Double-Blind 2-Site Randomized Clinical Trial of Neurofeedback for ADHD

ICAN Study
(International Collaborative ADHD Neurofeedback Study)

L. Eugene Arnold, M.D., Coordinating Principal Investigator

Roger deBeus, Ph.D. UNC Site Principal Investigator

Jill Hollway, Ph.D., Co-Investigator and OSU Clinical Site co-Director

Robert Rice, Ph.D., Director of Data Center

Xueliang (Jeff) Pan, Ph.D., Biostatistician

Consultants:

***Cynthia Kerson, Ph.D.
Helena C. Kraemer, Ph.D.
**Joel Lubar, Ph.D.
**Vincent Monastra, Ph.D.
***Laurence Hirshberg, Ph.D.
Keith McBurnett, Ph.D.
C. Keith Conners, Ph.D.
Martijn Arns, Ph.D.
Howard Lightstone
Nicholas Lofthouse, Ph.D.

* Note: Dr. Roger deBeus is the PI for the UNCA site, which will recruit and treat half the participants. He is an acknowledged neurofeedback expert who runs a clinic that includes neurofeedback in its repertoire of services. Although he and his neurofeedback trainers are experienced with neurofeedback, they will attend the intensive training and have fidelity monitoring by Dr. Monastra the same as at the OSU site to standardize the treatment between the two sites. Dr. Sudeshna Dasgupta is the physician for the UNCA site responsible for the initial medical screening to detect medical mimics of ADHD; she will also handle consultation with prescribers of the medicated participants if they should develop side effects as the neurofeedback benefit develops. She will also provide medical management of any mid-treatment dropouts from neurofeedback for lack of efficacy who wish to newly try medication.

**Note: Vincent Monastra, Ph.D, internationally recognized neurofeedback investigator and practitioner will provide the initial 3-day training for all neurofeedback administrators/trainers, review videotapes of treatment sessions to insure fidelity, and review EEGs to determine optimal personalized thresholds for reinforcement. He will also be available by phone for consultation to the trainers about issues that may arise in treatment.

***Note: Drs. Cynthia Kerson and Laurence Hirshberg, experienced and respected neurofeedback experts, will assist Dr. Monastra with training. Dr. Kerson will remotely program clinical site computers for the blinded treatment assignment. Dr. Hirshberg will review qEEGs for quality control.

ABSTRACT
Current established, evidence-based treatments for attention-deficit/hyperactivity disorder (ADHD) are incompletely effective and not universally acceptable, and appear to wane in effect over time despite significant immediate benefit. E.g., FDA-approved medication, which shows large acute benefit, leaves a third of children only partially treated even when combined with behavioral treatment, and has not been demonstrated effective beyond 2 years. Additional treatments are needed that are effective with persisting benefit, preferably related to a biomarker predicting treatment response. A good candidate is electroencephalographic (EEG) biofeedback, called neurofeedback (NF). It is based on 1) observations that patients with ADHD often have excessive theta band (4-8 Hz) quantitative EEG power, low beta band (13-21 Hz) power, and excessive theta-beta ratio (TBR), and 2) theoretical application of operant conditioning to correct this EEG imbalance. Meta-analysis of 6 randomized clinical trials found a large benefit for inattentive symptoms and medium benefit for hyperactive-impulsive symptoms. Unfortunately, none of these were blinded. Three of 4 small blinded studies found no advantage for NF over sham, but used suboptimal NF, leaving the situation inconclusive. Because of the expense and time required by NF, there is a public health need to determine whether it has a specific effect beyond the obvious nonspecific benefit of doing a focused activity several times a week with a friendly, encouraging adult who reinforces for attending to the task. Experts in NF, ADHD, clinical trials, statistics, and data management have joined to design a double-blind sham-controlled randomized clinical trial to answer several pressing scientific and clinical questions in a way that will be credible to all. At each of 2 sites (1 university & 1 NF clinic) 70 children (total N=140) age 7 through 10 with rigorously diagnosed moderate to severe ADHD and TBR>4.5 will be randomized in a 3:2 ratio to active TBR downtraining by NF vs. a sham training of equal duration, intensity, and appearance. To keep both participants and study staff blind, the sham will utilize pre-recorded EEGs with the participant's artifacts superimposed. The sham will be programmed into the equipment via internet by an off-site statistician-guided person who has no contact with participants. Treatment fidelity will be trained and monitored by an acknowledged NF leader in a manner that protects blinding. Multi-domain assessments at baseline, mid-treatment, treatment end, and follow-ups at 6 months, 1 year, and 2 years will include parent and teacher ratings of symptoms & impairment, neuropsychological tests, clinician ratings, a genetic sample, and quantitative EEG as well as tests of blinding and of sham inertness. Hypotheses include that NF will improve parent- and teacher-rated inattentive symptoms (primary outcome) and other outcomes more than sham, that benefit will persist for 2 years after training, that initial TBR will moderate treatment response, and that change in TBR will mediate response. Research Domain Criteria and EEG brain changes will be explored, including relationship of TBR to clinical symptoms, executive-function impairment, and sleep. An objective measure of sleep will be collected using Motionlogger actigraphy watch. Additionally, genetic samples will be analyzed to identify links between specific single nucleotide polymorphisms (SNPs), TBR, and response to neurofeedback.

Specific Aims:

The major aims are to test whether neurofeedback (NF, EEG biofeedback, neurotherapy) has specific benefit for attention-deficit/hyperactivity disorder (ADHD), whether benefit persists for 2 yr. beyond treatment end, and whether the putative mechanism and RDoC arousal/regulation biomarker for responsiveness, excess electroencephalographic (EEG) theta-beta power ratio (TBR), is valid. Current literature about NF's specific benefit in ADHD is inconclusive. The proposed double-blind randomized clinical trial will build on the recently completed NIMH-funded pilot feasibility trial to clarify the evidence base of a promising treatment that has the potential for filling a critical gap in the ADHD treatment armamentarium, esp. for treatment with enduring effect.

Question 1: Does NF have a specific benefit beyond nonspecific placebo response? (Primary Question)
Hypothesis 1 ***(Primary outcome):*** *Children randomly assigned to NF will, when assessed in an unmedicated state, show significantly greater reduction of inattentive ADHD symptoms rated by parents and*

teachers than those assigned to double-blind placebo sham treatment of equal duration, intensity, involvement, and appearance.

Additional Analyses: *In elucidation of the primary outcome, other outcomes, such as **impairment**, parent- & teacher-rated hyperactive-impulsive symptoms, other symptoms, clinical global impression, EEG measures, & neuropsychological test scores should also improve more with NF than with placebo sham.*

Question 2: Does NF benefit persist after termination of training?
Hypothesis 2: *At 6-month, 1-year, and 2-year follow-up, children who received NF will have equal or better levels of inattentive symptoms than at completion of training. When assessed in an unmedicated state, their inattentive symptoms will be significantly less severe than those who received sham/placebo NF.*
Hypothesis 2B: *At follow-ups, the NF group will have more medication discontinuers, fewer medication starters, and lower average medication dose (of those medicated) than in the sham/placebo group.*

Question 3: Are there subgrouping or other variables that moderate NF treatment response?
Hypothesis 3: *Initial EEG theta-beta ratio (TBR) will moderate treatment effect: those with higher baseline TBR will show significantly greater advantage of NF over sham placebo than those with a lower ratio.*

Additional Analyses: *Exploratory (hypothesis-generating) analyses will include other EEG variables and demographic and clinical variables to investigate other possible moderators and non-specific predictors of NF outcome, and to develop an optimal moderator paradigm combining multiple individual moderators.*

Question 4. Is NF benefit mediated by the hypothesized EEG power changes?
Hypothesis 4: *Decrease in TBR will significantly mediate therapeutic effect of NF, especially at follow-ups.*

Additional Analyses: *Improvement in event-related potential (ERP) and a measure of within-session EEG change will also be examined as possible mediators of NF therapeutic effect.*

Question 5. Does high TBR select a group that is uniformly responsive to treatment regardless of ADHD subtype? (Research Domain Criteria (RDoC) arousal/regulation treatment-response question)
Exploratory Analysis: *Variability in response on the primary outcome should be significantly less (variance of the change score will be lower) than for published medication trials, which do not select for a biomarker. TBR will correlate with severity of inattentiveness, sleep delay, and impairment of executive function.*

Question 6. . What deeper brain structures have their function affected by NF?
Exploratory Analyses: *Low Resolution Electromagnetic Tomography (LORETA) of event-related potentials (ERP) is an EEG-based form of brain imaging inexpensive enough for the budget cap. LORETA analysis will be applied to baseline and endpoint qEEG and ERPs from neuropsychological testing of all participants. The localized deep brain changes identified will be explored as outcomes & mediators.*

Question 7. What proportion of well-diagnosed ADHD has excess eyes-open TBR?
Although the literature substantiates a significant difference in TBR between normal controls and ADHD, the exact distribution of TBR power in ADHD is unclear because of varying conditions, definitions, & secular trend across studies. This study will standardize screening conditions in a large sample (250-300 to screen).
Exploratory Descriptive Analysis: *We expect that 40% to 80% of 7- through 10-year-old children with rigorously diagnosed ADHD will have eyes-open specifically defined TBR ≥4.5.*

Question 8. Do SNPs mediate treatment response to neurofeedback?
Exploratory Analysis: *We expect that SNPs associated with the dopaminergic and serotonergic pathways will mediate neurofeedback treatment response.*

Question 9. Are there identifiable genomic differences in children who have ADHD with a high TBR (≥4.5) and children diagnosed with ADHD who have a low TBR (<4.5)?
Exploratory Analysis: *Given the difference in TBR between the two groups, we expect that genomic differences will be found between children with ADHD who have a high TBR* (≥4.5) *and children with ADHD who have a low TBR* (<4.5).

Question 10. How does the presence of baseline sleep onset insomnia (SOI) influence the treatment effects of NF?

Exploratory analysis: *We expect that the presence of baseline Sleep Onset Insomnia (SOI) will increase the treatment effects of NF [i.e., baseline SOI will show greater treatment response to NF (be a moderator of response) than those without baseline SOI] and improvement of inattention symptoms will be mediated by the normalization of sleep onset.*

RESEARCH PLAN

Significance & Background:

Attention-deficit/hyperactivity disorder (ADHD) is a chronic, impairing neurodevelopmental disorder that costs billions annually in special education needs, lost productivity, traffic accidents, and delinquency (Arnold, 2004, Spetie & Arnold, 2007). The best documented, most successful, and most widely used treatment for ADHD is FDA-approved medication. However, even when administered in a careful algorithm with behavioral treatment, 32% of children with ADHD do not fully benefit from this presumed optimal combination (Swanson, et al., 2001). Further, even for those with good initial response, it is difficult to document persisting medication benefit beyond 2 years (e.g., Jensen et al., 2007; Molina et al., 2009). Additionally, an unknown percent of families refuse even to try medications, because of fears about side effects, possible addiction, and popular media scare stories. The 8-year follow-up of the Multimodal Treatment Study of ADHD (MTA, Molina et al., 2009) noted the disappointing long-term results of current treatments and the need for new treatments.

Reviews of complementary and alternative treatments for ADHD (Hurt et al., 2011[a], 2011[b];) identified neurofeedback (NF, also called EEG biofeedback or neurotherapy) as one of the most promising. NF uses operant conditioning principles based on real-time measurement of electrical activity from scalp electrodes to alter neural activation. The discovery of neural plasticity ushered in an explosion of nondrug neuromodulation interventions since 2000, especially relevant to ADHD because brain imaging shows deviant size & symmetry of brain structures in ADHD. Electroencephalographic (EEG) NF is the oldest & best established of these.

