center of a computer screen followed by 2 boxes arranged horizontally. "Cues" will be designated as one box illuminating blue. Cue locations will be placed 50% in the right and left boxes. Following the cue, a target square will appear inside the right or left box at an unequal rate. Participants will be instructed to respond as quickly and as accurately to the location of the target. For Task 1, 100 trials will be presented and will serve as a non-emotional baseline. Subjects will receive "Good job!" or "Incorrect!" feedback based on their performance. Prior to beginning Task 2, participants will be informed that they will be doing something similar but that they may be able to win some money based on how they perform. The task will consist of 50 trials where subjects will win or lose 25 cents on each trial based on accuracy ("Great Job! Win 25 cents" or "Wrong! Lose 25 cents"). The final and third task will also be similar. However, the feedback will be rigged to induce frustration in participants. On 44% of the correctly identified trials, correct responses will be provided true feedback + monetary reward ("You are Quick! Win 25 cents"). On the remaining 56% of correct responses, participants received rigged feedback, which will inform the participant that he/she was too slow and lost 25 cents ("Too Slow! Lose 25 cents"). Participants will be asked to rate happy/unhappy and calm/aroused feelings about the task, as well as rate their feelings about the rewards and the punishments following each task. These ratings will be completed using an analog scale with very happy/very unhappy or very calm/very aroused on each end.

Once this task is completed, participants will be debriefed about the partial disclosure regarding this set of tasks.

10. Statistical Analysis and Power Calculations

Overview: As a first step we will use graphical and numerical summaries to screen the data for outliers and violations of model assumptions and to assess the need for transformations or non-parametric methods. To check the success of randomization we will compare the groups at baseline on demographic characteristics using t-tests and chi-square tests as appropriate. Any variables that show significant differences will be included as covariates in subsequent models. We will also plot each of the outcome variables as a function of time for each of the study arms to determine the forms of treatment trajectories (e.g. linear, quadratic, piecewise linear with a change in slope at the end of acute treatment.)

Our primary analytic tool will be the general linear mixed model (GLMM), with treatment group (active vs. sham*)*, time, and a group by time interactions as the primary predictors along with subject level random effects. GLMMs properly account for the correlations induced by repeated measurements within subjects and allow for both fixed and time-varying covariates. They also automatically handle missing data, producing unbiased estimates as long as observations are missing at random. This allows the use of all available data from all subjects, thereby minimizing the effects of loss to follow-up and motion artifacts. We note that given the short time period of the study and low expectation of side effects that we expect minimal attrition. Nonetheless, we will compare drop out rates and patterns by treatment arm and if we detect differences will adjust the primary models using a propensity score to minimize potential bias.

Using GLMMs will permit us to seamlessly integrate longitudinal and cross-sectional analyses (for those variables such as adverse effect counts or sessions attended which are available only at end of study), as well as handling both continuous and binary outcomes in a common framework. To make the most efficient use of our data we will fit a single model for each outcome across all time points. Our hypotheses correspond to specific follow-up contrasts concerning the differential treatment effects over the acute intervention and follow-up periods. Post-hoc contrasts can similarly be used to identify the individual time-points at which there are significant differences between groups, which will be important for establishing the minimum necessary treatment period. We are well aware of multiple testing issues and minimize them by identifying a limited set of a priori primary measures and contrasts. However we note that this is a pilot study, designed to identify optimal measures, and protocols for a future definitive efficacy trial; thus identifying potentially meaningful outcome measures and effects is more important than minimizing Type I error. All results will therefore be reported using an uncorrected significance level of α=.05. Below we present a detailed analysis plan by specific aim.

For **Specific Aim 1** the primary outcome measures will be the ADHD-RS, which is administered weekly (a total of 9 time-points starting from baseline). Our primary interest is in group by time interactions during the intervention and follow-up periods, although main effects of group or time would also be of interest. We plan to treat time as a continuous piece-wise linear predictor, allowing for a change in slope at the end of the active intervention period, although as noted above we will explore other possible forms for the outcome trajectories.

For **Specific Aim 2** we will use the same analytic structure with measures of executive function (response inhibition (ANT), working memory (SWM) and the parent completed BRIEF), reaction time, reaction time variability and cortical activation (EEG profiles) as the primary outcome measures. These are also measured weekly except for EEG which is done at baseline, end of treatment, and end of follow-up.

