Official Title:	Feasibility Open Label Study Evaluating the Use of Process-instructed Self Neuro-Modulation (PRISM) for Attention Deficit/ Hyperactivity Disorder - Adults
NCT Number:	NCT04640766
Study Number:	20-01086
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• August 4, 2022

FEASIBILITY OPEN LABEL STUDY EVALUATING THE USE OF PROCESS-INSTRUCTED SELF NEURO-MODULATION (PRISM) FOR ATTENTION DEFICIT/ HYPERACTIVITY DISORDER- ADULTS

Principal Investigator:	Lenard Adler, MD Department of Psychiatry NYU Grossman School of Medicine, One Park Ave, New York, NY 10016 Lenard.Adler@nyulangone.org 212-263-3580
Additional Investigators:	Glenn Hirsch, MD Department of Psychiatry NYU Grossman School of Medicine, One Park Ave, New York, NY 10016 Lenard.Adler@nyulangone.org 212-263-3580 Marianne Guschwan, MD Department of Psychiatry NYU Grossman School of Medicine, One Park Ave, New York, NY 10016 Lenard.Adler@nyulangone.org 212-263-3580 Deepti Anbarasan, MD Department of Psychiatry NYU Grossman School of Medicine, One Park Ave, New York, NY 10016 Lenard.Adler@nyulangone.org 212-263-3580 Terry Leon RN Department of Psychiatry NYU Grossman School of Medicine, One Park Ave, New York, NY 10016 Lenard.Adler@nyulangone.org 212-263-3580
NYULMC Study Number:	S20-01086
IDE Number:	NSR-device Abbreviated IDE
Study Product:	GrayMatters Health PRISM (investigational device)
Study Product Provider:	GrayMatters Health Ltd.

Initial version: September 22, 2020
Modification 1: December 31, 2020

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor

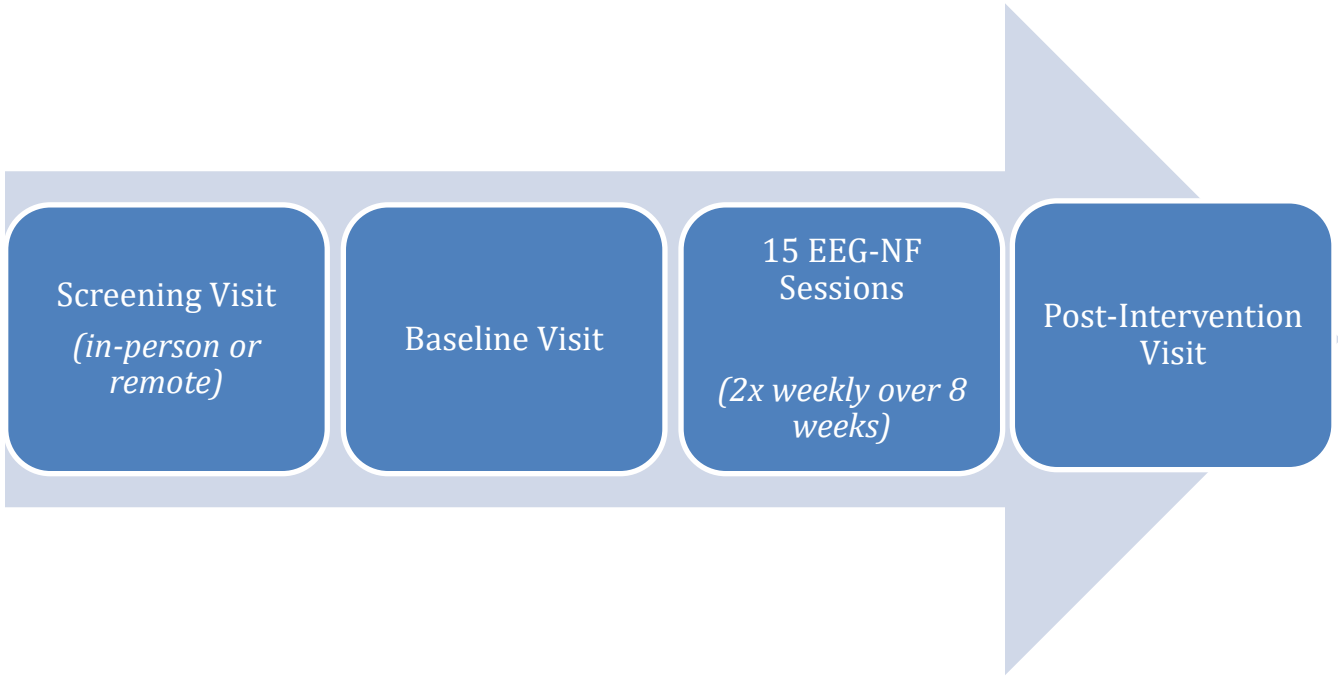
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	FEASIBILITY OPEN LABEL STUDY EVALUATING THE USE OF PROCESS-INSTRUCTED SELF NEURO-MODULATION (PRISM) FOR ATTENTION DEFICIT/HYPERACTIVITY DISORDER(ADHD)-Adults-
Short Title	PRISM ADHD
Brief Summary	This is a single-arm, open-label feasibility study. A maximum of 30 participants will be enrolled. 15 participants will be assigned and will undergo a novel neurofeedback intervention, targeting down-regulation of deep limbic structures, specifically the amygdalae. Participants will complete 15 neurofeedback sessions delivered twice weekly over 8 consecutive weeks. The intervention will be delivered via the PRISM platform.
Phase	Pilot
Objectives	1)Train the NYU team on the electric finger print electroencephalography neurofeedback (EFP-EEG-NF) technology and provide them with hands-on experience; 2) Assess participants' ability to learn the feedback paradigm (i.e. control the EFP-EEG-NF signal; time to achieve learning; assess learning curves); 3) Explore preliminary results assessing emotional dysregulation measured on subsets of AISRS and BRIEF-A.
Methodology	Open label
Endpoint	Primary: Demonstrate the NYU team can successfully recruit, enroll, and complete the protocol as proof of concept and collect high-quality analyzable data; Secondary: Clinically meaningful improvement on primary outcome measures (AISRS and BRIEF-A) demonstrated by effect size of change.
Study Duration	1 year
Participant Duration	11 weeks
Duration of IP administration	8 weeks

Population	Adults ages 18-60 with a diagnosis of Attention Deficit/ and Hyperactivity Disorder-Adults (ADHD) who otherwise meet study inclusion and exclusion criteria.
Study Sites	New York University School of Medicine
Number of participants	30 participants expected to be enrolled; 15 expected to complete the study
Description of Study Agent/Procedure	Neurofeedback sessions will be delivered via the PRISM system. This is a non-significant risk device.
Reference Therapy	N/A
Key Procedures	Clinical evaluation, EFP-EEG-NF training, EFP-EEG-NF sessions, AE evaluation, and participant satisfaction measures.
Statistical Analysis	This is a pilot study and is not formally powered to assess effect statistically. See Statistical Explanation section

Schematic of Study Design



1 Key Roles

Lenard Adler, MD, Principal -Investigator
Department of Psychiatry
NYU Grossman School of Medicine
One Park Ave, New York, NY 10016
Lenard.Adler@nyulangone.org
212-263-3580

Glenn Hirsch, MD, Co-Investigator
Department of Psychiatry
NYU Grossman School of Medicine
One Park Ave, New York, NY 10016
Glenn.Hirsch@nyulangone.org
212-263-3580