Rationale of NF for ADHD

NF involves deliberate self-modification of brain electrical activity by providing audiovisual information about this electrical activity. It *directly addresses a theoretical etiology* for some cases of ADHD: excess slow-wave theta-band EEG power & deficient beta-band power, with consequent high theta-beta ratio (TBR). Its theoretical and evidential foundation in the treatment of ADHD is: a) the idea that the brain's electrical activity can be conditioned (for historical review see Sherlin et al., 2011) and b) research on the physiological basis of ADHD and EEG dysfunctions and their relationship to underlying thalamocortical mechanisms:

a) Operant conditioning of EEG activity was first reported in the 1960s (Kamiya, 2011; Sterman et al., 2010). Recent studies demonstrated that not only can cortical EEG be conditioned (Sherlin et al., 2011), but it is also possible to condition more focal neuronal activity Schafer & Moore, 2011; Philippens & Vanwersch, 2010; Cerf et al., 2010; Shibata et al., 2011). Clinical utility in epilepsy was demonstrated in 1969 (Sterman, 1969, 2010); and treatment of ADHD was reported in 1976 (Lubar & Shouse, 1976).

b) Neuroimaging studies have found ADHD associated with smaller brain regions responsible for sustained attention, behavioral planning and motor control (e.g., Swanson & Castellanos, 2002); PET and SPECT research has indicated reduced blood flow/metabolism suggesting electrophysiologic under-arousal over frontal and central midline cortex in 80-90% of patients with ADHD (Clarke et al., 2001); EEG studies have demonstrated more slow-wave theta (3.5-8 Hz) power than normal controls, and conversely less beta (12-21 Hz) power, especially in central and frontal regions, probably reflecting under-arousal (Barry et al., 2003); and event-related potential (ERP) research has identified deviant sensory and cognitive processing (Barry et al., 2003). The most consistent EEG finding in ADHD is increased absolute power in the theta band (Bresnahan et al., 1999; Chabot & Serfontein, 1996; Clarke et al., 1998, 2001b; DeFrance et al., 1996; Janzen et al., 1995; Lazzaro et al., 1999, 1998; Mann et al., 1992; Matsuura et al., 1993). Three meta-analyses of the Theta/Beta ratio (TBR) found that it differentiates children with ADHD from control groups (Boutros et al., 2005; Snyder & Hall, 2006; Arns et al*, 2013*) (Fig. 1). This measure is in line with the EEG Vigilance model developed by Bente (1964) and refined by Hegerl (2010): decreased vigilance levels (excess theta) are hypothesized to explain impairments in sustained attention, and vigilance autostabilization syndrome explains

the hyperactive-impulsive behavior as a means to increase vigilance (Sander et al, 2010).

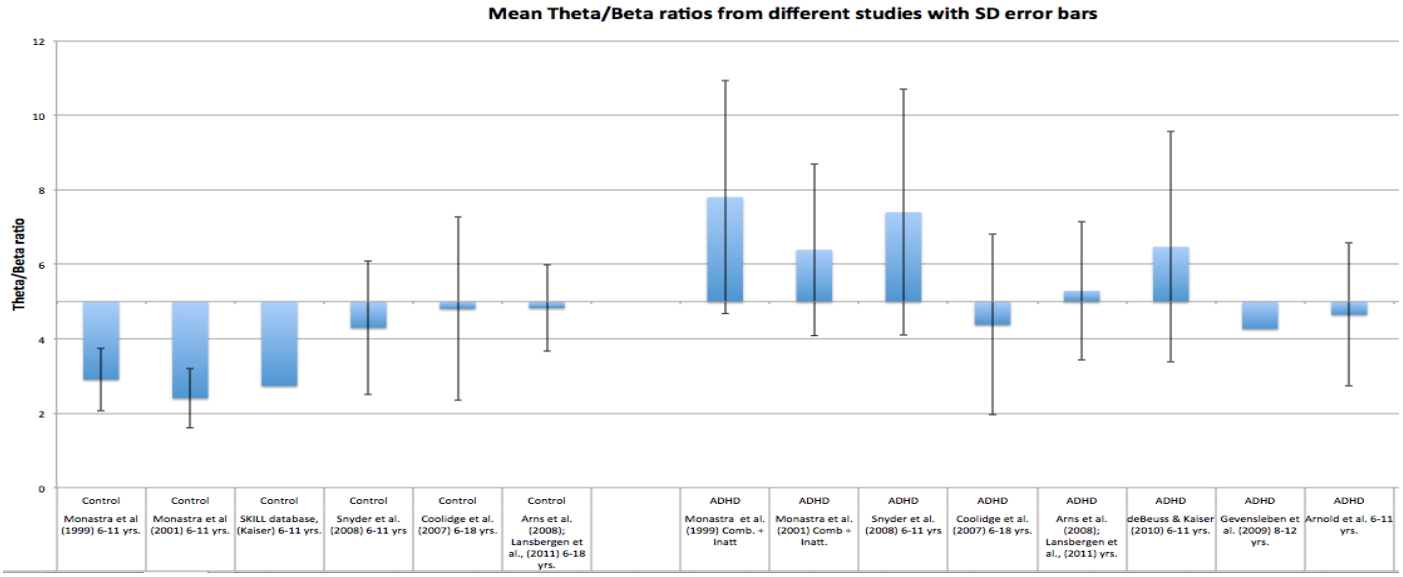
In addition to these frequently reported findings, three other neurophysiological sub-groups within ADHD have also been reported: 1) excess beta or beta spindling, which is more prevalent in males and responds well to stimulant medication (Chabot et al., 1996; 1999; Clarke et al., 1998; 2001; 2003; Arns et al., 2008; Hermens et al., 2005); 2) those with paroxysmal or epileptiform EEG activity, hypothesized to respond well to anticonvulsants and 3) those with a slowed individual alpha peak frequency (iAPF), in general considered non-responders to stimulants (Arns et al., 2008), rTMS (Arns et al., 2009) and antidepressants (Ulrich et al., 1984). Song et al. (2005) found that methylphenidate, a proven drug for ADHD, decreases theta in occipital and right temporal-parietal areas and increases beta in most areas.

Previous Randomized Clinical Trials (RCTs) of NF for ADHD

Consistent with the findings above, most studies of NF treatment of ADHD have used Theta-Beta NF (TBNF), downtraining theta and uptraining beta; 9/15 studies in a 2009 meta-analysis employed TBNF at fronto-central locations (Arns et al., 2009). To date, 11 published studies used a RCT design (Linden et al., 1996; Levesque et al., 2006; Leins et al., 2006; Gevensleben et al., 2009/2010; Holtmann et al., 2009, Perreau-Link et al., 2010; Lansbergen et al., 2010; deBeus & Kaiser, 2010 [a chapter]; Steiner et al., 2011; Bakhshayesh et al., 2011; Arnold et al, 2012). Most studies reported significant reductions in ADHD symptoms compared to a control condition and some showed neurophysiological changes specifically associated with NF. A meta-analysis by Arns (2009) of 6 peer-reviewed randomized trials (Levesque, 2006; Leins, 2007; Gevensleben, 2009; Holtmann, 2009; Strehl, 2006; & Bakhshayesh, 2011) found a large effect size (ES, d=0.80) for inattention and medium ESs for hyperactivity (d=0.40) and impulsivity (d=0.69). In a more recent review of 9 controlled RCTs that reported ESs (Lofthouse et al., 2011), there was a medium between-groups mean ES of *d*=0.54 for overall ADHD symptoms (0.54 & 0.55 for inattention & hyperactivity/impulsivity, respectively). In addition to these clinical improvements, normalization of Event Related Potentials (ERPs) after NF (Arns et al., in press; Heinrich et al., 2004; Kropotov et al., 2005, 2007; Wangler et al., 2011), normalization of EEG power post-Tx (Doehnert et al., 2008; Gevensleben et al., 2009[b]), and effects on neural substrates of selective attention imaged with fMRI (Lévesque et al., 2006) have been demonstrated. Gevensleben et al., (2010) reported stability of improvements and superiority over the control condition on parent ratings at follow-up 6 months post-Tx . Four uncontrolled follow-ups 3-6 months post-Tx (Heinrich et al., 2004; Strehl et al., 2006; Leins, et al., 2007) and 2 years post-Tx (Gani et al., 2008) also found persistence and a trend for further improvement. However, each study is limited in some manner, (Lofthouse et al., 2010), *and a 2013 meta-analysis (Sonuga-Barke et al) concluded, "Better evidence for efficacy from blinded assessments is required …before [neurofeedback] can be supported as treatment for core ADHD symptoms."*

Gevensleben et al. (2009[b]) found higher pre-Tx theta predicted larger clinical improvements after TBNF, explaining 20% of the variance. This suggests that pre-selection of patients by TBR might enhance the clinical effects of TBNF. In a nonrandomized study of TBNF for participants pre-selected for excessive TBR, Monastra et al (2002) reported the largest within-participant ES to date for a NF study (Hedges' d = 1.81). A similar effect size (d=1.78) was found when NF protocols were personalized (Arns et al., in press). These 3 studies support the notion that high TBR may be a *treatment-response biomarker for an arousal/regulation endophenotype compatible with research domain criteria (RDoC).* The proposed study will select based on the TBR in order to maximize clinical effects. To decide on a specific cut-off value for an inclusion criterion we reviewed the literature, focusing on the eyes-open TBR from the Cz electrode. Those results suggest an inclusion cut-off value of the TBR of 4.5 or more, using 4-8 Hz as Theta and 13-21 Hz for Beta recorded at Cz or Fz with Eyes Open for 1.5 minutes. The central horizontal line in Fig. 1 below, indicating the value from which the control and ADHD means deviate is at a TBR of 5. Controls are on the left, ADHD on the right. The threshold of 4.5 or more was decided on advice from a statistical/design consultant to be more inclusive than exclusive.

Fig. 1. Review of TBRs comparing ADHD to normal controls:



Recent OSU Randomized, Double-Blind, Sham-Controlled Feasibility Pilot Study (Arnold et al, 2012). An NIMH R34 award funded a pilot feasibility study at Ohio State University (OSU) with the goal of preparing for a more definitive large-scale double-blind sham-controlled study. In a sample (N=39) of currently unmedicated 6-12 year-olds with ADHD recruited in 2 school years, compliance/completion was good (87% for 40 treatments, 92% for 20 treatments); 3X/week treatment frequency was preferred over and was equally as effective as 2X/week; the blind/sham control worked as a blinded treatment (only 32% of children & 24% of parents guessed the condition correctly; 1/3 did not even have enough idea to take a guess); and 30 treatments appeared adequate for maximal benefit. However, this last finding – asymptote of effect by treatment 30 – is in some doubt because it is not clear that the particular technology used was as effective as the more generally used methods of most NF experts. Although we were successful in achieving the primary purpose of the study, the feasibility goals, the clinical and neuropsychological outcomes showed no advantage of active treatment over placebo (generally significant small to large pre-post ES improvements for both). *Detailed clinical & NP outcomes are tabulated below. No between-group differences were significant:*

