Neuromodulation treatments for ADHD: The ABCs of eTNS

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In April 2019, the Food and Drug Administration (FDA) issued the first device approval (FDA, 2019) for a neuromodulation technique called external trigeminal nerve stimulation (eTNS) for the treatment of ADHD among children 8-12 years old. As the primary investigators of the clinical trial and authors of the published results (McGough et al., 2019) upon which the FDA device approval is based, we now present background information, describe the treatment and treatment outcomes more fully, and answer questions that have been frequently asked in ensuing months.

WHAT IS NEUROMODULATION AND WHAT ARE DIFFERENT TYPES OF NEUROMODULATION TECHNIQUES?

While neuromodulation (also called neurostimulation) can broadly refer to a change in nervous system (central, peripheral, or autonomic) activity through the use of an external mechanism such as medication or electrical stimulation, we will focus here on alterations in brain activity that occur as the result of electrical or magnetic stimulation.

The invasive neuromodulation techniques involve implantation of devices that deliver targeted electrical impulses to specific nerves (such as vagal nerve stimulation) or electrodes in certain brain areas (such as deep brain stimulation).

The non-invasive neuromodulation techniques typically involve devices that are used or worn on the outside of the body, on the scalp or forehead, and commonly include transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and external trigeminal nerve stimulation (eTNS). New technologies based on alternating currents, random noise, and ultrasound are emerging rapidly. These non-invasive neuromodulation techniques can be used to assess and manipulate brain network functions as well as, increasingly, for treatment of neurological and psychiatric disorders such as epilepsy, depression, and anxiety.

WHAT IS eTNS?

eTNS is a non-invasive, minimal risk technique that delivers a mild electrical stimulation to the V1 branch of the trigeminal nerves, which are located in the forehead. The trigeminal nerves are part of the peripheral nervous system, which in turn stimulate the central nervous system (i.e., the brain). The FDA-approved device is the Monarch eTNS System manufactured by NeuroSigma Inc (Los Angeles, CA). eTNS is approved for the treatment of epilepsy in the European Union and Canada. It is becoming more widely available in the United States. A prescription is needed for treatment with the device.

WHAT IS THE RESEARCH UPON WHICH THE FDA APPROVAL IS BASED?

A recently published research study included 62 children aged 8 to 12 years old with a diagnosis of ADHD who were randomly assigned to 4-weeks of nightly treatment with active or sham (i.e., placebo) eTNS (McGough et al., 2019). Both researchers and participants were blind to treatment group assignment until the end of the trial. Children with current major depression, autism spectrum disorder, psychosis, mania, seizure disorder, head injury with loss of consciousness, or suicidal ideation were excluded from the study. The primary outcome was change in ADHD symptoms as measured by the ADHD Rating Scale (ADHD-RS). Baseline ADHD-RS scores did not differ significantly between groups, but by the end of Week 4, the active eTNS group exhibited significantly lower ADHD-RS scores when compared to the sham treatment group (p = 0.005). Another measure of clinical improvement, the Clinical Global Impression – Improvement (CGII) scale, also indicated that the treatment group favored active treatment (p = 0.003). Side effects were mild with an increase in appetite/weight, pulse, fatigue, and headache with active treatment. No participants reported serious problems or withdrew from either treatment group. Measures of treatment fidelity suggest that the double blind procedure was effective, meaning that parents and children did not know to which treatment group they had been assigned until the end of the study.

HOW WAS eTNS ADMINISTERED?

eTNS uses a small stimulator (similar to the size of a cellular phone) that is worn during sleep to emit a low-level current. The stimulator was worn on the child's pajamas or T-shirt and attached with thin wires to disposable, silver-gel, self-adhesive patch electrodes. Parents applied patches across their child's forehead to provide bilateral stimulation of V1 trigeminal branches for approximately eight hours nightly. Patches were removed each morning. Per instructions, each night parents turned on the device and pressed the "up" button until the stimulation was uncomfortable or until the device reached the maximum current, and then pressed "down" to decrease it by one 0.1-mA step. In active devices, current flowed to the patch and was limited to a safe range.

Active and sham systems were identical in appearance and operation. The sham group had an electrode on their forehead, but no current so participants adjusted settings without actually controlling current. The active condition

used a 120-Hz repetition frequency, with 250-ms pulse width, and a duty cycle of 30 seconds on and 30 seconds off. Stimulator current settings from 2 to 4 mA (range 0–10 mA) were established at baseline by titration, which identified a stimulation level below the participant's subjective level of discomfort. Power was provided by 9-Volt lithium medical-grade batteries which were replaced every day.

WHAT WERE THE PRIMARY OUTCOMES AND HOW WERE THEY MEASURED?

