Does enhancement of slow oscillation (SO) power during slow wave sleep using auditory closed-loop stimulation improve multiple symptoms of ADHD?

Specific Aims

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental health issues affecting children and adults, affecting over 6 million children in the US (Visser et al., 2015). There is substantial evidence for sleep pathology in ADHD, and short term enhancement of sleep via electrical stimulation has been shown to temporarily attenuate certain deficits associated with the disorder. However, no investigation of the long term, ethologically relevant effects of sleep enhancement on ADHD symptom severity has been done to date. The current treatment for ADHD relies primarily on stimulant medications, which incompletely treat the disorder and have substantial side effect profiles. Thus, there is an unmet demand for alternative treatments.

We propose sleep enhancement as a novel means of non-pharmacological treatment for ADHD. We will test whether boosting slow oscillation (SO) power during nightly slow wave sleep (SWS) using auditory closed-loop stimulation (ACLS) for 3 months reduces the severity of children's ADHD symptoms in the long term. ACLS is a safe, easily engineered method of SO enhancement that uses auditory stimulation delivered in-phase with the subjects own EEG oscillations. We expect that enhancement of SO via ACLS will improve performance on neuropsychiatric assessments used to diagnose ADHD, and will reduce the severity of symptoms measured by subjective reports from the patient, their parents, and their teachers. Our specific aims are:

Aim 1a. Develop a wireless, wearable, unobtrusive, user friendly ACLS device that subjects can wear while they sleep in their own beds.

Aim 1b. Determine if using our device to increase SO power over the long term can produce significant improvements in our objective and subjective measures of ADHD symptom severity.

Our novel ACLS device, if it produces a clinical benefit, will provide a medication-free, noninvasive therapeutic intervention for patients with ADHD that they can use in the comfort of their own homes. Furthermore, if modifying sleep indeed produces reduction in symptoms, we provide further evidence for a sleep dysfunction etiology of ADHD.

Significance

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most common mental health issues in children, affecting between 5% and 11% of children in the US. ADHD is not a purely pediatric disorder, however, and has been shown to frequently continue into adulthood (Visser et al., 2015). Individuals with ADHD show deficits in appropriate allocation of attention, motivation, memory, executive functions, and inhibition of impulsive behaviors or movements which impair functioning in school or work and result in difficulty with maintaining social relationships.

The most commonly prescribed medications for ADHD are stimulants, methylphenidate and amphetamine. Therapy to teach cognitive and behavioral strategies is also available, but is most effective if used in combination with drug treatment. However, as many as 17.5% of children diagnosed with ADHD are not receiving either behavioral or drug treatment (Visser et al., 2015).

The available medications for ADHD have many side effects ranging from mild to severe, a limited time window of effectiveness, and potential for abuse -- and still fail to treat all aspects of the disorder. New research also shows that chronic use of therapeutic doses of amphetamine, one of the most commonly prescribed drug for ADHD in the US (Visser et al., 2015), may also be associated with degeneration of dopamine axons in striatum (Ricaurte et al., 2005). Many parents choose not to treat their ADHD children for fear of these medications. **Our study will be the first to introduce sleep enhancement as an alternate or supplementary treatment for this disorder.**

There is substantial evidence for sleep pathology in ADHD. The symptoms of ADHD overlap substantially with those of sleep deprivation and sleep disorders such as sleep apnea and restless leg syndrome (Konofal, Lecendreux, & Cortese, 2010). Children and adults with ADHD have been repeatedly shown to sleep more poorly than otherwise matched control children without ADHD by several objective and subjective measures of sleep (Cohen-Zion & Ancoli-Israel, 2005). Preliminary evidence that enhancing sleep physiology may improve deficits found in ADHD individuals has begun to surface. Boosting the strength, or spectral power, of the large, slow oscillations (SO) that occur during the deepest stage of sleep, called slow wave sleep (SWS), via transcranial direct current stimulation (tDCS) has been shown to restore ADHD children's long-term memory retention to normal levels (Prehn-Kristensen et al., 2014). The same stimulation also improved performance on a behavioral inhibition task the morning following stimulation (Munz et al., 2015). However, no investigation of the long term, clinically and ethologically relevant effects of sleep enhancement on ADHD symptom severity has been done to date.

Auditory closed-loop stimulation (ACLS, Ngo et al. 2013) has been successfully used to boost SO power in healthy subjects, and has been used to successfully increase overnight memory retention. We choose to use this method over tDCS because it is simpler and equally effective. **This project will design and test a safe, non-pharmacological treatment for ADHD that can be easily implemented in patients' homes, and provides additional evidence for a sleep-dysfunction based mechanism of ADHD.**

Innovation

Interventions targeting sleep physiology have thus far been extremely difficult to implement outside of the lab because sleep recording technology has not caught up to current innovations in wearable tech. We will devise a wearable ACLS device to treat ADHD that can easily be used by patients at home, and allows them to sleep in their own beds. If successful in treating ADHD, this technology provides a much needed alternative or supplement to medications and therapy. Treating sleep may also provide increased clinical benefit for aspects of ADHD that medication improves the least, such as impulsivity. Finally, a better understanding the relationship between sleep and ADHD opens avenues for further exploration of more targeted therapeutics, preventative measures, or genetic interventions for ADHD, and paves the way for further exploration of the role of sleep in other neuropsychiatric disorders.