	Active Neurofeedback				Control (Sham) Condition			
	BL	Tx 24	Tx 40	FU	BL	Tx 24	Tx 40	FU
DSM-4 Symptoms	Rated by Teacher							
Total ADHD Sx	1.82 ±0.70	1.61 ±0.65	1.59 ±0.69	1.70 ±0.76	1.55 ±0.75	1.20 ±0.60	1.08 ±0.69	1.10 ±0.70
Inattention Sx	2.22 ±0.69	1.95 ±0.70	1.91 ±0.74	2.00 ±0.77	1.81 ±0.68	1.37 ±0.66	1.26 ±0.74	1.28 ±0.76
Hyperactivity Sx	1.42 ±0.90	1.28 ±0.84	1.28 ±0.89	1.39 ±0.98	1.29 ±0.94	1.03 ±0.63	0.90 ±0.72	0.92 ±0.72
Conners Teacher								
Oppositional	0.56 ±0.59	0.63 ±0.70	0.54 ±0.67	0.65 ±0.68	0.38 ±0.55	0.42 ±0.87	0.45 ±0.86	0.45 ±0.86
DSM-4 Symptoms	Rated by Parent							
Total ADHD Sx	1.91 ±0.51	1.48 ±0.60	1.56 ±0.70	1.60 ±0.59	1.86 ±0.44	1.56 ±0.52	1.42 ±0.58	1.58 ±0.49
Inattention Sx	2.36 ±0.48	1.87 ±0.64	1.95 ±0.82	2.02 ±0.65	2.19 ±0.42	1.78 ±0.55	1.66 ±0.68	1.87 ±0.59
Hyperactivity Sx	1.46 ±0.79	1.09 ±0.76	1.16 ±0.79	1.19 ±0.73	1.53 ±0.64	1.33 ±0.66	1.18 ±0.67	1.29 ±0.60
Conners Parent								
Oppositional	1.01 ±0.63	0.88 ±0.60	0.93 ±0.54	1.01 ±0.58	0.92 ±0.86	0.89 ±0.63	0.92 ±0.63	1.05 ±0.50
Cognitive Problems	2.16 ±0.50	1.85 ±0.55	1.96 ±0.57	1.87 ±0.62	1.89 ±0.49	1.75 ±0.60	1.64 ±0.59	1.75 ±0.46
Hyperactivity	1.33 ±0.84	1.12 ±0.78	1.13 ±0.77	1.11 ±0.75	1.32 ±0.73	1.13 ±0.73	1.04 ±0.64	1.02 ±0.56
Anxious/Shy	0.54 ±0.59	0.48 ±0.53	0.51 ±0.49	0.50 ±0.54	0.58 ±0.73	0.64 ±0.39	0.49 ±0.46	0.40 ±0.39
Perfectionism	0.53 ±0.57	0.46 ±0.43	0.50 ±0.51	0.49 ±0.50	0.75 ±0.72	0.71 ±0.60	0.71 ±0.74	0.68 ±0.73
Social Problems	0.65 ±0.51	0.67 ±0.66	0.68 ±0.62	0.67 ±0.65	0.71 ±0.83	0.76 ±0.83	0.73 ±0.68	0.73 ±0.68
Psychosomatic	0.47 ±0.55	0.32 ±0.39	0.37 ±0.42	0.34 ±0.47	0.48 ±0.79	0.61 ±0.60	0.41 ±0.38	0.38 ±0.48
ADHD Index	2.21 ±0.45	1.89 ±0.56	1.99 ±0.51	1.84 ±0.62	2.18 ±0.37	1.87 ±0.58	1.83 ±0.66	1.92 ±0.52
Restless-Impulsive	1.68 ±0.63	1.38 ±0.67	1.46 ±0.63	1.46 ±0.64	1.86 ±0.50	1.53 ±0.67	1.49 ±0.76	1.56 ±0.62
Emotional Liability	0.80 ±0.63	0.84 ±0.76	0.85 ±0.71	0.89 ±0.69	0.76 ±0.94	0.70 ±0.72	0.68 ±0.57	0.70 ±0.62
Total Global Index	1.42 ±0.55	1.22 ±0.61	1.28 ±0.53	1.29 ±0.57	1.53 ±0.53	1.28 ±0.62	1.26 ±0.63	1.30 ±0.55
BRIEF by Parent								
Inhibit	21.4 ±4.8	19.7 ±5.3	20.0 ±5.5	20.4 ±6.6	21.3 ±4.8	20.3 ±4.1	19.8 ±4.8	18.6 ±4.2
Shift	14.0 ±4.2	13.8 ±4.3	14.0 ±4.1	15.0 ±4.6	14.1 ±3.2	14.5 ±2.4	13.9 ±3.8	14.4 ±3.8
Emotional Control	18.7 ±4.6	18.6 ±5.8	18.8 ±5.1	19.1 ±5.9	17.6 ±5.4	17.7 ±3.8	17.5 ±3.8	16.1±3.8
Initiation	18.0 ±2.7	17.0 ±2.9	17.6 ±2.6	18.3 ±3.1	17.6 ±3.4	17.5 ±2.6	16.8 ±4.0	17.3 ±4.0
Working Memory	27.3 ±2.4	25.3 ±3.1	25.7 ±2.9	25.7 ±3.9	25.9 ±3.1	23.5 ±4.0	24.5 ±4.9	24.0 ±4.9
Plan/Organize	30.1 ±3.1	28.7 ±3.5	30.0 ±4.2	29.0 ±5.0	28.3 ±2.8	28.0 ±4.2	27.5 ±5.7	27.8 ±5.0
Monitor	20.2 ±2.9	19.1 ±3.3	19.3 ±3.1	18.9 ±3.4	19.4 ±2.8	19.1 ±2.0	18.3 ±2.7	17.7 ±2.9
Beh Regulation	54.1 ±11.0	52.1 ±12.4	52.8 ±12.5	54.5 ±15.7	53.0 ±10.7	52.5 ±7.9	51.3 ±9.3	49.1 ±9.3
Metacognition	111.8 ±8.8	106.0 ±11.3	108.6 ±11.2	107.9 ±14.6	107.2 ±10.2	102.9 ±12.6	102.5 ±16.3	101.8 ±16.8
Global Composite	165.9 ±17.6	158.1 ±20.3	161.3 ±21.3	162.4 ±27.7	160.2 ±17.1	155.4 ±17.9	153.7 ±23.4	150.9 ±23.9
Cognitive Problems	1.63 ±0.83	1.45 ±0.62	1.52 ±0.76	1.61 ±0.73	1.24 ±0.49	1.03 ±0.61	0.91 ±0.67	1.01 ±0.69
Hyperactivity	1.50 ±0.93	1.36 ±0.85	1.37 ±0.85	1.44 ±0.97	1.14 ±0.88	1.00 ±0.86	0.95 ±0.90	0.99 ±0.89
Anxious/Shy	1.01 ±0.61	0.91 ±0.59	0.83 ±0.67	0.91 ±0.73	0.52 ±0.35	0.38 ±0.37	0.44 ±0.44	0.33 ±0.44
Perfectionism	0.52 ±0.80	0.41 ±0.57	0.49 ±0.84	0.43 ±0.78	0.27 ±0.26	0.29 ±0.30	0.35 ±0.43	0.37 ±0.44
Social Problems	1.06 ±0.93	1.08 ±0.99	1.09 ±0.97	1.01 ±0.96	1.10 ±0.90	0.91 ±0.82	0.95 ±0.89	1.00 ±0.83
ADHD Index	1.95 ±0.79	1.87 ±0.66	1.88 ±0.75	1.94 ±0.84	1.72 ±0.76	1.50 ±0.80	1.31 ±0.89	1.42 ±0.96
Restless-Impulsive	1.97 ±0.80	1.87 ±0.77	1.84 ±0.79	1.90 ±0.89	1.68 ±0.88	1.52 ±0.81	1.26 ±0.86	1.37 ±0.98
Emotional Liability	0.75 ±0.77	0.86 ±0.90	0.76 ±0.93	0.92 ±0.95	0.40 ±0.57	0.40 ±0.65	0.45 ±0.67	0.40 ±0.70
Total Global Index	1.48 ±0.66	1.46 ±0.75	1.41 ±0.76	1.51 ±0.80	1.17 ±0.69	1.07 ±0.67	0.94 ±0.75	0.98 ±0.79
BRIEF by Teacher								
Inhibit	21.3 ±6.4	21.2 ±6.4	21.7 ±6.1	22.1 ±6.7	19.3 ±6.8	18.7 ±6.8	18.2 ±7.3	19.1 ±7.0
Shift	18.0 ±5.1	16.9 ±5.3	16.5 ±4.8	16.3 ±5.2	14.0 ±4.4	13.7 ±3.4	14.5 ±4.3	14.2 ±4.3
Emotional Control	16.6 ±5.0	15.9 ±6.0	15.5 ±5.5	16.1 ±6.3	12.7 ±4.2	12.5 ±5.2	12.9 ±5.2	12.9 ±5.1
Initiation	16.6 ±3.2	16.0 ±2.3	16.0 ±2.9	16.4 ±2.8	14.6 ±3.8	13.1 ±3.6	12.7 ±4.2	13.3 ±4.3
Working Memory	25.0 ±5.4	24.0±5.0	23.6±5.8	24.6 ±5.2	23.2 ±4.2	19.7 ±5.5	19.1 ±5.7	19.5 ±6.1
Plan/Organize	23.3±5.8	22.4 ±3.9	22.5 ±4.8	22.9 ±4.7	19.6 ±4.7	18.4 ±5.4	18.3 ±5.0	18.6 ±5.3
Monitor	23.4 ±4.4	23.0 ±4.0	22.7 ±4.4	23.5 ±4.1	22.0 ±5.1	21.0 ±4.4	20.6 ±4.6	21.2 ±5.5
Beh Regulation	56.0±13.3	54.0±15.5	53.6±14.4	54.6±16.2	46.0±12.1	44.9±14.5	45.6±15.7	46.2±15.1
Metacognition Index	104.5±20.8	101.5±16.1	100.8±19.3	103.7±18.1	92.9±18.0	84.6±21.0	83.4±22.6	85.6±23.9
Global Composite	160.5±32.1	155.5±27.9	154.4±29.8	158.2±31.0	138.9±29.2	129.5±33.9	129.0±37.0	131.8±37.7
CGI-I by Clinician		3.32 ±1.28	3.40 ±1.53	3.72 ±1.34		3.00 ±0.89	3.27±1.56	3.18 ±1.08
Timed Math Test								
Percent Correct	78.1 ±16.9	84.8 ±10.6	84.7 ±12.9	78.9 ±21.2	79.2 ±18.3	86.6±13.3	87.3 ±10.2	83.7±12.0
Number Correct	22.9 ±15.9	27.8 ±12.6	25.0 ±12.4	21.2 ±16.0	23.7 ±10.9	31.1±15.1	29.8 ±12.8	30.7±13.2
BRC (NP Tests)								
Attention	-1.06 ±1.22	-1.11 ±1.48	-1.41 ±1.33	-1.05 ±1.53	-1.14±1.08	1.13±1.85	-1.36±1.39	-.64 ±1.66
Working Memory	-.20 ±.85	-.07 ±.93	-.28 ±.83	-.20 ±.85	.11±.85	.46±.95	.17 ±.65	-.18 ±0.75

Exec. Function	-.97 ±1.23	-.65 ±1.72	-1.35 ±1.51	-.50 ±1.36	-.92 ±1.71	-.49 ±1.95	-1.16±1.56	-.78 ±1.11
Sustained Atten	-1.52 ±1.30	-1.16 ±1.56	-1.69 ±1.47	-1.28 ±1.85	-1.19±1.01	-.77 ±2.20	-1.85±1.72	-.88 ±1.78

The results of this small pilot trial should not be taken to negate accumulated findings from the positive nonblind randomized controlled trials in the literature. Due to limitations of the equipment used, it was not possible to establish whether any EEG learning took place. DeBeus & Kaiser (2010), using the same equipment, did not find effects of NF at the group level, but did find effects in EEG "learners." The OSU pilot employed technology that, although appearing optimal at the time, differed from most of the extant research -- and that many NF experts consider sub-optimal. Its limitations included: 1) auto-thresholding (making the learning goal a 'moving target'), 2) continuous rather than discrete feedback, 3) use of video-game feedback, possibly distracting rather than informative and 4) unconventional NF protocols. The sample may have been biased by an unintended selection for families willing to give up ADHD medication for 5 mo., which would tend to select for milder severity, unresponsiveness to medication, or prejudice against medication. The sample failed to show the EEG spectral characteristics found in other studies; baseline TBRs were intermediate between normal children and children with ADHD responding to NF in previous research. We also included some children under 7 yr old, slightly younger than most other studies. Finally, it is conceivable that sham placebo involving random, apparently noncontingent feedback may have been therapeutic (e.g. Skinner, 1948; Ono, 1987). The data from the technology employed did not allow testing this possibility, but the proposed study will track occasions when the random reinforcement inadvertently coincides with the training target. Thus the NIMH-OSU pilot (Arnold, 2012) and 2 other small placebo-controlled studies (Perreau-Link, 2010; Lansbergen, 2010) suffered methodological flaws precluding final conclusions. Therefore the RCT proposed here is designed by a collaborative group involving experts from all areas to insure a valid double-blind design.