Marianne Guschwan MD
Department of Psychiatry
NYU Grossman School of Medicine
One Park Ave, New York NY 10016
Marianne.Guschwan@nyulangone.org
212-263-3580

Deepti Anbarasan, MD
Department of Psychiatry
NYU Grossman School of Medicine,
One Park Ave, New York, NY 10016
Deepti.Anbarasan@nyulangone.org
212-263-3580

Terry Leon RN
Department of Psychiatry
NYU Grossman School of Medicine,
One Park Ave, New York, NY 10016
Terry.Leon@nyulangone.org
212-263-3580

Taylor Sardoff BA
Department of Psychiatry
NYU Grossman School of Medicine,
One Park Ave, New York, NY 10016
Taylor.Sardoff@nyulangone.org
212-263-3580

Donald Goff, MD, Medical Monitor
Department of Psychiatry
NYU Grossman School of Medicine
One Park Ave, New York, NY 10016
Donald.Goff@nyumc.org
646-754-4834

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by problems with sustaining attention, organization, planning, procrastination, day-dreaming, restlessness, impulsivity and hyperactivity. ADHD is most frequently associated with being a disorder impacting children and adolescents, however, its prevalence in the adult population is becoming increasingly more acknowledged. A replication of the National Comorbidity Study estimated approximately 4.4% of the U.S. population aged 18-44 years to meet criteria for adult ADHD (Kessler RC et al. 2006). Recent factor analyses (Adler et al. 2017) have underlined the importance of co-travelling symptoms of executive function deficits, such as difficulty with organization, planning, time management and working memory, in addition to the core symptoms of inattention and hyperactivity-impulsivity addressed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association 2013). According to Barkley and Murphy (2010), executive function deficits define the impairment in ADHD. Executive function deficits can cause impaired attention, impulsive decision making, irritability, and other common symptoms of ADHD (Barkley and Murphy 2010).

Pharmacotherapy is one of the most common forms of treatment for ADHD. Stimulant medications, such as amphetamine (i.e. Adderall- mixed amphetamine salts, Dexedrine-dextroamphetamine) or methylphenidate (i.e. Concerta, Ritalin, Focalin) formulations, have been shown to be highly efficacious treatments for child and adolescent ADHD (Newcorn et al., 2017) and for adult ADHD (amphetamine: Weisler et al., 2017; Spencer et al., 2008; methylphenidate: Bron et al., 2014; Adler et al., 2009).

Stimulant medications come in various dosages: long-acting doses, such as extended-release, that can last all day and short-acting doses, such as immediate-release, that only last a couple hours and can require multiple doses throughout the day. The most common side-effects reported with taking a stimulant are appetite suppression and sleep disruption, more particularly ability to fall asleep (Biederman et al., 2004). Non-stimulant medications are another efficacious treatment option for adults with ADHD. Medications such as atomoxetine (i.e. Strattera) and antidepressants (i.e. Wellbutrin) are commonly used non-stimulants to treat ADHD. Atomoxetine has been shown to be a clinically effective treatment option for ADHD. However, when compared to a stimulant, such as methylphenidate, it has been found that stimulant medications are more effective than non-stimluants (Liu et al., 2017; Newcorn et al., 2017). While pharmacological treatments of ADHD have shown to be very efficacious, they are not preferred by all due to the side effects and draw of psychological treatments. Thus, there is a need to explore alternative and adjunctive therapies to improve outcomes for those with ADHD.

Functional Magnetic Resonance Imaging (fMRI) studies conducted in subjects with ADHD suggest that, compared to healthy controls, those with ADHD may suffer from deficits in brain regions involved in emotion regulation and executive control (Hwang et al., 2015; Shaw et al., 2014). These areas include the amygdala (Maier et al., 2014; Brotman et al., 2010), a central area of the limbic system known as the "emotional brain," and the prefrontal cortex (Passarotti et al., 2010). To date, most findings indicate that, compared to healthy controls, ADHD subjects have increased activity in the amygdala in response to subjective unpleasant or fearful stimuli, and no amygdala activity when shown pleasant stimuli (Tajima-Pozo et al., 2018; Brotman et al., 2010). Furthermore, some studies have shown increased activity in frontal lobe regions associated with emotion processing, regulation and valence; most notably in the medial prefrontal cortex (mPFC) (Posner et al., 2011). Additional studies have found significant negative genetic correlations between ADHD, intracranial volume (ICV) and areas such as the amygdala (Klein et al. 2019).

Such hyperactivity in certain brain regions when viewing unpleasant or fearful stimuli suggests deficits in emotion regulation, which indicates the potential for reversing the pathological process that occurs in ADHD. That is, a relevant mental intervention that involves these areas and pathways may create a process that is opposite in direction relative to the pathology, and which may alleviate and improve the symptoms of ADHD. One of the common tools used for such therapeutic mental intervention is bio-feedback. The source of feedback can be related to blood pressure, pulse, cutaneous conductivity and more. It can also be based on brain activity as measured by EEG or by brain MRI scans; this method is called neurofeedback (NF).

During NF training, subjects are asked to change brain area activity based on feedback derived from signals coming from their own brain, which is mediated by some (visual or auditory) stimulus. The subject is asked to find the mental strategy to influence the characteristics of the stimulus, such as lowering the volume of music played to their ears or changing something visually in a visual interface. A change in stimulus properties is a recurrence of the change in activity in the target area of the brain (Myers & Young, 2012). There is a growing body of studies in the published literature, in which electrical brain activity (assessed using the EEG) served as the source for neurofeedback, as reviewed in:(Van Doren et al., 2019). These studies have shown that, in the context of feedback, humans are able to alter their brain activity and improve cognitive and behavioral control. Moreover, evidence supporting EEG-NF has accumulated as a therapeutic tool for ADHD (meta-analysis by Arns et al., 2020). However,

some studies have found conflicting evidence that does not support EEG-NF as an effective treatment for ADHD (Schonenberg et al., 2017; Cortese et al., 2016).

The significant drawback of existing EEG-NF methods lies in the fact that the EEG device has low spatial resolution, and therefore does not allow the detection of activity originating in deep brain regions, emotional regions known to be associated with ADHD development such as the amygdala, hippocampus and mPFC. In recent years, real-time fMRI (rt-fMRI) has been used to train subjects to regulate deep-area activity (reviewed in (Chiba et al., 2019; Linhartová et al., 2019; Young, 2019)). Multiple studies also show that subjects can be trained to regulate the activity of a network that includes mPFC and limbic areas, and thus can possibly have an effect on ADHD markers such as deficits in inhibition and decision making (Baumeister et al., 2018; Hauser et al., 2014; Vernon et al., 2004). Furthermore, it is also found that by providing fMRI, subjects can be trained to regulate the activities of networks that have been found to be associated with reward processing, an ability that is critical for managing symptoms of ADHD (Baumeister et al., 2019). The disadvantage of this method is that the fMRI test is expensive and cumbersome to the subject, and the MRI device through which it is performed is not portable and its accessibility is low. Relative to fMRI, Electroencephalogram (EEG) constitutes a much more scalable recording device, however, it suffers from the aforementioned drawbacks.