For **Specific Aim 3** we will focus on parent and teacher ratings of ADHD (Conners), physiological measures (height, weight, cardiovascular effects) and sleep (CHSQ), all measured weekly, as well as mood (CDI) and anxiety (MASC), measured 3 times. We will also examine tolerability of the intervention as measured by the side effects rating scale and adverse event inquiries. For the first set of measures we will use the same GLMM structure as in Aims 1 and 2. For the latter measures we will use total scores or cumulative counts over the study period (acute, follow-up, whole study) running standard ANCOVA or Poisson regression analyses with treatment group as the primary predictor.

Power Considerations - We plan to recruit 85-90 subjects total to obtain 72 completers (36 per treatment arm). Power calculations are conservatively based on these numbers; actual power should be higher since our GLMM structure allows us to use information from subjects with partial data. All calculations assume a 2-sided significance level of α=.05 and, where applicable, a moderate correlation of r = .5 between repeated measurements within subjects. Contrasts will be evaluated following significant omnibus tests to minimize Type I error rates. The primary hypotheses for all three aims correspond to group by time interactions over either the acute or follow-up treatment periods covering anywhere from 2 to 5 observations depending on whether the measure was collected weekly or at baseline, end of treatment and end of follow-up. Our design has 80% power to detect an interaction corresponding to a change from no difference at baseline to a difference of d = .59 (with 5 observations) or d = .66 (with 2 observations) at end of treatment (or equivalently a differential change in effect size of that magnitude across the follow-up period). These are just above a standard medium effect size using the conventions of Cohen. We are also interested in a variety of sub-contrasts. For example, we have 80% power to detect a within group change of d = .47 between any two time points and a difference between the treatment groups of d = .65 at any individual time point. In our preliminary study that used the same a dose of eTNS as our proposed active condition, In our preliminary study using the same dose of TNS

as in the proposed active condition, we observed within subject changes of d = 1.9 on the ADHD-RS (Aim 1 primary outcome), d = .46 on the ANT incongruent reaction time (Aim 2) and d = .84 on the Parent Conners ADHD rating (Aim 3) over a four week intervention. If the inactive treatment group remains stable over time then these within-subjects changes would be equal in magnitude to the differential treatment effects and both types of effects would be detectable with our sample size   Indeed, even with a substantial placebo response we would have adequate power for the interactions for the ADHD-RS and Conners. For the cross-sectional analyses in Aim 3 we have 80% power to detect a treatment effect that explains R^2 = 10% of the variability in tolerability or side effect measures. Overall, even under conservative assumptions, we are well powered to detect most effects of interest, and will certainly be able to obtain estimates of effect sizes and minimum treatment intervals to inform a future efficacy trial.

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

This study will recruit approximately 90 children ages 8 to 12 years who meet DSM-*5* criteria for ADHD. After diagnostic and clinical screening, eligible participants and their parents will be trained to administer eTNS each night, usually during sleep. Participants will be randomized to either active or sham eTNS treatment conditions. Participants, families, and most members of the study team will remain blinded to randomized condition. Participants will undergo eTNS for approximately eight hours each night, typically during sleep, for four weeks of acute therapy. Participants will have weekly research visits during the four weeks of treatment and one additional week after active treatment ends. Behavioral ratings and safety measures will be administered at each visit. Cognitive measures will be collected at baseline, end of treatment weeks 1 and 4, and at end of week 5. Additionally, participants will undergo EEG at baseline and week 4. Participation in the full protocol will require a total of 7 clinic visits over a 5-7 week period. Screening, baseline, week 4, and week 5 visits will require between one and two hours of participant time. Other visits will generally require less than one hour for parent completion of questionnaires (approx. 30 minutes). Parent and participant procedures will generally occur simultaneously.   Cognitive testing and EEG will be conducted simultaneously during visits when EEGs are obtained. Patients randomized to sham treatment will have the option of 4 weeks open eTNS treatment beginning after blind is broken at Visit 5. Two subsequent visits at two week intervals will be required to assess safety and behavioral responses. These visits should require approximately one hour of family time. Participants who achieve CGI-I scores ≤ 2 at the end of active treatment will be offered the opportunity to continue eTNS during a 12 –month open extension phase. Visits in this phase will occur every 3 months.