In sum, the NIMH-funded OSU pilot feasibility study indicates that a well-blinded large RCT of NF utilizing a sham control of equal intensity and duration is feasible and much needed. The discouraging exploratory comparison of active treatment to placebo (both showing comparable benefit) makes the proposed double-blind RCT *all the more necessary in view of the multiple positive unblinded studies and the elevation of NF to "Level 1 --Best Support" by PracticeWise (& consequently American Academy of Pediatrics (AAP, 2012).* Both AAP and the ADHD advocacy organization CHADD support the study (see letters). Our results suggest: 3 treatments per week as the most feasible, efficient, and palatable; a large sample, selectively recruited with a high TBR; age >7 years; including children on stimulant medication as well as unmedicated (for sample representativeness); and use of optimal NF treatment technology.

Standardization of Treatment is one of the important issues this study addresses. Currently anyone can obtain an EEG machine and offer neurofeedback. There are even "canned" systems commercially available that use games to provide feedback. One such was used in the pilot study. Neurofeedback experts, such as the consultants on this project, point out problems with those, such as the fuzzy logic that adjusts the reward threshold automatically every minute. They agree on the following points, which constitute the standardized but personalized optimal treatment to be used in this study: selection of treatment candidates for theta-beta training by high theta-beta ratio; review of qEEG to determine optimal electrode placement; adherence to learning principles; manual personalized threshold adjustments that allow the patient to consolidate success at each level; individualized coaching one-to-one; and appropriately trained administrators ("trainers"). At the OSU site, doctoral-level trainers will administer the neurofeedback after intensive training by Vincent Monastra, an acknowledged master in the field and other leading neurofeedback experts. At the UNCA site, either doctoral-level or graduate-student trainers or master's level trained and experienced neurofeedback trainers will administer the neurofeedback. In this study, treatment is further standardized by training of the trainers, supervision, and fidelity monitoring by 2 acknowledged neurofeedback experts.

Difference of the treatment in this study from that used in previous blinded studies: Other blinded studies did not adhere to the optimal treatment outlined above in a. For example, the OSU pilot used the Cyberlearning Technology system, which used fuzzy logic to adjust the threshold of theta-beta ratio every few seconds based on a moving 1-minute window, which could be confusing and frustrating to the patient. Further, the feedback was provided through a videogame in which the speed of a race car was governed by the theta-beta power. The neurofeedback experts who have reviewed this approach and are collaborating in this study do not expect it to be effective and note that it does not follow sound learning principles. They insist that although it may seem attractive to make the treatment fun with a game, it is better for the child to learn to

direct attention without the game with adult coaching and to experience success at each level before the reward threshold is changed. The approach to be used in this study was critiqued at a meeting of the International Society for Neurofeedback and Research and the treatment method is generally acceptable, in contrast to criticism of the previous blinded studies.

Cost Comparison*; The high up-front cost of NF ($100-$175 per treatment for 30-40 treatments) may appear to make it noncompetitive with the demonstrated short-term effectiveness of medication for ADHD, now available as generics for many extended-release(XR) formulations. However, if it results in permanent improvement making medication unnecessary, as suggested by the follow-up studies, it may be a good investment. Medication works only while taken. A discount drug web site listed prices for 30 generic XR doses from $110 (d-amphetamine) through $140 (mixed amphetamine salts) to $193 (d-methylphenidate LA). Thus if one capsule/day is sufficient, a month's med supply costs about the same as one NF treatment. --But some children require more than one capsule to make their dose or need it more than once/day, and these amounts do not include cost of physician monitoring. Thus if 30-40 NF treatments prevented 2-3 yr. of medication, it could be cost-effective as well as safer.*

Questions about Sham Double-Blinding. There has been a question whether NF should be evaluated as an unblindable psychological treatment using APA guidelines (Arns, 2009; Sherlin, 2010a; 2010b) or as a blindable treatment requiring double-blind placebo controlled trials (Lofthouse, 2010; 2011). La Vaque and Rossiter (2001) argued ethically against sham, citing the Declaration of Helsinki (World Medical Assoc., 2000), which "prohibits designs that would withhold the best proven diagnostic and therapeutic Tx" (p. 23). Others reject this position for several reasons, including: problems with defining "best-proven" Tx; the Declaration of Helsinki being aspirational, not mandatory; the difficulty of interpreting no significant difference between two active treatments; the clinical and scientific necessity of a placebo study when there is minimal risk, informed consent, and need of important research for future clinical care; and the probability that placebo controls require fewer participants than active controls, reducing exposure to risks (e.g., Lofthouse, 2010). On such rationales the FDA often requires placebo-controlled studies for new drugs.

The practical question about sham Tx in NF research involves three issues. First, NF researchers have questioned whether a sham Tx can be truly inert and not lead to learning via unintentional feedback. There could be times when the child's brainwaves fall in the desired target range as random reinforcement is given. Training could also occur via random reinforcement cuing the participant to pay attention, moving naturally into the desired EEG Tx target range. In some non-NF studies non-contingent feedback resulted in 'superstitious behavior' (Skinner, 1948; Koichi, 1987). None of the three RCTs that used a sham Tx (Perreau-Link, 2010; Lansbergen, 2010; Arnold, 2012) investigated the possibility of unintended feedback. However, Hill and Zaidel (2011) used a sham NF vs. real NF (with a non-ADHD sample) and time-marked participants' EEGs with rewards; they found no unintended feedback with the sham. A 2nd practical issue is whether a sham Tx that is truly inert can be blinded to participants, informants, and experimenters. As none of the three RCTs tested the inertness of their sham, there are no data on this issue specific to ADHD. However, Hill & Zaidel (2011), using technology similar to that in the study proposed here, found participants were unable to guess their assignment better than chance, and by the 4th Tx the 2 randomly assigned groups diverged significantly in EEG measures. This suggests that the active Tx but not the sham affected the EEG, and subjects could not tell the difference. In fact, one subject worked elsewhere as a NF technician and was convinced she was receiving "real" NF even though actually assigned to sham. In addition, Arnold et al. (2012) examined blinding validity for participants and parent informants and found their guesses about Tx assignment no better than chance. *Thus practical questions of sham inertness and blindability appear to be resolved adequately for implementation.*

The final practical concern regarding a sham control is whether a sample can be recruited and retained through assessments and 40 Tx sessions when using a blind sham Tx. Some NF investigators thought families would not consent to a sham condition. However, Arnold et al. (2012) recruited 39 participants in two school years with 87% retention for 40 Tx, with excellent blinding of children and parents.

The proposed design will, for the first time in ADHD, incorporate time stamping of sham-condition reinforcement events on the sham subject's real EEG, making it possible to determine post-hoc if there may be any inadvertent contingencies generated by the sham condition. Trainer/technician blindness will also be insured by a carefully crafted technology described below and will be checked by trainer guesses at Tx end.

Research Domain Criteria Issues. The proposed study provides an opportunity to explore research

domain criteria (RDoC) for a clinical phenotype with an arousal/regulation biomarker that predicts response to a specific treatment. We will examine the biomarker of EEG TBR, with sleep delay as part of its clinical phenotype, along with inattentiveness & impaired executive function. Recent studies suggest sleep-onset insomnia in 70-80% of children (Van der Heijden, 2005; 2007) and adults with ADHD (Van Veen, 2010; Rybak, 2007), present before age 3 years (van der Heijden, 2005). This sleep onset insomnia (delayed sleep phase) results in an accumulating sleep deficit with a dose-response effect on attention (Axelsson, 2008; Belenky, 2003). Extended sleep restriction can induce 'ADHD-like' behavior in healthy children (Fallone, 2001; 2005; Sadeh, 2003; Beebe, 2008). A meta-analysis with 35,936 healthy children found sleep duration positively associated with school performance & executive function and negatively associated with behavior problems (Astill, 2012). Thus the increased theta and elevated TBR reported for ADHD may reflect drowsiness from sleep delay. Furthermore, daytime NF training produced increased sleep-spindle density during sleep in cats (Sterman, 1970) and humans (Hoedlmoser, 2008), as well as shorter sleep onset in insomnia patients (Cortoos , 2009,) suggesting sleep-normalizing effects of NF. Chronobiological treatments such as melatonin, which also increases sleep-spindle density (Dijk, 1995) have been reported efficacious for sleep in ADHD (van der Heijden, 2007; Hoebert, 2009). In a NF study personalized on the individual QEEG, Arns (2011) found an effect of d=1.78 for inattention, and improved sleep tended to precede improvements of attention. Thus we hypothesize an ADHD subgroup (40-80% of children with ADHD) identifiable by high TBR, responsive to theta downtraining, with sleep delay, inattentiveness, and executive function impairment.

Genetic Factors

Research has demonstrated a significant link between several genes and the development of attention-deficit/hyperactivity disorder (ADHD; e.g., Jain et al., 2012). Genes associated with ADHD play a role in the dopaminergic and serotonergic pathways and include DAT1, DRD4, DRD5, 5HTT, HTR1B, and SNAP25 (Gizer, Ficks, & Waldman, 2009). Specific SNPs (e.g. LPHN3, SLC6A3), have also been identified to mediate treatment response to stimulants (Arcos-Burgos et al., 2010). Of note, research has also demonstrated the role SNPs [e.g., DRD4-7-repeat allele (Bakermans-Kranenburg et al., 2008), rs4657412 (LMX1A; Bellander et al., 2011); and SLC613 (DAT1; Soderqvist et al., 2012) play in the mediation of specific training techniques aimed at improving working memory and cognition and reducing externalizing behaviors. Therefore, identification of specific single nucleotide polymorphisms that are associated with elevated TBR and treatment response to neurofeedback may help physicians and mental health practitioners individualize and increase the efficiency and effectiveness of ADHD treatments through personalized medicine/intervention.

Sleep Parameters

Because fatigue and sleep deprivation are believed to contribute to the day-to-day variability of TBR, we propose more in-depth studyassessment of sleep context in theis study. It has been shown that sleep onset insomnia results in accumulating sleep deficit with a dose-response effect on attention (Axelsson, 2008; Belenky, 2003). Approximately, 70-80% of children as well as adults with ADHD have sleep onset insomnia (Van der Heijden, 2005; 2007; Van Veen, 2010; Rybak, 2007). In addition, it has been shown that daytime SMR NF training increased sleep spindles during sleep in cats (Sterman et al., 1970) and humans (Hoedlmoser et al., 2008) and resulted in a reduced sleep onset in insomnia patients (Cortoos, 2010), suggesting the clinical effects of NF are mediated by sleep normalizing effects. Recent evidence supports the hypothesis that a sub-group of individuals with ADHD may be characterized by circadian rhythm sleep delay (CRSD) and indeed that the clinical effects of ADHD were mediated by normalizing sleep (Arns & Kenemans, 2014; Arns, Feddema & Kenemans, 2014). By identifying the possible moderating effects of baseline SOI and the mediating effects of sleep normalization we will aid clinicians and therapists in the development of individual training plans that may be more effective and efficient for youth with ADHD who have with baseline SOI.

Summary of Scientific, Clinical, and Public Health Importance:

Current evidence-based treatments for ADHD (medication & behavior modification) are incompletely effective for ~1/3 of children, do not have long-term effects documented beyond 2 yr, and are declined by some families. Perhaps the most promising additional intervention is NF, which, despite its difficulty and

expense, has become increasingly popular. *PracticeWise, on which the American Academy of Pediatrics bases its practice recommendations, recently (2012) recommended "elevating biofeedback to 'Level 1 - Best Support' for ADHD." Although NF has significant initial costs, it may be cost–effective (and safer) by preventing long-term medication.* However, despite 11 RCTs with a medium mean effect size (ES) for ADHD symptoms and a meta-analysis of 6 with a large ES for inattention, medium for hyperactivity/impulsivity, most of these studies did not use adequate blinding. Four small double-blind studies are inconclusive.