Prof. Hendler's team implemented the amyg-EFP in a neurofeedback (NF) paradigm (termed the amyg-EFP-NF) and demonstrated, through randomized controlled studies, that: healthy individuals can learn to down-regulate the EFP signal (Keynan et al., 2016; Meir-Hasson et al., 2016), and that this translates into down-regulation of the amygdala blood oxygen level–dependent activity (BOLD) activity, as measured by real-time fMRI(Keynan et al., 2016, 2019). This was the first ever EEG-NF intervention that enabled precise, targeted self-modulation of a sub-cortical region. Furthermore, results from these studies demonstrated that participants who were trained outside the fMRI-scanner to down-regulate their amygdala EFP index not only successfully decreased amygdala BOLD activity during fMRI-NF in a following session, but also showed reduced amygdala reactivity to threatening visual stimuli (Keynan et al., 2016). In addition, amyg-EFP-NF led to improved emotion regulation as demonstrated behaviorally by a well-stablished emotional conflict task, and in the neural aspect by enhanced amygdala-vmPFC functional connectivity (Keynan et al., 2019).

2.2 Name and Description of the Investigational Agent

The device to be used in this study (called PRISM) constitutes a non-significant risk device (see rationale below). It is an investigational software under development, intended to be used in research studies testing the clinical efficacy of an innovative paradigm for EEG-based neurofeedback.

Off-the-shelf research-grade EEG hardware (Nautilus: Nautilus Research Wearable EEG Headset, wireless 16 electrode cap and amplifier system) will be used in conjunction with the PRISM software.

The EEG-based neurofeedback device (PRISM) to be used in this study is/does NOT:

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
- For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

2.2.1 Clinical Data to Date

Earlier studies have pointed to hyper-activation of the amygdala as an indication of lower emotional processing and less control of impulsivity in those with ADHD (Tajima-Pozo et al., 2018; Brotman et al., 2010), and suggested that down-regulating or reversing its activity may address emotional reactivity and regulation deficits common in ADHD patients (Schulz et al., 2014).

The amyg-EFP-NF method was thus applied in a randomized controlled study (NCT02020265) involving a large cohort of healthy military cadets undergoing stressful boot camp training (Keynan et al., 2019). Results indicated that repeated amygdala-EFP training sessions, as compared to a common form of EEG-neurofeedback, based on the alpha/theta ratio, had a beneficial effect on neural and behavioral indices of stress resilience, pointing at EFP-NF as a plausible, scalable, non-pharmacological yet neuroscience-based training method to prevent stress-induced psychopathology.

Amyg-EFP-NF was further tested in a randomized controlled trial (NCT02544971) aimed at down-regulating amygdala activity in PTSD patients. Results showed that patients learned to volitionally down-regulate their Amyg-EFP signal and demonstrated reduction in PTSD symptoms, compared to the No-NF (control) arm (Fruchtman-Steinbok et al., 2019). Here too, superior down-regulation of amygdala BOLD signal during fMRI-NF following the intervention in the treatment arm, compared to controls, confirmed target engagement. These results establish the Amyg-EFP as a plausible, mechanism-driven, intervention for PTSD.

Finally, in a separate line of research, EFP-NF was administered to patients suffering from Fibromyalgia, a chronic pain syndrome that involves, among other symptoms, sleep disturbance and emotion dysregulation (Goldway et al., 2019). These symptoms are known to be mediated by heightened limbic activity and so it was speculated that Amyg-EFP-neurofeedback training aimed at limbic down modulation (relative to sham-training) would improve the clinical status of Fibromyalgia patients. Results indeed revealed an improvement in objective sleep measures as well as delayed improvement in chronic pain and subjective sleep experience, indicating that EFP-NF may serve as a novel approach to treat Fibromyalgia.

Altogether, these studies conducted by the Hendler lab demonstrate GrayMatter Health's ability to develop and utilize a scalable EEG-NF probe in order to precisely modulate deep mesolimbic sub-cortical regions, such as the amygdala. Importantly, the effects of the NF training via the EFP were not restricted to neural indices, but also facilitated real-life psychological changes in

regulating stress, suggesting its potential in modifying other regulatory mechanisms, such as emotion regulation. To date, there have been no studies testing Amyg-EFP-NF on patients, more specifically adults, with ADHD. This pilot study serves to set the course for the analyzing how this tool can help regulate symptoms or behaviors common in ADHD patients.

2.3 Rationale

Approximately 4.4% of the U.S. population aged 18-44 years meet criteria for adult ADHD based on a replication of the National Comorbidity Study (Kessler RC et al., 2006). ADHD is a neuropsychiatric disorder characterized by problems with sustaining attention, organization, planning, procrastination, day-dreaming, restlessness, impulsivity and hyperactivity. Psychostimulant medications are the mainstay for treating ADHD as they have shown to be highly effective in symptom reduction. Non stimulant medication is highly recommended as a first-line of treatment for ADHD as well for those who cannot tolerate the side effects some stimulant medications may carry. Psychological treatments have been found to be moderately effective for treating ADHD. Compared to pharmacotherapy, the effect sizes are smaller but the promise for treating ADHD with nonpharmacological interventions is there (Cortese et al., 2015; Sonuga-Barke et al., 2013). Cognitive Behavioral Therapy (CBT) has been shown to be efficacious in improving symptoms of ADHD in various clinical and randomized controlled trials. Especially when combined with a pharmacotherapy, CBT has shown positive results in controlling symptoms of ADHD (Ramsay & Rostain 2014). However, the evidence basis for psychosocial therapies as a stand-alone treatment for ADHD still require more research. Thus, there is a clear need to expand upon the nonpharmacological evidence base and explore alternative and adjunctive therapies to improve outcomes for patients with ADHD. This pilot study will demonstrate that the NYU team can successfully recruit, enroll, and complete the protocol as proof of concept and collect high-quality analyzable data in preparation for later clinical trials.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Risk of Breach of Confidentiality: Participation in research involves potential loss of confidentiality or privacy. To mitigate this risk, research records will be kept as confidential as possible through use of a coding system with linkage restricted to IRB-approved NYU study personnel. All data will be stored confidentially, as described in sections 11 and 13.5.

Risk of Assessment Procedures: There are no known psychological risks associated with the clinical interview or questionnaires used in this study and all have been used extensively in clinical populations. It is possible that discussion about psychiatric symptoms may cause emotional discomfort or temporary distress in some participants. To mitigate this risk, the consent form will fully inform participants about the nature of the information to be disclosed and that they may refuse to answer individual questions or withdraw from the study in its entirety at any time. Qualified research staff is available to provide support to participants who experience emotional distress. Elevated distress (e.g. anxiety) is not expected to persist beyond the timeframe of the assessment.

Risk of Neurofeedback Procedures:

The EEG test is a tool that is routinely used in medicine for recording brainwaves. The received signals are based on the electrical activity of the brain. There is no known risk in EEG recording; however the EEG electrodes may cause slight discomfort. If there is a great deal of discomfort, the examination will be terminated at the request of the participant. EEG electrode contact with the scalp is augmented using special gel that is applied to the scalp. This gel can easily be removed by washing the hair after the neurofeedback session.

2.4.2 Known Potential Benefits

Participants may or may not experience clinical benefit from this study. Aspects of study participant likely to provide direct benefit to participants include close psychiatric monitoring.

3 Objectives and Purpose

3.1 Primary Objectives

The primary objectives of this pilot study are as follows:

1. To train the NYU team on EFP-EEG-NF technology and provide them with hands-on experience.

2. To assess participants' ability to learn the feedback paradigm (i.e. control the EFP-EEG-NF signal; time to achieve learning; and assess learning curves).