The primary outcome of the research study was ADHD symptomatology as measured by a clinician (blind to treatment assignment) rated ADHD-RS. For context, the highest possible ADHD-RS score is 54. Baseline ADHD-RS scores for both the active and sham treatment groups were 32 and 33, respectively, indicating that the sample had moderate to severe ADHD. The active treatment group exhibited significant reductions in both inattentive and hyperactive/impulsive behaviors.

Slightly over half of the participants (52%) in the active eTNS group showed improvement that was "clinically meaningful" compared to 14% in the placebo group by the end of the 4-week trial. Clinically meaningful improvement was defined as a participant's score of 1 (very much improved) or 2 (much improved) on the CGI-I scale, a widely used measure of treatment related improvement. Scores were assigned by blind clinician ratings at the end of 4-week treatment.

ARE THE EFFECTS LONG LASTING?

More research is needed to examine this question more systematically. In the clinical trial, ADHD symptom scores worsened for both the active and sham (placebo) treatment groups after one week of discontinuation. While the groups were still significantly different in terms of their ADHD-RS scores ($F(1, 57) = 4.18$, $p = 00.5$), both groups declined about the same amount. Week 4 mean scores for the active and sham groups were 23.39 (standard deviation [*SD*] 7.88) and 27.50 (SD 8.08), respectively, and week 5 scores were 25.52 (SD 7.84) and 29.11 (SD 7.79).

HOW DOES ETNS COMPARE TO MEDICATION TREATMENTS FOR ADHD?

Direct comparison studies of eTNS versus medication treatments or eTNS plus medication have not yet been done. A way to compare efficacy is by examining the effect size of the treatments. Based on the clinical trial results, the estimated treatment effect size (Cohen's *d*) at week 4 was .5, suggesting a medium-size treatment effect. The eTNS effect size of .5 is similar to the .57 effect size of non-stimulant medications (atomoxetine, guanfacine) but smaller than stimulant medications, which have an average effect size of ~.95, which is considered a large effect size (Faraone 2009).

HOW DOES eTNS COMPARE TO NON-MEDICATION TREATMENTS FOR ADHD?

In general, omega fatty acid supplementation, child or parent training and behavioral interventions have received moderate support and cognitive behavioral therapy (CBT), cognitive training, neurofeedback, and herbal interventions/dietary approaches have received equivocal evidence as non-pharmacological interventions for ADHD (Goode et al., 2018). In the current research study, eTNS had a higher effect size than the pooled effects size of nearly all other non-pharmacological treatments. In addition, the study employed rigorous scientific methods such as double-blind placebo control, which is sometimes lacking in these studies. However, more studies of eTNS are needed so that it is possible to look across studies to produce a pooled effect size representing a larger number of children and (ideally) diverse settings.

HOW DOES eTNS AFFECT BRAIN FUNCTION?

eTNS is believed to stimulate the nucleus tractus solitarius, which relays signals to cortical and subcortical structures such as the thalamus, hypothalamus, amygdala, locus coeruleus, reticular activating system, anterior cingulate and insula (Nolte, 1999, Mercante et al., 2017, McGough et al., 2015). A previous positron emission tomography study showed that acute eTNS activated several brain regions implicated in ADHD and executive function, including the anterior cingulate cortex, inferior and middle frontal gyri (Cook, Espinoza, & Leuchter, 2014).

In the clinical research study, the active treatment group displayed significantly increased electroencephalogram (EEG) power in frontal brain regions at the end of active treatment compared to sham treatment. Specifically, significant treatment group by time (i.e., baseline or end of treatment) interactions were found for frequency bands in the mid- (Fz, gamma [30-50 Hz] band, $p = .05$)) and right-frontal (F4, delta [1-3 Hz], theta [4-7 Hz], beta [13-25 Hz], gamma bands, p's = .03-.01) electrodes, with trend level effects for frequency bands in the mid frontal region (Fz delta, theta, beta, p's =-.06-.10). The left frontal region (electrode F3) had effects in the same direction but did not reach statistical significance ($p > .2$ for all comparisons). No significant effects were observed in central or parietal electrodes ($p > .2$ for all electrodes). Pearson partial correlations (controllling for age) suggest that treatment-related power increase in frontal brain regions were associated with lower ADHD-RS scores, particularly total and hyperactive-impulsive scores (r = -.34 to -.41, p<.05) at trial end. These findings are consistent with previous scalp EEG studies, which have reported higher power in right frontal electrodes with successful stopping within a stop signal task (Huster Enriquez-Geppert, Lavalle, Falkenstein, & Hermann, 2013), suggesting a significant 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 frontobasal ganglia network used in suppression of motor behavior (Wessel & Aron, 2017). Taken together, we hypothesize that the neurophysiologic mechanism underlying TNS treatment

effects in ADHD is activation of the fronto-basal ganglia network, resulting in increased EEG power in middle and right frontal electrodes and subsequent improvement in hyperactive and impulsive behaviors.