The lack of a large well-controlled double-blinded examination of NF has been a critical barrier to progress; NF experts and most mainstream ADHD investigators disagree about interpretation of available data. The p*atient advocacy group CHADD, the American Academy of Pediatrics (see support letters), and* both the ADHD and NF research communities have a strong interest in finding whether NF can demonstrate a specific effect. By examining pre/post QEEG and ERP for the sham condition and retroactively studying the relationship between the sham participant's actual EEG and the timing of sham "contingencies", we can see whether our sham condition is really the inert placebo it is intended to be or whether it inadvertently reinforces the participant, leading to QEEG/ERP changes. This would resolve the debate whether the double-blind placebo-controlled standard or the nonblind standard of psychotherapy RCTs is most appropriate to NF.

If NF shows significant clinical benefit beyond the sham –i.e., beyond nonspecific placebo response--, whether or not the sham also shows unintended EEG training, it will be evidence of specific NF effect suitable for adoption as an efficacious treatment for ADHD. Especially if the benefit persists over time, this evidence will significantly inform decisions about inclusion of NF in comprehensive care. *With demonstration of specific and enduring effect, insurance coverage and routine inclusion in clinics will make it accessible to those who need it.* However, if no clinical outcome difference is found, and if the sham did not inadvertently train the EEG, it allows a conclusion that NF did not have significant specific clinical effects beyond placebo response. Then consumers, insurers, practitioners, and investigators may choose to redirect their resources to other new treatments for ADHD. *If the specific effectiveness of NF is demonstrated in this study, it will pave the way for other valuable studies, such as open comparison to medication (perhaps in a 2X2 design)* or computer-based cognitive training, and cost-effectiveness studies. Of equal scientific interest are the RDoC possibilities: testing the high-TBR biomarker, ERP imaging, moderator & mediator analyses, and relationship of TBR to *impairment*, sleep, & executive function. Although NF is initially expensive and time consuming, it would, if proven specifically effective in a double-blind RCT, have clinical and public health advantages over both medication (safety) and widely used psychosocial treatments that cannot clearly differentiate placebo effect from specific effect because of double-blinding difficulties.

INNOVATION The proposed RCT is innovative on several fronts:

This will be the first sham-controlled RCT of NF with a large enough sample to detect a medium specific effect. Previous sham-controlled trials had too small a sample to rule out type 2 error, and the large studies showing a significant effect were not sham-controlled so that we cannot be sure the effect is specific rather than nonspecific placebo response. This study will for the first time address both shortcomings.

Second, the *investigative team is unique for the NF field.* Previous literature and conference presentations reveal considerable tension between mainstream ADHD experts and NF experts. In contrast, the planning and execution of this RCT involved both mainstream ADHD scientists and RCT experts (to insure credible scientific rigor) and NF experts (to insure credible, rigorous treatment). Because all stakeholders have input, the results, whatever they are, will be credible to all. Planning was undertaken by a *group formed at the November 2010 ChADD annual meeting following presentation of the NIH/OSU pilot study results.* For over a year this group teleconferenced weekly to plan a large double-blinded RCT of NF in ADHD. The proposed protocol, the natural follow-up to the NIH pilot feasibility trial, received plenary critique at the 2011 meeting of the International Society for Neurofeedback & Research. The cross-site investigational team was selected not only for balance between NF and mainstream ADHD investigators, but also for expertise in treatment strategy, assessment, design, biostatistics, data management, and multisite RCT execution. There will be 2 sites, one university-based (OSU, L. Eugene Arnold, M.D., PI) and one at a NF clinic in North Carolina associated with UNCA (Roger deBeus, Ph.D., PI), each of which will recruit 70 participants. *Dr. Arnold will be coordinating PI for the study as well as site PI for OSU. Dr. deBeus has conducted NF research funded by state (Virginia Health Research) and private foundations (Riverside Healthcare and Edwin Joseph foundations). In a previous 44-visit ADHD NF study, he coordinated 4 treatment sites (two schools, a hospital setting, and a university*

setting), approved by 2 IRBs (hospital and university). Within one and a half years, 92 children were screened and 56 entered the study. Upon funding of this grant, Dr. deBeus will visit OSU to become familiar with specifics involved in federally funded studies; he is affiliated with University of NC, Asheville, which will administer the grant fiscally.

In addition to these investigators, the study will include a consultation team of experts in the fields of NF (Vincent Monastra, Ph.D., Cynthia Kerson, Ph.D., Laurence Hirshberg, Ph.D., & Martijn Arns, Ph.D.), ADHD RCTs (Keith Conners, Ph.D., Helena Kraemer, Ph.D., L. Eugene Arnold, M.D., Keith McBurnett, Ph.D.), statistics (Helena Kraemer, Ph.D., Jeff Pan, Ph.D.) and data management (Robert Rice, Ph.D., of the OSU Center for Clinical and Translational Science).

Third, *new double-blinding technology* will be used that has been demonstrated by Hill & Zaidel (2011) in a non-ADHD study: Feedback for sham will be based on a pre-recorded EEG on which the participant's eye muscle and other artifacts are overlaid so that the trainer/technician (as well as participant) has no clue.

Fourth, for the first time the *sham condition will be checked for unwitting reinforcement* by time-marking the reinforcements on the participant's EEG for later inspection. This provides a check on the sham inertness.

Fifth, in accord with RDoC, we include data and exploratory analyses to examine TBR as a possible biomarker for treatment response that cuts across ADHD subtypes and identifies a clinical phenotype characterized by inattentiveness, impaired executive function, sleep-onset insomnia, and sleep deficit.

Sixth, a cost-effective physiological neuroimaging strategy (LORETA) will be used to explore *effects of NF on deeper brain structures* known to be involved in ADHD.

APPROACH:

Design. The design will be a 2-site, parallel-group, double-blind randomized comparison of active NF (n=84) to sham NF (n=56) for up to 38 treatments in a 13-week period, with 6, 13, and 25 month follow-ups, in 140 children age 7-10 with rigorously diagnosed DSM-IV ADHD.

Randomization Ratio: At each site, participants will be randomized to active vs. sham in a 3:2 ratio, in blocks of 5, balanced on current ADHD medication. Woods et al. (1998) have recommended a less than 1:1 proportion of placebo assignment when the main interest is in comparing issues of active treatment. With Dr. Kraemer's consultation, we have decided on 40% of the sample with sham as statistically adequate and ethically desirable (as well as useful for recruitment) to minimize the sham exposure, in view of the fact that the sham participants will be considerably inconvenienced. A 3:2 randomization ratio requires only negligible increase of the N and has been considered in the power analysis below. Randomization will be supervised by the study biostatistician and data management center staff who will not have any contact with participants or assessments, and will be implemented by an unblinded consultant who has no contact with participants.

Participants

Inclusion Criteria*:* Participants will be 140 boys and girls age 7 through 10 years with IQ≥80 and rigorously diagnosed DSM-5 ADHD inattentive presentation or combined presentation (structured interview and doctoral-level clinician using DSM criteria). *Hyperactive-impulsive type are excluded because we expect very few at this age and they might complicate use of inattention as the primary outcome.* To insure clinically meaningful severity, all participants will have an item mean ≥1.5 sd above norms on a 0-3 metric both on parent ratings of either DSM-IV inattentive symptoms or all 18 ADHD symptoms and on teacher ratings of either inattentive symptoms or all 18 ADHD symptoms (while off medication for purposes of assessment). For this purpose, the parent ratings on the appropriate items from the screen Conners 3 scale and the abbreviated form of the Conners 3 restricted to ADHD symptoms will be used for initial inclusion. Ratings will be rechecked at baseline on the Conners 3 by each informant. If a baseline teacher (or parent) rating of inattention decreases more than 25% from screen, but still meets inclusion criteria, the subject will begin treatment and the ratings will be discussed with the teacher (or parent) to make sure it is accurate. If a baseline teacher (or parent) rating of inattention falls below the screen inclusion threshold, it will be discussed with the teacher (or parent) to make sure it is accurate, and if it is, it will be brought to the cross-site clinical/case panel before treatment starts for a decision about inclusion. Children also must have an eyes-open QEEG with theta-beta power ratio ≥4.5 at Cz or Fz, above the normal mean for age based on norms by Monastra et al. (1999) and Snyder & Hall (2006).

Exclusion Criteria*:* Participants will be excluded if they have a comorbid disorder requiring psychoactive medication other than FDA-approved ADHD medication, a medical disorder requiring systemic chronic

medication with confounding psychoactive effects, convergence insufficiency, sleep apnea, restless legs syndrome, IQ <80, plans to move requiring school change during the next 3 months, plans to start other ADHD treatment in the next 3 months, antipsychotic agent in the 6 months prior to baseline assessment, fluoxetine in the 4 weeks prior to baseline, atomoxetine in the 3 weeks prior to baseline, alpha-2 agonist or other non-stimulant psychotropic medication for ADHD as the primary ADHD medication, other psychiatric medication in the two weeks prior to baseline, or >5 previous NF treatments. *Concomitant psychosocial Tx is not allowed.* Participants who are taking stimulants for their ADHD may continue taking them during the study but *must discontinue for 5 days including at least 3 days at school, such as a weekend and 3 school days, before major study assessments* (baseline, treatment 20, treatment 40, and follow-ups) to prevent biasing the data. *They will be reminded at preceding visits about temporary medication withdrawal and for follow-ups will have a phone reminder.* Any permissible, non-stimulant psychotropic medication taken as the secondary ADHD medication does not need to be washed out. Vitamin D deficiency will be a temporary exclusion; after repletion, candidates who still meet diagnostic categorical and severity criteria may enter.

In equivocal cases of inclusion/exclusion, the final decision will be made by a weekly cross-site case panel consisting of the steering committee.

Treatment (Tx) Strategy and Number of Treatments

The intended treatment is downtraining of theta power and uptraining of beta power for 38 treatments of active NF vs. 38 treatments of sham NF using stored EEGs to preserve the blind. It has been conventional in both clinical and research NF to administer between 20 and 40 treatments. The OSU pilot feasibility study suggests asymptote of improvement by Tx 24, but that result is questionable for reasons discussed above. The Arns et al. (2009) meta-analysis shows the best ES to be in studies that used 35 treatments or more. In this study, we are planning 40 sessions; however, sessions 20 and 40 will be used for major assessments, leaving 38 sessions of actual treatment, which the NF experts on the team assure should be sufficient.

Management of the monetary reinforcement during treatment: The treatment is based on reinforcement of the desired brain wave frequencies by points that can be cashed for money. This is part of the optimal neurofeedback treatment. It is necessary for some reward to be earned each session for reinforcement to occur, but that the maximum possible not be consistently earned in order not to satiate and reduce motivation; these are standard learning principles. Therefore the child's reward per treatment session will vary,

Each session, the child participates in 5 training tasks. Each task lasts 5 minutes at the beginning and gradually increases to 9 minutes per task over the course of the neurofeedback as the child's attention span improves. We record four results for each of the 5 tasks:

1. The number of half-second periods that they met the reward parameters (i.e. theta mV below threshold; beta mV above threshold)
2. Average voltage of theta waves
3. Average voltage of beta
4. Average ratio of theta to beta power (TBR)

Each time the patient's score is better than the threshold on any of the 4 measures, they earn a point. Four possible points on each of 5 tasks makes a total of 20 points that can be earned each session. When the child earns 20 points, he/she is given $15.00. If they earn fewer than 20 points in a session, we "bank" their points and add them to the next session's total. When a child totals 20 points, he/she is given $15.00. It is rare for a child to earn the whole 20 points each session. More likely, they will earn 9-14 points per session.

The initial training thresholds are based on the child's baseline qEEG. setting the theta threshold at a mV level that enables the child to be below the "theta threshold" approximately 60% of the time to start. The beta threshold is set so that the child is above the "beta threshold" approximately 40% of the time to start. These thresholds are not changed for the first five sessions, allowing the child to experience considerable success. After the 5th session, we calculate the average theta and beta output (mV) over the 5 sessions, and adjust the thresholds using the same process employed in Monastra's 2002 study: Mean mV theta minus 1 mv, and mean mV beta. The child will continue to be awarded "points" based on his/her ability to reduce mV theta in any task, increase mV beta in any task, decrease the TBR on any task, or increase the number of half-seconds meeting the reward thresholds on any task relative to their personally set threshold (total of 20 points possible per session). Every 20 points can be cashed for $15. The threshold is reset after another 5 sessions in the same manner.