3. To explore preliminary results assessing emotional dysregulation measured on subsets of AISRS and BRIEF-A.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a single-arm, open-label feasibility study. 30 subjects will be screened and consented for a maximum enrollment of 15 participants. All participants will undergo a novel neurofeedback intervention, targeting down-regulation of deep limbic structures, specifically the amygdalae. Participants will complete 15 neurofeedback sessions delivered twice weekly over 8 consecutive weeks. The intervention will be delivered via the PRISM platform. Parts of this study will be conducted in clinic and parts are conducted remotely. Clinician assessments and self-questionnaires will be done remotely. The Prism intervention will be conducted in the clinic.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Demonstrate the NYU team can successfully recruit, enroll, and complete the protocol as proof of concept and collect high-quality analyzable data.

4.2.2 Secondary Study Endpoints

30% meaningful improvement on primary outcome measures (AISRS and ASRS/BRIEF-A) demonstrated by effect size of change scores.

5.0 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

#	Criteria	Method of Assessment
1	Adults ages 18-60 years, inclusive at the time of consent	ID
2	Able to provide signed informed consent	ICF Teach-Back
3	Any gender	Self-Report
4	Subjects with a current primary DSM-5 diagnosis of ADHD (including predominantly inattentive presentation, hyperactive presentation, or combined presentations) as confirmed by the ACDS Version 1.2.	Clinical Interview
5	Subjects who are not receiving any pharmacological treatment for ADHD must have an AISRS score of ≥ 28 at screening. Subjects who are receiving pharmacological treatment for ADHD at screening must have a minimum AISRS score of ≥ 22 at screening	
6	Not requiring treatment for any comorbid psychiatric condition for at least 2 months	
7	Normal or corrected-to-normal vision	Self-Report
8	Normal or corrected-to-normal hearing	

9	No intention of changing medication or psychotherapy for the duration of the study at the time of recruitment	

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

#	Criteria	Method of Assessment
1	Concurrent substance abuse and/or history of substance use within 6 months	Clinical Interview
2	Use of any prescribed benzodiazepine	
3	Lifetime bipolar disorder, psychotic disorder, autism, intellectual disability. Comorbid mood and anxiety disorders determined by the MINI will be permitted if they are not the primary focus of clinical attention	
4	Active suicidality within past year, or history of suicide attempt in past 2 years	
5	Any history of severe past drug dependence determined by the MINI (i.e., a focus of clinical attention or a cause of substantial social or occupational difficulty)	
6	Any unstable medical or neurological condition	
7	Any history of brain surgery, of penetrating, neurovascular, infectious, or other major brain injury, of epilepsy, or of other major neurological abnormality (including a history of traumatic brain injury [TBI] with loss of consciousness for more than 24 hours or posttraumatic amnesia for more than 7 days)	
8	Any psychotropic medication	
9	Recent initiation (within the past 3 months) of cognitive-behavioral therapy or any evidence-based PTSD psychotherapy (Cognitive Processing Therapy [CPT], Prolonged Exposure [PE], Eye Movement Desensitization and Reprocessing [EMDR]); continuation of established maintenance supportive therapy will be permitted	
10	Significant hearing loss or severe sensory impairment	Self-Report

11	Enrollment in another research study testing an experimental, clinical, or behavioral intervention intended to affect symptoms initiated within the last 2 months, or intended enrollment within the next 2.5 months	

5.3 Vulnerable Subjects

The study will not enroll any vulnerable populations. Children, neonates, and prisoners are not eligible for enrollment. Pregnant women may be included because the intervention poses no physical risk; however no information about pregnancy status will be collected.

5.4 Strategies for Recruitment and Retention

At least 30 men and women with ADHD may be recruited from the community and from local clinical programs through a multi-modal outreach program. IRB approval of all recruitment materials will be obtained **(via modification as needed)** prior to use. Potential participants will contact the study site if interested in participation and will be scheduled for a pre-screen by IRB-approved study personnel.

The pre-screening phone interview will be conducted under a partial waiver of documentation of HIPAA authorization and waiver of documentation of consent. Screening answers will be retained for data analysis (e.g. identify trends in rule-outs) along with identifiers for participants who agree to be re-contacted for future research purposes. The pre-screening phone interview procedures collect the minimum amount of PHI necessary to determine study eligibility. Names, dates, phone numbers, and email are required to determine eligibility, contact participants regarding their eligibility status after consult with study clinicians, and to facilitate re-contact for future research purposes (optional). All data is collected though secure mechanisms, such as phone, WebEx and REDCAP. All data will be stored in restricted drives on the NYULH network and limited to authorized study personnel.

Potential participants will be asked whether they would like their information retained so they can be contacted for future research purposes and whether their information may be retained for analysis. Study personnel administering the pre-screening phone interview consent will document opt-in/opt-out status in a restricted tracking log (either Excel or REDCAP).

1. Identifiers from the pre-screen will be destroyed if the participant is not eligible for a screening visit unless the participant authorizes saving their information for contact regarding future research opportunities. They may opt in or opt out of future contact as part of the phone consent. Information collected from participants who opt out of future contact will be destroyed once the pre-screening interview has ended.

2. Information collected from participants who opt in to future contact AND who provide verbal HIPAA authorization to allow retention of their data for analysis purposes will be coded with a unique identifier and stored securely.

3. Data for eligible participants will be coded with a unique identifier and stored securely as described in the protocol.

All potential participants will be asked questions about basic inclusion and exclusion criteria including medication history, medical history, psychiatric history, potential Attention Deficit Hyperactivity Disorder Symptoms If the participant voluntarily discloses suicidal ideation or intention during the screen, trained study staff will follow the Phone Screen Protocol and Columbia-Suicide Severity Rating Scale and consult with the clinician on-call. Study personnel may ask follow-up questions to clarify responses and assess eligibility. Potential participants who meet minimum eligibility criteria will be invited for a Screening Visit.

Social Media and Online Forums	
	Craigslist
Online Research Recruitment Sites	
	Research Match
	StudyKik
	TrialFacts
Online Periodicals	
	Time Out Magazine
	Military Times
	Schneps Media
Print Media(cost)	
	Bushwick Daily
	Queens Chronicle
Electronic Newsletters/	
	Division of Veteran Services
	Social Services Agencies
	Community Mental Health Clinics
	Community Organizations
	Local Professional Organizations
	Regional Employee Assistance Programs
	Religious Organizations
	Cultural Centers
	Social Clubs
	Local Universities

Medical and Psychiatric Clinics	
	Cohen Veteran Center
	Family Health Centers at NYU Langone and NYU Brooklyn
	Military Family Clinic at NYUMC
	Other VA Medical Centers within the greater NYC-area
	Psychiatry Outpatient Clinic at Bellevue Hospital
	Primary Care Clinic at Bellevue Hospital
	Federally Qualified Health Center (FQHC)
	NYU Lutheran Medical Center Outpatient Psychiatry Clinic
	Nathan Kline Institute / Rockland Psychiatric Center and Gouverneur Health
	NYU-Psychiatry Associates
Clinical Trials (if opted in for Future Contact)	
	Study of the Duration and Efficacy of MYDAYIS on Adult ADHD Symptoms and Executive Function throughout the Day into the Early Evening" IRB# s19-00046 P.I. Adler
	Adler ADHD Trials

Based on successful recruitment in current and past ADHD trials and the low enrollment goal, we do not expect any significant barriers to recruitment. We expect to recruit the majority of participants from NYULH clinical referrals. If recruitment lags, strategies would include altering staffing patterns and increasing advertisement and outreach to clinical programs as described above.