WHAT FURTHER RESEARCH IS BEING CONDUCTED ON eTNS IN ADHD?

Applications for funding of further research on eTNS in ADHD are underway. Questions of replicability (how well does the treatment effect replicate in independent samples of children with ADHD?), generalizability (will individuals with ADHD of different ages respond to eTNS?), and durability (how long do treatment effects last when eTNS is withdrawn?) are primary. Because the response rate in the first study was 52%, we will examine whether there are measures that predict treatment response. In addition, questions regarding underlying neural mechanisms, effect on long term brain development, usefulness as adjunctive therapy to medication or psychotherapy, and functional effects of eTNS treatment will be studied.

Given the 50% response rate, it is critical to investigate whether there are subject characteristics, behavioral, cognitive, or EEG, that are predictors of positive response to TNS treatment. A recent presentation at a scientific meeting examined this question and the preliminary results are reproduced here. We plan to submit a manuscript on these data in the coming months.

Within the active treatment group, there were 16 responders and 13 non-responders. At trial end, the sham TNS group was allowed to crossover into four weeks of open-label treatment, which resulted in a final sample of 28 responders and 23 non-responders. The responders did not differ from non-responders in age, IQ, gender, socioeconomic status, or baseline ADHD Rating Scale Total Score [ADHD-RS], or degree of change in ADHD scores after four weeks of TNS treatment. - (all p's > .2). At baseline, several measures differentiated eTNS responders from non-responders: lower resting state EEG power in the right frontal region and lower scores on measures of emotion dysregulation such as the Child Depression Inventory (CDI Total Score p = 0.05). Specifically, alpha band (8-12 Hz) power at the F4 electrode was significantly lower in participants in responders when compared to non-responders. Furthermore, using a regression analysis, baseline F4 alpha power significantly predicted post-treatment ADHD-RS scores (β =.45, t =.45, p = .003). In terms of emotional dysregulation, the baseline CDI Total Score significantly predicted post-treatment ADHD-RS Inattention scores (β =.29, t = t = 3.2, p = .05). Finally, treatment responders had worse baseline cognitive functioning as measured by several subscales of the Behavioral Rating of Executive Functions (BRIEF): Initiate, Planning, Working Memory, Organization, and Metacognition (all p's <.05) and the Wide Range Achievement Test (WRAT) Spelling and Math subtests (p's <.05). After eTNS treatment, responders showed significant improvements in BRIEF (general executive composite [GEC]) executive functioning, whereas non-responders were unchanged (p <.001). Strong and significant correlations between treatment change in BRIEF working memory, metacognition, and GEC emerged between treatment changes in ADHD-RS inattention and total scores (r(45) = .58 to .76, p<.001) and repeated measures ANOVAs support a significant responder status by time (pre- to post-treatment) interaction effects (F(1,45) range = 21.4 - 28.7, p <.001). These data suggest that eTNS responders saw corresponding improvements in ADHD symptoms and executive functions with treatment whereas non-responders did not.

To summarize, external trigeminal nerve stimulation is a non-invasive, well tolerated, minimal risk neuromodulation method that has demonstrated efficacy for ADHD in a blinded, sham-controlled trial, with estimated treatment effect size similar to non-stimulants. Children with lower levels of emotional dysregulation as well as poorer executive functions at baseline appear to be more likely to be eTNS treatment responders. The neural mechanism underlying treatment effects may be increased cortical activity in mid- and right frontal regions, which makes sense with the hypothesized eTNS neural effects of activation of anterior cingulate, inferior frontal and medial frontal gyri, and insula (Cook, Espinoza, Leuchter, 2014; Mercante B, Enrico P, Floris G, et al 2017). These changes in frontal brain activity may result in treatment-related improved executive functioning, which occurs commensurate with ADHD symptom reduction. Successful treatment response to eTNS appears to address a number of deficits typically associated with ADHD, however, more research on underlying neural mechanisms as well as independent replication are needed.

IF THE FDA DEVICE APPROVAL IS BASED ON ONE STUDY, IS IT PREMATURE TO TRY eTNS? SHOULD I TRY eTNS FOR MY CHILD?

Most scientists would agree that more research is needed before eTNS will be properly considered an empirically supported treatment for ADHD. After all, the *sine qua non* of science is replication (and independent replication at that), which still needs to occur. On the other hand, this is a minimal risk treatment that is administered at home while the child sleeps. If the child is not responsive to or experiences significant side effects with medication therapy, eTNS, while experimental, may represent one of the better non-medication treatment options for ADHD. Those factors will need to be weighed along with cost (since insurance is not likely to cover in these early days), availability, and other individual factors. As always, we recommend *caveat emptor* (buyer beware).

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Neither of the principal investigators (James McGough, M.D. or Sandra Loo, Ph.D.) have any financial stake or financial relationship in the product or company.

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