Mid-treatment Decision about Continuing: We are deliberately recruiting only from late August through February so the child has the same teacher for baseline, mid-treatment, and end-of-treatment assessments in the 3-month treatment. Those recruited in August will have delay of baseline for 3 weeks of school to get a valid teacher baseline rating. Parent ratings are also considered in the decision to abort treatment. We have found by review of data from several studies that those who do not show at least a 10% improvement in parent or teacher rating by 19 treatments do not respond after 38 treatments. Therefore those who do not show a 10% improvement in the average of parent and teacher ratings at the midpoint assessment will exit neurofeedback treatment and receive standard ADHD treatment (e.g., FDA-approved medication and/or parent training or other behavioral treatment) for the remaining time.

As part of the protocol, without breaking the blind, all participants will have clinical progress (parent and teacher ratings of inattention) evaluated at session 20 (after treatment 19). Those who have not shown a beginning of response (10% decrease in average symptom score) will for ethical and cost reasons exit double-blind study treatment (but not the study) and have conventional clinical follow-up with some assistance to reimburse treatment costs such as prescription co-pays or behavior therapy. (The saved subject reimbursement from the last 19 treatments can be used for this.) Data from 2 studies show that those who do not have at least 10% improvement on parent rating by midpoint do not respond to the full treatment, whether NF or control condition. Every treatment has some nonresponders, so it should not be surprising that we expect some nonresponders in this trial. Because of the patient & family time/effort burden and the cost of wasted treatments, it is desirable not to continue a treatment that we can tell with confidence is not working. Active NF and placebo participants will be treated alike in this regard, without breaking the blind. All participants will be included in follow-up assessments and in ITT analyses, and all treatments received will be tracked for subgroup and covariate analyses. To insure good clinical practice, cases with marginal improvement (under 10%) by average of the parent and teacher rating that the site PI thinks could benefit from the full treatment trial may be appealed to a cross-site clinical panel for decision about continuing. Marginal cases are defined as having discrepancy between parent and teacher inattentive ratings, discrepancy between inattentive ratings and other information, or 8-10% average inattention improvement with other encouraging information.

Treatment Fidelity. An important issue will be quality assurance of optimal and reliable NF. All trainers/technicians will receive initial reliability training from Vincent Monastra, PhD, an acknowledged leader in the field. Then Dr. Monastra will monitor and promote treatment fidelity by reviewing videotapes of treatment sessions 5 times during treatment for each participant, by visiting each site yearly to observe, and by phone consultations as needed.

Follow-up Times. The 1-year follow-up will be done at 13 months from baseline, making it 10 months from completion of the 3-mo. NF treatment, the same time lapse from Tx end as the 24-month assessment was from the end of the 14-mo. Tx of the Multimodal Treatment Study of ADHD (MTA, a “gold-standard” of Tx outcome studies in ADHD). Similarly, the 2-year follow-up will be 25 months from baseline, 22 months from treatment end, the same time lapse from treatment end as the MTA 36-month assessment. The importance of this is that the MTA medication advantage had attenuated by 24 months and was lost by the 36-month assessment (22 mo. post-Tx). If NF advantage persists to 25 mo., it will suggest more “staying power.”

NF Equipment/Technology: NF training will use the FDA-registered EEGer NF system (EEG Software LLC , Northridge, CA),), using either a Thought Technology or BrainMaster Atlantis amplifier. Although the two amplifiers are considered equally effective, the amplifier for a given subject will be assigned randomly by the statistician, balanced for treatment assignment, and the same brand of amplifier with be used for all sessions of a given child. The brand of amplifier will be checked as a potential moderator in the analyses. The basic training screens allow for operant training of three bands of EEG activity, two to be set for reduction of theta & increase of beta, and one to remove any reward when EMG activity (>35 Hz) increases. All contingencies and threshold changes are time stamped on the EEG record, which is stored for later analysis. At baseline, end of treatment, & 1-year follow-up, a multi-channel EEG will be recorded. EOG correction based on Gratton, Coles & Donchin (1983) will be applied to the 19-channel recording and these data will be further de-artifacted (from muscle artifact and residual EOG) using BrainVision Analyzer2 (Brain Products, Germany).

Blinding Strategy. *The blinding technology has been successfully tested by Hill & Zaidel (2011).* Participants assigned to sham and their trainers will be fed EEG data from pre-recorded files (recorded during live clinical

NF) rather than from the participant's live signal. Everything else is the same as using live data. In order to prevent unblinding of experienced NF trainers/technicians, artifacts from the participant's EMG and EOG are blended into the pre-recorded EEG so that the trainer controlling the feedback cannot differentiate between live and simulated data. The simultaneously saved real EEG, which is time-marked with the rewards provided by the sham feedback, will allow checking the possibility of unintended reinforcement. To insure trainer/technician blindness, the pre-recorded EEG will be 38 consecutive EEGs from the same age-matched clinical case so that EEGs of the sham group will also show "training progress" over successive sessions, like real NF. Some or all of these pre-recorded EEGs will be from clinic archives where patients signed a general permission for use of stored EEGs for research; if there are not enough of those meeting the criteria, additional treatment EEGs will be recorded specifically for this purpose using an appropriate IRB-approved consent form.

Even the treatment fidelity monitor(Dr. Vincent Monastra) will maintain the blind. Although they will review actual EEG summary data for all participants and make sure the training parameters are reset for all participants according to protocol, this will not unblind them. They will implement the same process for all participants without knowing whether the participant received "real" or "sham" feedback; they do not need to see the actual EEGs to make sure that the time per task increases after the 10th, 20th, and 30th sessions. They only need to inspect the computer data that indicates time per task and review the participant-therapist interactions (videotaped or on site visit) to confirm that coaching is optimal.

Actigraphy. The actigraphy data will be scored in the Motionlogger Micro Watch software, and data will be exported into a database from that software. A report will be generated and from that tThe following values will be used (all averaged across the week's wear time): Sleep Onset Latency (minutes to fall asleep after lights out); Bed time in 24 hr. notation; Sleep duration (hrs.); Time in bed (hrs.); Sleep efficiency (%); minutes awake after sleep onset (WASO). The actigraph will be optional for each participant. Because we have only 9 actigraphs for this no-cost add-on, it is likely that we may not have actigraph data for all three time points for all participants in this cohort. We will summarize the patterns of SOI, and other sleep parameters using descriptive statistics such as means and standard deviations. The subgroup analysis of the short term treatment effect based on the presence of baseline SOI will be visualized by the longitudinal plots for each group and estimated using the mixed models for repeated measures in SPSS.

Table 1 Schedule of Measures	Screen	BL	Session 10	Session 20	Session 30	Post-Tx (session 40)	6-Mo FU	13-Mo FU	25-Mo FU
CHILD INFORMANT									
Clinical Interview	X			X		X	X	X	X
ChIPS --child	X							X	X
PE & Vitamin D Blood Test	X								
Saliva Collection	X								
Vital Signs	X	X	X	X	X	X	X	X	X
WASI-II	X							X	X
1-channel qEEG recording	X						X		X
Multi-channel qEEG w/ERPs and Oddball task, etc.		X		X		X		X	
IVA Test		X		X		X	X	X	X
Timed math test		X		X		X	X	X	X
WIAT II-A		X					X	X	X
**Motionlogger Micro Watch	X			X		X			
Consumer Satisfaction & Blinding Questionnaire				*		X			
PARENT INFORMANT									
Clinical Interview	X			X		X	X	X	X
ChIPS --Parent	X							X	X
Medical & Psychological History Forms	X								
Conners-3 Parent Scale	X	X	X	X	X	X	X	X	X
Children's Sleep Habit Questionnaire		X		X		X	X	X	X
FAC		X	X	X	X	X	X	X	X
Sluggish Cognitive Tempo Scale		X		X		X			
Peterson Pubertal Development Scale						X		X	X
Adverse Events		X	Every Week				X	X	X
Concomitant Treatment / Education Services Form	X		Every Week				X	X	X
Consumer Satisfaction & Blinding Questionnaire				*		X			
TEACHER INFORMANT									
Conners-3 Teacher Scale		X	X	X	X	X	X	X	X
Abbreviated Conners	X								
FACT		X		X		X	X	X	X
Sluggish Cognitive Tempo Scale		X		X		X			
CLINICIANS/STAFF									

NORS			Every Treatment Visit						
Session Report Form			Every Treatment Visit						
CGI – Severity		X		X		X	X	X	X
CGI – Improvement			X	X	X	X	X	X	X
Blinding question				*		X			

*Those who, according to protocol, terminate study treatment at Session 20 for lack of benefit will answer the Satisfaction and Blinding Questionnaire and staff will answer the blinding question at that time.
CGI = Clinical Global Impression; ChIPS = Children's Interview for Psychiatric Syndromes; ERP = event related potentials; FAC = Functional Assessment Checklist; FACT = Functional Assessment Checklist for Teachers; IVA = Integrated Visual & Auditory test (a continuous performance test); NORS = Neurofeedback Observer Rating System; PE = physical exam; qEEG = quantitative electroencephalogram; WASI II = Wechsler Abbreviated Scale of Intelligence-2nd Edition; WIAT = Wechsler Individual Achievement Test, version II Abbreviated. **Motionlogger Microwatch will be used to record sleep onset behavior take home 5 days prior to BL, Session 20, and Session 40.

Measures

Repeated outcome measures (Table 1) include parent and teacher rating scales of ADHD and other psychiatric symptoms, *functional impairment*, sleep, neuropsychological tests, assessments of EEG and Event Related Potentials (ERP), LORETA imaging of EEG and ERP components, monitoring of adverse effects and changes of concomitant treatments, treatment satisfaction, blinding, and compliance/adherence.

The *standardized diagnostic interview* at screening and follow-ups will be the Children's Interview for Psychiatric Syndromes -child (ChIPS) and -parent (P-ChIPS) versions (Weller et al., 1999[a]; 1999[b]).

Parent-rated scales will include the Conners -3rd Edition: Long Version (C-3:P, Conners, 2008), Functional Assessmen Checklist (FAC; Monastra, 2014), Sluggish Cognitive Tempo Scale (K-SCT; McBurnett et al, 2014; Lee et al, 2014), and the Children's Sleep Habits Questionnaire (CSHQ, Owens et al., 2000).

Teacher-rated scales will include teacher versions of the C-3 (C-3 T) and Functional Assessment Checklist for Teachers (FACT; Monastra, 2008), and the Sluggish Cognitive Tempo Scale. The DSM-5 ADHD symptoms from the parent C-3 and phone-administered teacher SNAP(Swanson, Nolan, and Pelham scale; adhd.net) will be used for the severity inclusion criterion.

Clinician & staff ratings will be the Clinical Global Impression (CGI, Guy, 1976) and the Neurofeedback Observer Rating Scale developed for the pilot feasibility study.

Neuropsychological function will be measured by the Wechsler Abbreviated Scale of Intelligence, 2nd ed. (WASI-II, Wechsler, 2011), Wechsler Individual Achievement Test –2nd Edition - Abbreviated (WIAT-II-A, Wechsler, 2001), the Human Brain Institute auditory oddball task (Brown et al., 2005), the Integrated Visual and Auditory (IVA) continuous performance test (CPT), and a timed arithmetic test found to be a sensitive measure of treatment effect in drug studies (e.g., Arnold et al., 2004). The auditory oddball paradigm (Arns, 2008) has a quasi-random sequence of 280 background tones (500 Hz) and 60 infrequent nonconsecutive target (1000 Hz) tones. Each stimulus lasts 50 ms (5 ms rise and fall time), presented binaurally at 75dB SPL with a 1000 ms inter-stimulus interval. Instructions are to press 2 buttons simultaneously (one with each index finger) for a target tone and to ignore background tones, stressing speed and accuracy equally. A brief practice session clarifies the instructions. Arns (2008) reported reliability/validity.

Adverse effects and changes in concomitant treatments will be monitored by the Adverse Events Tracking Form (AETF) and Concomitant Treatment/Education Services Form (CTESF) successfully used in the NIMH-OSU pilot feasibility study of NF.