We expect the study population to be approximately 50% male, 50% female, 7% Hispanic, 60% non-Hispanic Caucasian, 30% Non-Hispanic African American and 3% Other.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

The study will utilize EPIC to identify potential participants. DataCore will request a report from EPIC monthly to gather information necessary to identify patients who did not opt out of being contacted for research and who fit eligibility criteria for the study. The PI, co-I, research coordinators, and research nurse practitioners will have access to the EPIC search results. The following data points will be used for the search:

- Ages 18 to 60
- Diagnosis of ADHD
- Diagnoses of any exclusionary medical conditions or surgeries
- Vision and hearing status

- Medications

Once potential participants have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate and that study team will contact these patients directly by letter, phone, or email. Any recruitment information sent via email will use Send Safe email.

Once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and patients will be asked if they are interested in participating in the study. Should the patient agree, the study team will provide information regarding the next steps for participation. Data will be retained through study completion to ensure that patients who opt out are not contacted multiple times.

If a patient requests information regarding opting out of further recruitment for all research, they will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

5.5 Duration of Study Participation

Total duration of study participation is 11 weeks. Participants will be assessed for eligibility at the Screening Visit (Week 0) and will be seen for 17 additional visits: Baseline, 15 intervention sessions, and 1 Post-Intervention Visit.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 30 participants are enrolled. It is expected that approximately 30 participants will be enrolled in order to produce 15 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

Every effort will be made to continue follow-up of withdrawn or terminated participants or participants who discontinue the study intervention but remain in the study for follow-up. If a participant is lost to follow-up, the study team will attempt contact up to 15 times via phone or email to capture adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (Ups). Participants who withdraw or discontinue early will not be replaced.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and IRB.

6.0 Study Agent (device) and Procedural Intervention

6.1 Study Agent Description

The device to be used in this study (called PRISM) constitutes a non-significant Risk device (see rationale in Section 2.2 above). It is an investigational software under development, intended to be used in research studies testing the clinical efficacy of an innovative paradigm for EEG-based neurofeedback.

Off-the-shelf research-grade EEG hardware (g.Nautilus: Nautilus Research Wearable EEG Headset, wireless 16 electrode cap and amplifier system) will be used in conjunction with the PRISM software.

6.1.1 Acquisition, Labeling, and Storage

EEG hardware was acquired and maintained by NYULH Department of Psychiatry. The investigational (PRISM) software will be provided by Gray Matters, pre-installed on a standard laptop computer. The device is not available for commercial use. All hardware and software will be stored in restricted offices at NYULH Department of Psychiatry.

6.1.2 Duration of Intervention

The study will include 15 EEG-NF sessions, administered twice per week for a duration of 8 "active" weeks in total. Twice weekly sessions will be held on non-consecutive days. Each session will last approximately 30 minutes.

6.1.3 Device Specific Considerations

- Device size(s): Not applicable
- Device model(s): PRISM
- Device settings and programming: Not applicable
- Duration of implant or exposure: Not applicable
- Frequency of exposure: Twice weekly for eight weeks

7.0 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

Procedure	Staff	Screening	Baseline	15 x EEG-NF sessions, (2 SESSIONS per week, 8 weeks) Clinical Assessments done once per week	Post-Intervention Visit Week 11
Consent	RA	X			
Demographics	RA	X			
MINI	MD	X			
ACDS v1.2	MD	X			
AISRS	MD	X	X	X	X
CGI S	MD	X	X	X	X
Webneuro (CPT/stroop/go-no-go included in same PTSD battery	Research staff		X		X
ASRS	Self-report	X	X	X	X

BRIEF A	Self-report	X	X	X	X
PHQ9	Self-report		X		X
PSQI	Self-report		X		X
HAM-A	MD		X		X
Medical History	MD/RA	X			
Psychiatric History	MD	X			
Review Eligibility	MD	X			
C-SSRS	MD	X	X	X	X
Prior/Con Meds	MD/RA	X	X	X	X
Adverse Events	MD/RA	X	X	X	X
Participant satisfaction	RA		X	X	X

7.1.1 Study Specific Procedures

Measures are listed below, organized by domain. The assessment schedule is summarized in the table above.

1. Clinical Interview: ADHD diagnosis and severity will be assessed with Adult ADHD Clinical Diagnostic Scale-Version 1.2 (ACDS v1.2), a semi-structured diagnostic interview widely used in adult ADHD studies to evaluate both childhood and adult symptoms of ADHD, the Clinical Global Impression Scale (CGI-S), a widely used clinician-rated measure of global ADHD impairment and severity and Mini International Neuropsychiatric Interview (**MINI**). These measures will be administered by a trained licensed psychologist, nurse practitioner, or MD. Participants will be invited to consent to having their clinical interviews video and/or audio-recorded to ensure clinical adherence and to monitor inter-rater reliability. Discrepancies that result from evaluation of participants will be resolved by group consensus at team meetings.

2. Mood, ADHD and Anxiety Symptoms: The Patient Health Questionnaire-9 (**PHQ-9**) will be utilized to objectify degree of depression severity and the Pittsburgh Sleep Quality Index (**PSQI**) will be used to measure participants' quality and patterns of sleep. The Hamilton- A Scale (HAM-A) will be used to assess anxiety symptoms. ADHD symptoms will also be measured using the Adult ADHD Investigator Symptom Rating Scale (AISRS) and the 6-question Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5 (**DSM-5 ASRS**). Severity of executive function will be assessed via the Behavioral Rating Inventory of Executive Function- Adult version (BRIEF-A) self-report. Suicidality and suicidal ideation will be assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS).

3. Neurocognitive Testing: Participants will complete a standardized, neuropsychiatric battery through WebNeuro, an abbreviated form of IntegNeuro. WebNeuro is a well-validated, HIPAA-compliant internet-delivered testing battery that probes a wide range of neurocognitive functions. The battery consists of performance-based tests previously validated for remote delivery. Domains include executive functions such as attention/working memory, focus/inhibition, task-shifting, emotion recognition, emotional biasing of attention, and emotion regulation. Data from WebNeuro is linked to the standardized and integrative Brain Resource International database and cognitive functioning domain outputs are computed via WebNeuro software algorithms.

4. EFP-EEG-NF training: Each NF training session consists of 5 consecutive sequences of NF presentations. Prior NF session initiated a global BL is performed (3 minutes). Following the global baseline a "watch" condition (60 seconds), in which participants are instructed to passively view the animation, and are told that the scenario is not influenced by their brain activity. In the "regulate" (3 minutes) participants are instructed to lower the room's unrest level. A "rest" phase (30 seconds) follows each sequence, allowing participants to relax.

7.2 Study Schedule

7.2.1 Week 0 - Screening Visit

- Obtain informed consent of potential participant.
- Obtain audio/video consent of potential participant.
- Clinical Interview – ACDS v1.2 and MINI
- AISRS
- CGI-S
- C-SSRS
- DSM-5 ASRS (EXPANDED)
- BRIEF-A

7.2.2 Week 1 - Baseline Visit (1 week +/- 5 days)

- AISRS
- CGI-S
- C-SSRS
- ASRS (EXPANDED)
- PHQ9
- PSQI
- HAM-A
- BRIEF- A
- WebNeuro

- Adverse Events

7.2.3 Intermediate Visits (1 week +/- 1 days)

7.2.3.1 Week 2, Visits 1 and 2

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.2 Week 3, Visits 1 and 2 (Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.3 Week 4, Visits 1 and 2 (Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.4 Week 5, Visits 1 and 2(Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS

- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.5 Week 6, Visits 1 and 2(Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.6 Week 7, Visits 1 and 2(Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.3.7 Week 8, Visits 1 and 2(Clinical Assessments are done once per week)

- EFP-EEG-NF training
- AISRS
- CGI-S
- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.4 Week 9, Final NF Session

- EFP-EEG-NF training
- AISRS
- CGI-S

- C-SSRS
- BRIEF-A
- ASRS (EXPANDED)
- Adverse Events

7.2.5 Week 11 - Final Study Visit (2 weeks +/- 5 days)

- AISRS
- CGI-S
- C-SSRS
- ASRS (EXPANDED)
- BRIEF-A
- PHQ9
- PSQI
- HAM-A
- WebNeuro
- Adverse Events
- Participant Satisfaction

7.2.6 Withdrawal/Early Termination Visit

Participants who are withdrawn or terminated early will be asked to complete a Final Study Visit.