Inclusion criteria are: 1) male and female children ages 8 to 12 years with DSM-5 ADHD, any current presentation, as determined by KSADS and clinical interview; 2) minimum scores of 12 on both the inattentive and hyperactive/impulsive subscales of the baseline ADHD-RS; 3) CGI-S score at baseline ≥ 4; 4) no current medication with CNS effects; 5) parents able and willing to monitor proper use of the stimulation device and complete all required rating scales; 6) estimated Full Scale IQ ≥ 80 based on WASI subtests; 7) parent and participant able to complete rating scales and other measures in English; 8) able to cooperate during EEG.

Exclusion criteria are: 1) impaired functioning to a degree that requires immediate initiation of ADHD medication in the opinion of the parents and/or investigator; 2) current diagnosis of autism spectrum disorder or major depression; 3) history of lifetime psychosis, mania, seizure disorder or head injury with loss of consciousness; 4) baseline suicidality.

b. Sources of Materials

Information about study participants will be obtained through clinical interviews, structured interviews, cognitive testing, brain imaging (EEG), and rating scales completed by the participant's parent/guardian,

teachers, and study clinicians. Parents/participants will be asked to provide authorization for exchange of data between clinical and research databases, as required by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Source documents that might contain indentifying information will be retained in the participant's clinical research chart, which will be stored in a locked file cabinet in our clinical research offices. All data will be collected on Case Report Forms (CRFs). Data will be entered into a password protected electronic database under control of the principal investigator. All entered data will be identified only by the participant's study ID number. No personally identifying information will be entered into the electronic record. The link between the clinical research record and the electronic database will be kept by the PI in a separate locked file. Access to the electronic database will be password protected and limited to study staff.

After conclusion of all research activity and planned analyses, the link between paper based research records and the electronic database will be destroyed. Subsequently, the de-identified electronic database will be available for additional analyses or sharing with other investigators under procedures to be approved by the UCLA IRB. Participant will be informed about the possibility of future sharing of de-identified data on NIH or other government sponsored public research databases.

c. Potential Risks

Risks of Assessment Procedures: There is a chance that participants and/or parents will become upset during initial or subsequent evaluations. Potential risks associated with medical and cognitive testing include 1) embarrassment or anxiety when asked to discuss personal medical history, 2) anxiety about performance during completion of cognitive tests, and 3) fatigue or boredom during cognitive tests and EEG. These risks are not beyond those of a standard medical and psychological assessment and are considered minimal risk. There is also some particular risk of getting upset after administration of the Affective Posner Task. This risk will be minimized by informing participants in the ICF that some procedures won't be explained completely and by debriefing participants about the partial disclosure immediately after completion of the task.

Risks of eTNS: Study stimulators have been used previously and are considered by the FDA to be non-significant risk devices. Tingling or pressure in the scalp or teeth, headache, and eye blinking have been reported, but generally respond to adjustments in stimulus intensity [54]. Risk for these effects, as well as mild discomfort, might occur during the initial dose adjustment. Some patients wearing the device up to 24 hours developed mild skin irritation which responded to decreased wear times and cortisone cream.

Risks of Behavioral Worsening: It is not known if active or sham eTNS will have any effect on ADHD symptoms or cognition. While nothing suggests this is likely, ADHD symptoms could also worsen. Unanticipated negative changes in behavior could also occur. Finally, participants who respond positively might suffer loss of benefits after their participation ends.

Risks of Breaches in Confidentiality: There is a rare possibility, as with any research study, that participant confidentiality will be breached.

The overall risk classification for this project is **minimal risk** with an expectation of participant benefit.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

All procedures for recruitment and informed consent will be reviewed and approved by the UCLA IRB. Parents will be informed about the study in several ways. Families will be solicited through flyers posted in public places and referral from other UCLA ADHD research studies. We may also actively recruit for the study through advertisements on television, radio, or in print media. Once parents initiate contact with study staff they will be provided with a brief study overview of the project, and if interested, undergo initial eligibility screening using an IRB approved telephone-screening script. Eligible families who chose to participate will be scheduled for an initial appointment. It is expected that we will receive a Wavier of Signed Informed Consent for Screening as these procedures are generally deemed minimal risk.