Approach

To determine whether enhancing SO power can be an effective alternative or supplement to drug therapy in the long term, we will administer ACLS every night for three months, and track subjects progress periodically throughout the duration. We selected this three month study duration to give the treatment enough time for behavioral changes to be detected, and to determine how benefits of this treatment may evolve over time.

ACLS (Ngo et al., 2013) uses EEG recordings to detect slow oscillations naturally generated during slow wave sleep, the deepest stage of sleep. At the peak of these oscillations, a 50ms pulse of auditory pink noise is delivered via in-ear headphones. This in-phase auditory stimulation potentiates further slow oscillations. Our ACLS device will be a wearable headset which includes a prefrontal EEG electrode, two earlobe clip electrodes for reference signal, and in-ear headphones for delivery of the auditory stimulus. EEG computations will be accomplished by a 16-bit microcontroller unit (MCU) coupled to a microcomputer (such as Raspberry Pi) or a 32-bit ARM-based MCU and a real-time digital signal processing (DSP) chip located inside the headset. Whole-night EEG will be recorded to internal storage. We choose to use ACLS rather than tDCS to boost SO power because it is technically simpler to engineer than a tDCS device, and because patients and their caregivers will perceive it to be safer than tDCS: tDCS applies current directly to the patient's brain, and can cause motor or vestibular side effects. ACLS only requires the measurement of brain oscillations from three electrode locations, and only requires delivery of auditory pink noise.

Subjects will be 160 children from the NYC area who have been diagnosed with ADHD. In an attempt to preserve the significant effects of SO enhancement on ADHD children found by Munz (2015), Prehn-Kristensen (2014), and colleagues, subjects will be between the ages of 10-14. In contrast to those works, however, we will include both boys (N = 80) and girls (N = 80) in order to detect possible sexual dimorphisms in ADHD's relationship to sleep.

We will recruit 80 (40 boys, 40 girls) unmedicated children with ADHD, and 80 (40 boys, 40 girls) who are receiving stable drug treatment for ADHD. The patient or his/her parents, must already have decided not to medicate by choice, and cannot cease medication solely to qualify for participation. We will include both medicated and unmedicated children in this study to examine any interactions between our sleep treatment and medication status, but do not want to deprive children of a therapeutic benefit from drugs unless they already choose to abstain. Subjects may withdraw from participation at any time, for any reason.

Half of each group will be randomly assigned to an active stimulation (STIM) condition or a sham stimulation (SHAM) condition (20 boys and 20 girls receiving medication; 20 boys and 20 girls not receiving medication in each condition). Assignments will be double blinded. Subjects in the STIM condition will have ACLS applied during SWS as outlined in the methods detailed by Ngo and colleagues (2013). Subjects in the SHAM condition will be administered a control auditory stimulus during SWS that does not produce SO entrainment.

Before the start of the experiment, subjects, their parents/caregivers, and their teachers will be asked to complete Conners symptom rating scales (Conners, Sitarenios & Parker, 1998). The responses will be collected online for convenience, which we hope will increase subject retention. Subjects will be administered neuropsychological assessments including a Go/No-Go (Munz et al., 2015) task and a Goldman Fristoe Woodcock Test of Auditory Discrimination (TOAD) (Corbett & Stanczak, 1999) to obtain a baseline level of performance. Both measures were selected for their wide usage by clinical practitioners to evaluate ADHD symptom severity. These tests and ratings will be re-assessed three more times, once every 30 days until the end of the study. We will compare these measures of impairment and symptom severity between subjects in the STIM and SHAM conditions, and examine any interactions with sex or medication status. A significant improvement in symptoms between the STIM and SHAM group will indicate whether our treatment has any benefit over placebo, determining whether ACLS is a feasible treatment for ADHD.

Expected Outcomes and Pitfalls:

We will not include healthy control children in this analysis. While ADHD children stand to benefit from any additional therapeutic effects, this study provides no benefits to healthy children. Thus, there is no benefit to healthy children that would outweigh any risk (though minimal) involved in participation. However, we cannot compare our results to the effect of ACLS in control children, and this is a shortcoming of our study.

As the SHAM condition is akin to a placebo condition, some improvement in these subjects' symptoms is expected. However, we expect that children in the STIM condition will experience a greater improvement in ADHD symptoms than children in the SHAM condition. If no difference in symptoms is detected, we can conclude that any effects

of sleep enhancement on ADHD are not large enough to be detectable on the scale of patients' daily functioning, and this type of sleep enhancement is not an appropriate therapeutic for ADHD.

Since this is the first study of its kind, we have no specific predictions about the timecourse of any benefit from treatment, and no predictions on how treatment will differentially affect medicated and unmedicated children, or boys and girls. This study will be somewhat exploratory, and we look forward to learning from any observed effects.

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