7.2.7 Unscheduled Visit

Unscheduled visits (e.g., in case of unexpected urgent or emergent clinical situation) will be documented on an unscheduled visit form.

7.3 Concomitant Medications, Treatments, and Procedures

All concomitant medications taken during study participation will be recorded on the case report forms (CRFs). Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

7.4 Prohibited Medications, Treatments, and Procedures

See Exclusion Criteria.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets <u>all</u> of the following criteria will be documented as an ***unanticipated problem (UP) involving risk to subjects or others***:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Intervention

The clinician's assessment of an AE's relationship to study agent (drug, biologic, device) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related or Possibly Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

AEs will be reported in accordance with federal law and IRB requirements. Reporting procedures vary depending on the severity of the AE. All non-reportable AEs and other Ups not related to study activities and that do not increase the risk of harm or result in harm to participants will be reported to the IRB at the time of continuing review.

8.4.2 Serious Adverse Event Reporting

SAEs considered at least possibly related to the study procedures will be reported to the IRB within 48 hours of discovery by the PI. The PI will distinguish SAEs from AEs and provide attributions (severity, relationship, expectedness).

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 48 hours of the investigator or other qualified designee becoming aware of the event.

- Any other UP will be reported to the IRB within 5 working days of the investigator or other qualified designee becoming aware of the problem.

8.5 Study Halting Rules

The medical monitor will convene to determine whether the study should be halted after three severe AEs with probable relationship to the study procedures are discovered. The PI or qualified designee will inform the medical monitor within 24 hours of this occurrence, cease screening and enrollment of new participants, and will provide the medical monitor with a list of AEs. The medical monitor will convene an ad hoc meeting by teleconference or in writing as soon as possible and will provide recommendations for proceeding with the study to the PI. If the medical monitor finds it is likely that the study procedures

contributed to negative outcomes, they will consider solutions including protocol modifications or potentially terminating the study.

8.6 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. A summary of adverse events, deviations, and findings by the medical monitor will be submitted to the IRB as part of an annual progress report with each Continuing Review submission.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Senior Site Staff will be responsible for local quality assurance, will verify that the study procedures are properly followed, and will ensure that site staff are trained and able to conduct the protocol appropriately. If the Senior Site Staff's review of study documentation indicates that additional training of study personnel is needed, or that other corrective action is required, arrangements will be made via the PI. Senior Site Staff will review data for completeness, accuracy, and fidelity to the protocol.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

This pilot study is not formally powered to assess effect statistically. We will: demonstrate the NYU team can successfully recruit, enroll, and complete the protocol as proof of concept and collect high-quality analyzable data; and assess clinically meaningful improvement on primary outcome measures (AISRS and ASRS/BRIEF-A) as demonstrated by effect size of change.

As this is a pilot study and the full estimation of the potential magnitude of the effect is not known, we are planning an interim analysis after completion of approximately 10 patients with treatment data. This interim analysis examine the magnitude of clinical effects on clinical measures of AISRS expanded AISRS subsets (clinician symptom measure), ASRS (self-report symptom measure), BRIEF (self-report measure of executive function) and CGI (measure of impairment) via examination for means, SDs and magnitude of effect. Safety data will also be examined.

<u>ADHD Rationale</u>

In this study, approximately 30 subjects will be phone prescreened, which will give us at least 30 participants coming in for screening and consenting for participation. Up to 30 patients will be enrolled/consented to be sure that 15 evaluable/assigned

patients reach the end of PRISM Intervention. We expect some of the subjects to screen fail either during the telephone phone screen or during the hybrid remote visit. Screen failures can occur during the MINI (psychiatric interview), ACDS (ADHD diagnosis interview) or upon discretion of the principal investigator. Subjects are also given the opportunity to continuously decide participation throughout the study. Subjects can opt out of the study at any time.

10.1.1 Safety Review

See Section 5.6 Premature Termination or Suspension of Study and Section 8.5 Stopping Rules.

10.2 Sample Size

We will consent approximately 30 participants to meet our goal of 15 completers.

10.3 Measures to Minimize Bias

10.3.1 Enrollment/Randomization/Masking Procedures

Blinding, randomization, and masking are considered unnecessary for this pilot study. All subjects will undergo the same procedures.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and

quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study procedures, potential risks, and potential benefits will be given to participants and written documentation of informed consent will be obtained prior to starting intervention. The following consent materials are submitted with this protocol:

- Request for Waiver of Authorization and Waiver of Documentation of Consent (Pre-Screen)
- Pre-Screen Consent Phone Script
- Informed Consent Form
- Informed Consent Quiz
- Audio/Video Release Form
- Health Release Form
- Covid 19 participation info sheet

Audio/Video Release Form: This form will be provided to participants and will include a description of the audio/video recording procedure, risks and benefits of the procedure, confidentiality, a statement that patients will be informed of any new findings affecting the risks or benefits of the study; a statement that participation is voluntary and that the patient may withdraw at any time; and information about whom to contact with questions or in case of emergency

Health Release Form: This form will be obtained to authorize release personal information in records from hospitals, clinics, or doctor's offices where participants have received care in the past. The form also authorizes the study team to speak with clinicians who have treated the patient for medical and/or psychiatric conditions but will not reveal the nature of the study without the patient's permission. The release will be only be utilized by the study team if necessary to determine study eligibility. Participants who do not authorize release may still participate in the study if there are no eligibility concerns. Participants who do not authorize release and for whom eligibility concerns have been raised will be assessed by the Principal Investigator and may be enrolled or withdrawn at his discretion.

13.3.2 Consent Procedures and Documentation

Phone Pre-Screen: Participants will provide verbal consent to participate in the phone pre-screen under a partial waiver of authorization and waiver of documentation of consent. The phone pre-screen procedures pose no more that minimal risk and do not normally require written consent outside the research context. Interested participants who meet minimum eligibility requirements and pass phone pre-screening will be invited for a screening visit and emailed a copy of the IRB-approved consent form to read and review in advance of their visit.

Screening Visit: Participants will indicate consent by providing a written or electronic (REDCAP) signature on the Informed Consent Form (ICF), Audio / Visual Release Form, and Health Release Form. REDCAP consent forms are identical to hard copy consents.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. The discussion will be conducted as follows:

- The consent discussion will take place with IRB-approved research staff in a private room, via phone or via WebEx. Participants who are consented remotely will be asked to show if they are in a private location and to show identification prior to initiating the discussion. Extensive discussion of risks and possible benefits of participation will be provided to the participants.

- Participants will be permitted (but not required) to provide written or electronic consent at the time of the consent discussion. Participants may choose to discuss the study with their family or friends or think about it prior to agreeing to participate.

- Participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Comprehension will be ensured using a standard teach-back approach. Subject will be given opportunity to ask questions and later will take comprehension quiz on redcap as part of the ICF process.