Motionlogger Micro Watch. Actigraphy provides an acceptably accurate estimate of sleep patterns. It is indicated to assist in the evaluation of certain sleep disorders, such as advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS) (Litner et al., 2002). In assessing response to therapies, actigraphy has proven a useful outcome measure for individuals with circadian rhythm disorder and insomnia (Litner et al.). In children, actigraphy has proven useful for summarizing sleep patterns and documenting response to treatment. We intend to use the Motionlogger Micro Watch to evaluate the possible moderiating effects of baseline SOI on the effects of SMR NF and to determine whether improved baseline SOI mediates treatment response.

Blinding Checks. The Consumer Satisfaction and Blinding Questionnaire (CSQ, Parent and Child) used in the OSU pilot study will measure parent and child satisfaction with NF treatment and blinding to assigned treatment condition. The same "blinding" question will be administered to clinicians and study staff.

EEG data will mainly track changes in the *Theta/Beta ratio*, the primary training target. Resting EEG will also be examined by a region-of-interest analysis to identify functional changes in pre-frontal cortical areas (dorsolateral, orbitofrontal, ventrolateral) & dorsal anterior cingulate. Cortical response during attentional and cognitive processing will be measured through analysis of event-related potentials (ERPs). ERPs show time-locked EEG responses to either external or internal stimuli while the participant is performing a neuropsychological task such as oddball.Responses are averaged over many trials and reflect early attentional and higher cognitive processing, such as memory and expectation (Brown et al., 2005). The oddball ERP tasks will be used to investigate if normalization of ERPs occur by a) comparing the pre- to post-treatment ERPs and b) comparing both of these to the sham control group, with a specific focus on the late-cognitive parts of the ERP (e.g. P300). Further, these ERPs will be submitted to source localization using *Low Resolution Electromagnetic Tomography* (LORETA) to investigate deeper functional areas.

Functional Brain Imaging Strategy. Possibilities for functional brain imaging include fMRI, PET scans,

and various EEG approaches, including event-related potentials (ERPs) (Bush et al., 2005). EEG measures the brain's spontaneous electrical activity, the result of post-synaptic potentials, and has a high temporal resolution. On the other hand, fMRI and PET scans have very high spatial resolutions of deeper brain areas but poor temporal resolution, and are too expensive for this project. *LORETA* uses an inverse solution equation to locate deeper grey-matter structures based on cortical surface EEG signals. In a meta-analysis of rostral anterior cingulate predicting response to antidepressants, LORETA-interpreted EEGs yielded similar effect sizes as fMRI and SPECT scans, demonstrating LORETA's utility as a reliable alternative to fMRI (Pizzagalli, 2011). *While the analysis of the EEG will track cortical changes, in particular the reduction of TBR from baseline, addition of the LORETA analysis of the ERPs will track subcortical changes in the NF & sham groups under the task conditions, comparing group mean changes from baseline to end of treatment*.

Genetic Data: Saliva samples (2 mL) will be collected using kits produced by DNA Genotek and provided by the National Institute of Health, National Human Genome Research Institute. Saliva samples will be shipped to NIH for exploratory analysis to examine the link between Specific Nucleotide Polymorphisms (SNP), TBR, and response to treatment. Genetic data will be submitted to dbGaP, however precise data points and certification materials have yet to be approved. Parents will be re-contacted to provide consent for inclusion of genetic data to dbGaP. When study participants turn the age of majority, the study team will attempt to re-contact them in order to provide consent for maintaining their genetic data in dbGaP.

Summary of Procedures & Timetable (See also Table 2, Work Plan, below)

The study will run for 5 years; 4 for participant recruitment and NF treatment (active or sham) and the remaining year to complete follow-ups for the later-recruited participants, complete the data cleaning, run statistical analyses, and present and publish study findings. Assessments will run throughout. In order to capture teacher data each year, recruitment will begin with the school year and continue until 3.5 months before the end of the school year, similar to the OSU pilot study, which recruited 39 participants in 2 school years. All participants will undergo a comprehensive psychiatric, medical, and QEEG screen, with parent-, teacher-, and clinician-based assessment to determine study eligibility. Medical problems that could mimic ADHD will be ruled out by medical review, physical exam, and any indicated laboratory work. Vitamin D will be tested in all participants because one of the planning group has data showing a high rate of D deficiency in ADHD, responsive to repletion. Those found deficient will be re-evaluated for entry after supplementation.

After clinical eligibility criteria are met (DSM-IV-TR diagnosis and 1.5 sd above norms on teacher and parent inattentive or total ADHD symptom ratings) a one-channel EEG will be recorded at Cz. If the TBR is 4.5 or more at either of these midline sites,the most deviant of the 2 sites will be used for training. A 19-channel qEEG will also be done, but it is not used for entry criteria or selection of training site.

Parent and teacher ratings, including inattentive symptoms as well as other symptoms & impairment, will be obtained at baseline, every 10 treatments, at post-treatment, and at 6, 13 and 25-mo. FU.

Other measures (neuropsychological tests, clinician ratings, QEEG & ERP data, IQ & academic achievement, adverse events, NF Observer Rating System, changes in concomitant treatments, and child and parent satisfaction and child, parent and trainer blinding) will be collected as in the Schedule of Measures. Staff administering assessments will also receive the blinding questions.

Table 2. Work Plan

Year 1	Year 2	Year 3	Year 4	Year 5
Hire & train staff; Equipment, supplies Recruit & treat ~30; reliability checks; 6-mo. follow-ups (FUs)	Enter & clean data, recalibrate staff; Recruit/treat ~40; 1-yr FUs of 1st cohort; 6-mo FUs of 2nd	Enter & clean data, recalibrate staff; Recruit/treat ~35; 2-yr FU of 1stcohort; 1-yr of 2nd; 6 mo 3rd	Enter & clean data, recalibrate staff; Recruit/treat ~35; 2-yr FU of 2nd cohort, 1-yr FU 3rd; 6-mo 4th	Finish DB & data cleaning; DB analyses 2-yr FU of 3rd cohort, 1-yr FU of 4th. Write mss., present results.

Data Management: Data will be centrally managed by the OSU Data Management Center (DMC) under the direction of Robert Rice, Ph.D., who has worked closely with the coordinating PI on other multi-site trials. Using Teleform (Cardiff Software) the DMC will employ fax technology to convert completed forms to TIFF images that will be e-mailed and processed through Teleform into a SQL server database. The DMC will invoke 25 procedures and programs to scrub and clean the data. The DMC will provide sites with monthly productivity reports that will include missing forms, missing data, late visits, accrual information, and adverse events. The

de-identified data from this project will be uploaded to the National Database for Autism Research (NDAR), for storage and future analyses by other research groups. (This data repository is maintained by the National Institute of Health, and the National Institute of Mental Health has designated it as repository for all NIMH-sponsored data, whether about autism or not.) Ohio State will be certifying and submitting data to NDAR for both study sites (OSU and UNCA).The following data will be completely de-identified and deposited into the NDAR repository: EEG data; surveys, questionnaires, and ratings completed by parents, teachers, and clinicians; neuropsychological and cognitive assessments; adverse events and concomitant treatment information; diagnostic interview data; and blinding checks. Participant data will be submitted to NDAR with a GUID (Global Unique Identifier). In order to obtain a GUID, demographic data will be entered into a secure, online tool provided by the NIH. Demographic data include first name, last name, middle name, date of birth, city of birth, and state of birth. For participants who did not provide middle name, city of birth, and state of birth to the study team during the screening visit, a REDCap survey will be emailed to parents for them to provide this additional demographic information. The study team will not attempt to re-contact and consent study participants when they reach the age of majority.

Statistical Considerations:
Participants will be centrally randomized to treatment (T) and control (C), stratified by site, with probability 60% into T. Sample sizes at each site will be approximately equal. The primary outcome measure (and most secondary outcomes) will be obtained (blinded to treatment group) at baseline and periodically throughout.

Analytic Strategy.

After blinded data cleaning, demographic and recruitment information will be summarized by randomly assigned treatment groups. Outcome measurements will be plotted and summarized over time by treatment group. Visual displays of each measurement will be generated. Missing data patterns will be summarized.

The conclusion comparing T versus C will be based on the primary outcome variable (average of z scores of parent and teacher ratings of inattentive symptoms), tested at a significance level of 0.05. *The chief secondary outcome, impairment, will also be tested at a significance level of 0.05.* Holm's procedure will be used for testing of other secondary outcomes, *including EEG changes of TBR, ERPs, and LORETA measures of deep brain function.* . Exploratory analyses will generate hypotheses for future studies and detect possible moderators of treatment response *(*baseline, pre-randomization variables *such as TBR* that identify patients in whom the effects of T versus C differ). Such moderators are important both scientifically and clinically, suggesting etiologies and helping target treatments to those most likely to respond positively, and are relevant to the RDoC interest. The effect size (with 95% CI) for all outcome measures will be summarized after 19 and 38 treatment sessions and at follow-ups. *Mediator analyses (changes or events during treatment that are correlated with treatment assignment and might help explain how and why treatment effects are as they are) will include correlation of post-treatment TBR decrease with clinical improvement.* Changes in medication use (binary) and dose (dimensional) will be important outcomes at follow-up, comparing original Tx groups to examine NF's ability to prevent need for medication.

The primary analysis of treatment effect at 38 sessions will be based on a linear mixed model with repeated measurement, assuming a linear response on ln(t+1), where t is time from randomization, in order to fit the curvilinear response trajectory typically seen in randomized clinical trials (RCTs). *Site & siteXtreatment interaction will be included in the model to account for possible population or PI/staff differences at the sites.* The focus is to show that the trajectories, here determined by the individual slopes of the response on ln(t+1), in the T-group are clinically preferable to those in the C-group. Analyses of the effect at FU will be based on the corresponding contrast of mixed models for repeated measurement with autoregressive covariance matrix over time (assuming that measurement at two close time points will be more closely correlated than those farther apart). Moderator and mediator analyses will be based on the same model, but including also the potential moderator or mediator, and its interaction with treatment. A baseline variable will qualify as a moderator if there is a significant baselineXtreatmentXtime interaction. A change or event during treatment qualifies as a mediator if either its main effect or its interaction with treatment on the response slope is significant. Recently developed moderator and mediator effect sizes and confidence intervals will be shown.

In multisite RCTs, although all sites adhere to the same protocols, there are often site differences. With the planned fidelity monitoring, we do not expect treatment-by-site interaction (effect size differences from site

to site), but a main site effect (from different populations and different research staffs) would not be surprising, so site is included in the model. Analysis will be done by intention to treat, --i.e., every patient randomized will be taken into account. While every effort will be made to avoid missing data or dropouts, mixed models are particularly useful in dealing with missing data problems. In addition, sensitivity analyses will be carried out using data imputation techniques based on propensity score or linear regression models.
Power and Sample Size. The critical effect size has been set at Cohen's d=0.5 (standardized mean difference between T and C, corresponding to a Number Needed to Treat=3.6), generally considered a moderate effect. We plan to randomize at least 140 participants (70 at each site) with a T:C ratio of 3:2 (42 & 28 at each site). With this sample size, the power to detect any effect greater than d=0.5 using a two-tailed 5% significance level will be greater than 80%. Based on pilot experience, we expect attrition of <10%. We will continue to recruit until 130 completers, but all patients will be included in the "intent to treat" analysis.

Alternatives Considered and Rationale for This Design

In 2 years of teleconference & email discussions leading to the proposed design, we considered many alternatives. In the choice of control group, considerable sentiment supported using a clinically practical comparator such as optimal medication, electromyographic biofeedback, or a computer-based training of attention and cognitive skills. Although these were attractive possibilities, we agreed, after considerable debate, that the most pressing issue was to establish whether NF has a specific effect beyond nonspecific benefit; and a comparison to medication would best await *resolution of that issue*.