At the initial visit, parents and potential participants will be provided with the IRB approved Parent Permission and Child (ages 8-12) Assent Forms and given time to read and discuss these in a private office. Subsequently, the PI or other physician designee will provide parents and potential participants with a thorough verbal explanation of study requirements, including its purpose, procedures, risks, and potential benefits. Written informed consent forms will be reviewed with the family by the physician investigator to ensure the forms are understood. After reading the permission/assent forms, patients and their parents will queried by the investigator to ascertain their understanding of study requirements and will also be encouraged to ask questions of the investigator. After signing the informed consent forms, families will be provided with copies to take home. The process of informed consent will be documented with a note in the participant's research record and in a CRF. No study procedures will begin until after written permission/assent is obtained.

b. Protections Against Risk

Participants and their families will be informed of the exact nature of all study procedures prior to providing signed permission/assent. All medical and other testing procedures will be conducted in private offices to ensure participant comfort and privacy. A study physician will monitor participants weekly. Parents will be told to contact the study coordinator or physician if the child's behavior deteriorates between scheduled visits, or if unanticipated side effects or other emergencies arise.

Potential adverse events will be assessed and recorded at each study visit with an open-ended adverse event inquiry as well as a structured parent completed rating of expected side effects. The study clinician will assess the severity of any reported adverse event and determine the likelihood of its relation to study procedures.

If at any time an individual participant exhibits one of the following, s/he will be immediately withdrawn from the study: 1) psychiatric hospitalization; 2) CGI-I of 6 (much worse) or 7 (very much worse); 3) clinically significant exacerbation of suicidality as assessed by clinical interview; 4) inability to tolerate TNS; 5) risk of failure in the home, school, or social setting that, in the opinion of a parent or physician investigator, necessitates immediate titration with an approved ADHD medication. Participants who are withdrawn from the study by physicians will be managed clinically in the UCLA ADHD clinical program or referred to other clinically indicated treatment.

Strict standards of confidentiality will be maintained throughout this study. We will take every reasonable precaution to avoid any possibility of unauthorized release of any information gathered in this study. All data entered into the electronic database will be identified by coded participant identifiers only. All paper records containing identifying information (including the participant contact list and linking codes) will be stored in locked files in locked offices under the PI's jurisdiction at UCLA. Participants will remain anonymous in all publications.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

All participants will receive thorough medical and psychiatric evaluations that might assist in future treatment planning. eTNS might also lead to decreases in ADHD symptoms and improved cognition. Ultimately, development of an efficacious non-medication treatment for ADHD will have huge societal and public health benefits.

4. Importance of the Knowledge to be Gained

The results of this study will inform the on feasibility and design choices for future definitive studies of TNS in ADHD. Information derived from this study will be critical in determining whether or not additional research on eTNS in ADHD is warranted. Positive outcomes would support the likelihood of developing eTNS as an effective non-medication treatment for ADHD. Negative results would suggest that additional research on eTNS in ADHD is unlikely to provide benefit, and would therefore help to avoid the expense of larger trials and exposure of larger numbers of participants to an ineffective treatment.

5. Data and Safety Monitoring Plan

The principal investigators will be responsible for monitoring the safety and wellbeing of study participants over the course of this investigation. Participants will be assessed for safety at each study visit by a physician investigator. Parents/patients will also be provided with 24-hour pager numbers and instructed to contact study staff or physician investigators immediately in case of any significant reaction or emergency. All treatment emergent adverse events, side effects, or serious adverse events will be reported as required by the IRB.

Our previous research with TNS for ADHD confirms that these procedures are minimal risk, with virtually no past reports of clinically meaningful adverse events. However, if any unexpected risks are identified, immediate steps will be taken to protect all participants, and the IRB will be contacted according to regulations and requirements.

6. ClinicalTrials.gov Requirements

This project is registered as a clinical trial at the ClinicalTrials.gov Protocol Registration System Information Website (http://prsinfo.clinicaltrials.gov/).

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