- Participants will be assured that their participation in the study is voluntary and that they may withdraw at any time. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

- Participants will have the opportunity to ask questions of the research staff at any point during the discussion. Participants will have the opportunity to carefully review the written consent form and ask questions prior to providing a written or electronic signature.

Participants will provide a written or electronic signature on the informed consent document prior to any procedures being done specifically for the study. Participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to

the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

Re-Contacting Screen Failures: In the event the protocol inclusion/exclusion criteria is updated, participants who failed screening will be re-evaluated for inclusion in the study. If a participant who failed screening appears to be eligible under the updated inclusion/exclusion criteria, they will be contacted via phone or email to ascertain whether they are still interested in participating in the study. If interested, the participant will be brought in for re-consent and a new screening visit.

Re-Consent: If the consent is revised (e.g.: new procedures, risk information, compensation, data sharing, etc.) Participants will be re-consented with the most updated version of the consent form at their next visit. New information that could substantially affect a participant's desire to continue in the study will be communicated via phone, followed by re-consent at the next study visit.

13.4 Posting of Clinical Trial Consent Form

13.5 The study's informed consent form will be posted on the Federal website clinicaltrials.gov after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject. Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The study team will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13.5.1 Research Use of Stored Human Data

- Storage: Standard institutional practices will be followed to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these policies. Only IRB-approved NYULH study personnel will have access to identifiable data. Subjects will be assigned a code that will be used instead of their name, medical record number, or other personally identifying information. Electronic files for data analysis will only contain the subject code. The code will not contain any part of the 18 HIPAA identifiers. The key associating the codes with the subjects' personally identifying information will be restricted to the principal investigator and designated IRB-approved study staff. The key will be kept secure on a restricted NYULH network drive in a limited access folder. Electronic data will be stored on REDCap and will require NYULH ID/password authentication. All paper files containing restricted information will be secured in locked filing cabinets in restricted offices.

- Tracking: Data will be tracked using REDCAP. EEG-related data generated during the neurofeedback sessions will be produced, processed and stored on the local computer on which the PRISM software is installed. The data is stored as standard EEG data using EDF/BDF formats and includes both the raw EEG as well as the computed EFT values. The data will remain locally on the secure NYULH platform.

- PRISM Support: Gray Matters will provide technical support and service the PRISM software as needed during the study. To do so, Gray Matters personnel will connect remotely to the local computer on which the PRISM software is installed by connecting to the IP address of the computer. Remote support will entail accessing usage and error logs from the PRISM

software as text files and HTTPS event logs. Gray Matters will remotely access anonymized participant EEG data generated by PRISM software. Error and events logs as well as anonymized EEG data will be uploaded to a secure and HIPAA-compliant cloud server, Amazon Web Service, AWS, to further develop and improve the PRISM software.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into REDCAP a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. REDCAP data will be stored indefinitely and may be used for future research purposes.

14.2 Study Records Retention

Study source documents will be retained for the longer of 3 years after close-out or 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

Protocol deviations that are not Ups must be reported to the local IRB at continuing review. Protocol deviations that are UPs must be reported within 48 hours of discovery.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This pilot study is funded by the NYULH Department of Psychiatry.

15.2 Costs to the Participant

Participants will not incur any costs as a result of participating in the study.

15.3 Participant Reimbursements or Payments

Participants will receive payments for the time, effort, and inconvenience of study participation. Payments will be made for completed visits by either check or CliniCard after completed visits indicated below. Participants will be given the option to choose payment by check or ClinCard. Their selection will be documented on the consent form, the subject binder, and the administrative binder.

Visit	Compensation
Week 0 – Screening Visit	$50
Week 1 – Baseline Visit	$75
Week 2 – Session 1	$25
Week 2 – Session 2	$25
Week 3 – Session 1	$25
Week 3 – Session 2	$25
Week 4 – Session 1	$25
Week 4 – Session 2	$25
Week 5 – Session 1	$25
Week 5 – Session 2	$25
Week 6 – Session 1	$25
Week 6 – Session 2	$25
Week 7 – Session 1	$25
Week 7 – Session 2	$25
Week 8 – Session 1	$25
Week 8 – Session 2	$25
Week 9- Final NF Session	$25
Week 11 – Post-Intervention Visit	$75
Total	**$575**

16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. All study group members are required to disclose all conflicts of interest and management of all reported dualities of interest will be addressed.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

17 References

Adler, L. A., Faraone, S. V., Spencer, T. J., Berglund, P., Alperin, S., & Kessler, R. C. (2017). The structure of adult ADHD. *International journal of methods in psychiatric research*, *26*(1), e1555.

Adler, L. A., Zimmerman, B., Starr, H. L., Silber, S., Palumbo, J., Orman, C., & Spencer, T. (2009). Efficacy and safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, double-blind, parallel group, dose-escalation study. J Clin Psychopharmacol, 29(3), 239-247. doi:10.1097/JCP.0b013e3181a390ce

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Arns M, Clark CR, Trullinger M, deBeus R, Mack M, Aniftos M. Neurofeedback and Attention-Deficit/Hyperactivity-Disorder (ADHD) in Children: Rating the Evidence and Proposed Guidelines. *Appl Psychophysiol Biofeedback*. 2020;45(2):39-48. doi:10.1007/s10484-020-09455-2

Barkley, R. A., & Murphy, K. R. (2010). Impairment in occupational functioning and adult ADHD: the predictive utility of executive function (EF) ratings versus EF tests. Arch Clin Neuropsychol, 25(3), 157-173. doi:10.1093/arclin/acq014

Baumeister S, Wolf I, Holz N, et al. Neurofeedback Training Effects on Inhibitory Brain Activation in ADHD: A Matter of Learning?. Neuroscience. 2018;378:89-99. doi:10.1016/j.neuroscience.2016.09.025

Biederman, J., Spencer, T., & Wilens, T. (2004). Evidence-based pharmacotherapy for attention-deficit hyperactivity disorder. International Journal of Neuropsychopharmacology, 7(1), 77-97.

Bron, T. I., Bijlenga, D., Boonstra, A. M., Breuk, M., Pardoen, W. F., Beekman, A. T., & Kooij, J. J. (2014). OROS-methylphenidate efficacy on specific executive functioning deficits in adults with ADHD: a randomized, placebo-controlled cross-over study. Eur Neuropsychopharmacol, 24(4), 519-528. doi:10.1016/j.euroneuro.2014.01.007

Brotman MA, Rich BA, Guyer AE, et al. Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *Am J Psychiatry*. 2010;167(1):61-69. doi:10.1176/appi.ajp.2009.09010043

Chiba, T., Kanazawa, T., Koizumi, A., Ide, K., Taschereau-Dumouchel, V., Boku, S., Hishimoto, A., Shirakawa, M., Sora, I., Lau, H., Yoneda, H., & Kawato, M. (2019). Current status of neurofeedback for post-traumatic stress disorder: A systematic review and the possibility of decoded neurofeedback. *Frontiers in Human Neuroscience*, *13*(July), 1–13. https://doi.org/10.3389/fnhum.2019.00233

Cortese S, Ferrin M, Brandeis D, et al. Neurofeedback for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):444-455. doi:10.1016/j.jaac.2016.03.007

Cortese, S., Ferrin, M., Brandeis, D., Buitelaar, J., Daley, D., Dittmann, R. W., Holtmann, M., Santosh, P., Stevenson, J., Stringaris, A., Zuddas, A., Sonuga-Barke, E. J., & European ADHD Guidelines Group (EAGG) (2015). Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. Journal of the American Academy of Child and Adolescent Psychiatry, 54(3), 164–174. https://doi.org/10.1016/j.jaac.2014.12.010

Fruchtman-Steinbok, T., Cohen, A., Jaljuli, I., Keynan, J. N., Drori, G., Routledge, E., Krasnoshtein, M., & Hendler, T. (2019). *Feasibility and Effectiveness of Personalized Amygdala-related Neurofeedback for Post-Traumatic Stress Disorder*. https://doi.org/10.31234/osf.io/qmsz3

Goldway, N., Ablin, J., Lubin, O., Zamir, Y., Keynan, J. N., Or-Borichev, A., Cavazza, M., Charles, F., Intrator, N., Brill, S., Ben-Simon, E., Sharon, H., & Hendler, T. (2019). Volitional limbic neuromodulation exerts a beneficial clinical effect on Fibromyalgia. *NeuroImage*, *186*, 758–770. https://doi.org/10.1016/j.neuroimage.2018.11.001

Hauser TU, Iannaccone R, Ball J, et al. Role of the Medial Prefrontal Cortex in Impaired Decision Making in Juvenile Attention-Deficit/Hyperactivity Disorder. JAMA Psychiatry. 2014;71(10):1165–1173. doi:10.1001/jamapsychiatry.2014.1093

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., . . . Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry, 163(4), 716-723. doi:10.1176/ajp.2006.163.4.716

Keynan, J. N., Cohen, A., Jackont, G., Green, N., Goldway, N., Davidov, A., Meir-Hasson, Y., Raz, G., Intrator, N., Fruchter, E., Ginat, K., Laska, E., Cavazza, M., & Hendler, T. (2019). Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. *Nature Human Behaviour*, *3*(1), 63–73. https://doi.org/10.1038/s41562-018-0484-3

Keynan, J. N., Meir-Hasson, Y., Gilam, G., Cohen, A., Jackont, G., Kinreich, S., Ikar, L., Or-Borichev, A., Etkin, A., Gyurak, A., Klovatch, I., Intrator, N., & Hendler, T. (2016). Limbic Activity Modulation Guided by Functional Magnetic Resonance Imaging–Inspired Electroencephalography Improves Implicit Emotion Regulation. *Biological Psychiatry*, *80*(6), 490–496. https://doi.org/10.1016/j.biopsych.2015.12.024

Klein M, Walters RK, Demontis D, et al. Genetic Markers of ADHD-Related Variations in Intracranial Volume. *Am J Psychiatry*. 2019;176(3):228-238. doi:10.1176/appi.ajp.2018.18020149

Linhartová, P., Látalová, A., Kóša, B., Kašpárek, T., Schmahl, C., & Paret, C. (2019). fMRI neurofeedback in emotion regulation: A literature review. *NeuroImage*, *193*, 75–92. https://doi.org/10.1016/j.neuroimage.2019.03.011

Liu Q, Zhang H, Fang Q, Qin L. Comparative efficacy and safety of methylphenidate and atomoxetine for attention-deficit hyperactivity disorder in children and adolescents: Meta-analysis based on head-to-head trials. J Clin Exp Neuropsychol. 2017;39(9):854-865. doi:10.1080/13803395.2016.1273320

Maier SJ, Szalkowski A, Kamphausen S, et al. Altered cingulate and amygdala response towards threat and safe cues in attention deficit hyperactivity disorder. Psychol Med. 2014;44(1):85-98. doi:10.1017/S0033291713000469

Meir-Hasson, Y., Keynan, J. N., Kinreich, S., Jackont, G., Cohen, A., Podlipsky-Klovatch, I., Hendler, T., & Intrator, N. (2016). One-class FMRI-inspired EEG model for self-regulation training. *PLoS ONE*, *11*(5). https://doi.org/10.1371/journal.pone.0154968

Myers, J.E., & Young, J.S. (2012). Brain Wave Biofeedback: Benefits of Integrating Neurofeedback in Counseling. Journal of Counseling and Development, 90, 20-28.

Newcorn JH, Nagy P, Childress AC, Frick G, Yan B, Pliszka S. Randomized, Double-Blind, Placebo-Controlled Acute Comparator Trials of Lisdexamfetamine and Extended-Release Methylphenidate in Adolescents With Attention-Deficit/Hyperactivity Disorder. CNS Drugs. 2017;31(11):999-1014. doi:10.1007/s40263-017-0468-2

Passarotti, A. M., Sweeney, J. A., & Pavuluri, M. N. (2010). Emotion processing influences working memory circuits in pediatric bipolar disorder and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 49(10), 1064–1080. https://doi.org/10.1016/j.jaac.2010.07.009

Posner, J., Maia, T. V., Fair, D., Peterson, B. S., Sonuga-Barke, E. J., & Nagel, B. J. (2011). The attenuation of dysfunctional emotional processing with stimulant medication: an fMRI study of adolescents with ADHD. Psychiatry research, 193(3), 151–160. https://doi.org/10.1016/j.pscychresns.2011.02.005

Ramsay, J. R., & Rostain, A. L. (2014). Cognitive behavioral therapy for adult ADHD: An integrative psychosocial and medical approach. Routledge.

Schönenberg M, Wiedemann E, Schneidt A, et al. Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: a triple-blind, randomised, controlled trial. *Lancet Psychiatry*. 2017;4(9):673-684. doi:10.1016/S2215-0366(17)30291-2

Schulz, K. P., Clerkin, S. M., Newcorn, J. H., Halperin, J. M., & Fan, J. (2014). Guanfacine modulates the emotional biasing of amygdala-prefrontal connectivity for cognitive control. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, 24(9), 1444–1453. https://doi.org/10.1016/j.euroneuro.2014.06.016

Sonuga-Barke EJ, Brandeis D, Cortese S, et al. Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry*. 2013;170(3):275-289. doi:10.1176/appi.ajp.2012.12070991

Spencer, T. J., Adler, L. A., Weisler, R. H., & Youcha, S. H. (2008). Triple-bead mixed amphetamine salts (SPD465), a novel, enhanced extended-release amphetamine formulation for the treatment of adults with ADHD: a randomized, double-blind, multicenter, placebo-controlled study. J Clin Psychiatry, 69(9), 1437-1448. doi:10.4088/jcp.v69n0911

Tajima-Pozo K, Yus M, Ruiz-Manrique G, Lewczuk A, Arrazola J, Montañes-Rada F. Amygdala Abnormalities in Adults With ADHD. *J Atten Disord*. 2018;22(7):671-678. doi:10.1177/1087054716629213

Van Doren, J., Arns, M., Heinrich, H. *et al.* Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry* **28,** 293–305 (2019). https://doi.org/10.1007/s00787-018-1121-4

Vernon, D., Frick, A., & Gruzelier, J. (2004). Neurofeedback as a treatment for ADHD: a methodological review with implications for future research. *Journal of Neurotherapy*, *8*(2), 53-82.

Weisler, R. H., Greenbaum, M., Arnold, V., Yu, M., Yan, B., Jaffee, M., & Robertson, B. (2017). Efficacy and Safety of SHP465 Mixed Amphetamine Salts in the Treatment of Attention-Deficit/Hyperactivity Disorder in Adults: Results of a Randomized, Double-Blind, Placebo-Controlled, Forced-Dose Clinical Study. CNS Drugs, 31(8), 685-697. doi:10.1007/s40263-017-0455-7

Young, K. D. (2019). *Current State of fMRI Neurofeedback for Psychiatric Disorders.*