The sham itself and related blinding strategy also entailed much discussion. *The technology used in the pilot feasibility study was not appropriate because the NF it supported was not optimal.* To give NF its best chance to demonstrate a specific benefit, we needed to use the most widely established, optimal treatment: manually set thresholds & active coaching. How to double-blind this? One possibility might be to train posterior alpha as the control Tx. However, circulation of this idea to the NF community elicited concerns, including that posterior alpha training would probably benefit some. Thus the use of a stored EEG on which the participant's eye-movement and other artifacts are overwritten seemed the optimal method for double-blinding: the coach dispenses rewards based on the stored EEG rather than the participant's actual EEG. This strategy was fortuitously "field-tested" by Dr. Andrew Hill in a different type of study, and the double-blinding was impressive. We will, of course, check on the adequacy of blinding by an end-of-study questionnaire, and will examine the participants' EEGs with rewards time-marked, to check that sham was not accidentally reinforcing.

Another area of discussion was whether to allow stimulant medication. Having participants drug-free would be "cleaner", but it could increase attrition and make the sample unrepresentative because many of those taking medication would not be willing to give it up for 3 mo. We decided that the best solution is to allow established stimulant to continue through the trial but wash it out for 5 days before each major assessment.

The tension between our desire for optimal, comprehensive assessment and the practicalities of participant burden and cost was resolved by reducing from 6 neuropsychological tests to 4, discarding several nonessential scales, and reducing a comprehensive blood battery to a test for vitamin D and anything the history/physical exam raise suspicion about. We retained the Sleep Habits Questionnaire because of data suggesting sleep improvement as a mediator of NF benefit, and sleep data seem necessary for exploration of a possible RDoC phenotype. These reductions resulted in 3-4 hour visits at major assessments, similar to the pilot feasibility study, acceptable to families and IRB.

Healthy Controls Perform IVA Task Sub-Study:

50 healthy control subjects (non-ADHD diagnosis) will be recruited to do the Integrated Visual and Auditory (IVA) Continuous Performance Task. The IVA data from the control subjects will be compared to the original study subjects (with ADHD diagnosis) to learn more about the how brains respond to perceptual information, how quickly decisions are made, and what the hallmarks are of children diagnosed with ADHD. The control subjects will be the same age range (7-10) of the original subjects. They will come in for 1 visit with a parent/guardian. The child will do the IVA task while the parent completes Conners-3 parent and Demographics forms.

HUMAN PARTICIPANTS RESEARCH

1. Risks to Participants

Human Participants Involvement and Characteristics. The participants will be approximately 140 outpatient children age 7-10 with a diagnosis of ADHD in general good physical health. Parent and teacher must be willing to provide ratings of behavior and attention during the double-blind phases. Psychosis or other major psychiatric disorders (bipolar, major depression, PDD, severe anxiety) requiring intensive treatment will exclude, but common comorbidities (disruptive behavior disorder, mild anxiety, and mild secondary depression) not requiring intensive treatment will not exclude. The decision of whether the comorbid disorder requires treatment will be made by a doctoral-level child clinician (psychologist or psychiatrist). The elementary and middle school age population is targeted because this is the usual age of first diagnosis of ADHD. Participants will have ADHD because that is the disorder for which the treatment is being studied. In addition to receiving NF or sham, all participants will have a baseline medical history and physical exam, blood test for vitamin D, baseline brainwave measures, intelligence and achievement tests, numerous parent and teacher ratings, neuropsychological tests, and several other assessments.

Sources of Research Materials. All participants will have demographics, ratings, and test results collected, including behavior ratings by parent and teacher, neuropsychological test results, electrophysiological measures, DNA sample, and physical exam. These are to be collected for research purposes. The vitamin D test is to screen for an alternative cause of ADHD symptoms as a temporary exclusion.

Potential Risks. The risks and discomforts are the nuisance; effort and time of 45 trips to the center; a 40% chance of being assigned the 38 sham treatments; confidentiality; and discomfort of blood draw, saliva sample, and wearing the actigraph. The alternatives to these (open trial rather than controlled, fewer treatments) are not scientifically acceptable for the purpose of the study. Those who exit study treatment at session 20 for lack of response may have clinical treatment with medication and/or behavior therapy as routinely done in clinical practice, and in that case would have the usual risks of those treatments.

NF and/or EEG by itself does not appear to carry any risk other than accidental injury or possible rare itch from the preparation cleansing gel. Monastra (2005) states “None of the studies to date describes adverse effects when EEG biofeedback is provided in the absence of stimulant medication.” Monastra et al. (2005) and deBeus et al. (2003) noted that adverse effects can occur during the mid-phase of EEG biofeedback (sessions 20 or more) in children who are being treated with biofeedback and stimulant medication concurrently. Monastra and his colleagues reported that as children begin to demonstrate improved self-regulation of cortical arousal via EEG biofeedback, they may exhibit increased irritability, moodiness, and hyperactivity as stimulant side effects. They indicated that reduction in medication dose (rather than increase) typically resolves these symptoms. Each site will have medical coverage to advise prescribers about this phenomenon. If NF does not work, it could delay other treatment that has been proven to help the majority; this is itself a risk, but this risk does not apply to stimulant medication, the most common of the standard treatments, because it is allowed for both ethical and recruitment/retention reasons.

As child participants are required not to be medicated for ADHD for 5 days prior to each major assessment (baseline, treatment 20, treatment 40, and 3 follow-ups), there is a possible risk that stopping a medication helpful for ADHD symptoms may lead to a temporary reoccurrence of inattention, hyperactivity and/or impulsivity.

Use of Sham Condition. It is necessary to have a control condition for comparison to demonstrate an effect beyond maturation and the placebo response involved in a treatment of such glamour, popularity, and public interest, in which the investment of time, energy, and money undoubtedly predispose to placebo response. This requires the random assignment to NF vs. sham. The alternatives, an open trial or comparison to another active treatment, would not provide the comparator needed to test for specific effect and interpret the results and would not be an advance beyond what has already been done. It is conceivable that the sham condition, by noncontingent feedback, could induce a temporary state of learned helplessness that might interfere with later active NF treatment. deBeus (personal communication) noted a tendency to that, but reported that it did not prevent eventual significant gains from 20 sessions of NF. Arnold et al (2012) did not note any deleterious effect of the sham feedback; those assigned to sham showed a large improvement by parent ratings and smaller improvements on other measures.

Importantly, the estimated placebo response rate in ADHD is 10-30% (12.5% in the MTA double-blind titration), and with no side effects or time-action problems. Thus a patient on placebo (sham) has a 10-30% chance of good response without the risks and side effects of active treatment. One of the hopes of this study is to prepare the way for a study that could establish a safer and possibly more effective treatment, improving the response rate in ADHD, but to do that credibly requires a sham/placebo control. Because ADHD is a chronic condition, the participant may benefit later if NF is proven to be an effective treatment. Patients who are not benefitting by treatment 20 will exit the study treatment (but not assessments) and be treated clinically. Thus the sham condition in this study does not pose an undue risk and the participants, by risking 2-3 months of placebo, stand to gain directly in several ways by improvement of their future care. The participants eligible for this study will be either treatment-naïve or dissatisfied with current treatment in some way. No patient will have satisfactory current treatment stopped in order to be in this study: In fact, such families will probably not even apply.

The participants attracted to this study will be those who have found medication alone unsatisfactory or have not tried it and are interested in alternatives, but some will be medicated with partial benefit. For them, there can be some deterioration in behavior and academic performance if medication is withdrawn for ***5 days*** at a time for the required assessments. While obtaining informed consent, this will be explained as a potential risk. All participants will be told that they can discontinue the study at anytime. The studies that have documented the effect of stimulants show a response rate considerably less than 100%. The usually quoted response rate is about 2/3. Even that may be high if the standard is normalization. For example, the Multimodal Treatment Study of Children with ADHD (MTA) found that only 25% of the 145 children who received routine community-managed medication were “normalized” by 14 months of treatment (Swanson et al, 2001). About 56% of those who received a very intensive medication management algorithm were “normalized,” but this intensity of treatment is not usually available in the community. Thus even the most optimistic estimate of optimal results would leave almost half the patients with a less than optimal outcome with current medication, and the actual numbers as done in the real world have been even worse. It is common practice with ADHD to try a drug holiday occasionally to see whether the patient still benefits or still needs the medication. Thus stopping medication for 5 days 6 times over the course of 2 years does not seem an undue risk.

2. Adequacy of Protection against Risk

Recruitment and Consent. Participants will be recruited by university press release, by notification of university and community child psychiatrists, pediatricians, and other professionals, and by advertisement. Also, calls will be made to a list of families who have asked to be put on a waiting list for future studies of ADHD treatment. These methods have been highly successful in the past in attracting sufficient samples of children with ADHD for treatment trials. Advertisement copy and the text of the circular for professionals will be approved by the IRB and the press release will follow IRB guidelines.

Informed consent will be written, using format and text approved by the IRB. It will take place in the research offices of the PIs. The PIs or their designate will give the child and parent/guardian a thorough explanation of the study and the treatments, going through the items on the consent form. The signature of parent or guardian will be obtained as permission and the child’s signature or verbal assent will be obtained, as determined by the local IRB.

Protection against Risk. For the risk to confidentiality, the usual precautions of locked files, participant numbers rather than names, and anonymous group mean publication will be observed. The file security at Ohio State University has a long track record of effective protection of confidentiality. Saliva samples will be labeled with a unique identification number and identifying information will not be placed on the samples, data sheets or any material disseminated or published. The samples will be sent to an off-site contract center that the National Institutes of Health use for the purpose of DNA analysis. When this is completed, the results of the DNA analysis will only be labeled with an ID number so it will not be possible to identify participants. Scientists at the NIH and at other approved institutions will have access to these data to study genes for ADHD, related mental health conditions and behaviors, and other medical and/or mental health conditions that may not be related to ADHD. They will only have access to interview, EEG, and genetic data coded only by ID number. Only staff at the Ohio State University and the University of North Carolina at Asheville have access to the password-protected file that links names and identification numbers. This file is stored on a secure computer and protected with a password. The risks and discomforts of the sham

(and of ineffective active NF) will be minimized by assessing benefit at treatment midpoint and switching those who are not benefitting (whether they are getting NF or sham) to clinically indicated treatment. The inconvenience and cost of making 45 trips is minimized by reimbursement, which in the past has seemed effective. The discomfort of *the* single blood draw will be minimized by numbing cream. ***The risk of temporary withdrawal of stimulant medication prior to each major assessment is minimized by making it 5 days (a weekend and 3 school days). This is less than the standard 1-week washout usually done before baseline assessment on entry into many studies and does not pose undue risk in our experience. Further, if 5 days proves intolerable, we will invoke an emergency option of doing the major assessment a day or two sooner to shorten the drug-free period even more.We expect that as NF takes effect, tolerance of drug withdrawal will improve and this is even an important secondary outcome measure.*** A physician or licensed nurse practitioner with access to a physician will be on call to provide medical help in the unexpected event of any accident or other medical problem, such as the need to reduce stimulant dose as the NF takes effect. As additional medical back-up, the university emergency room is available 24 hours a day, 7 days a week.

As with all studies involving human participants, if at any point in the study a child participant is thought to be suicidal or homicidal, he/she will be referred to mental health services or the child's primary care physician for their safety.

If the child should find the cleansing gel uncomfortable/itchy, it will be removed.

Data and Safety Monitoring Plan. A simple plan is justified by the low risk. The proposed plan for data and safety monitoring has two components, statistical and clinical:

A. The statistical part of the Data and Safety Monitoring Plan will be carried out by the data management center under Dr. Robert Rice's direction and by the study statistician, Dr. Xueliang Pan. Adverse events will be compared in real time (as they are entered) between those assigned to active NF and those assigned to sham. Any imbalance disfavoring the active treatment will elicit clinical attention from the coordinating PI.

B. The clinical part of the Data and Safety Monitoring Plan will make use of the weekly cross-site teleconferences and weekly site staff meetings. In addition to reviewing the statistical reports from the data center, any severe adverse event (on a "mild, moderate, severe" scale) will be brought up and discussed. No serious adverse events are anticipated, but if one should occur, it would precipitate an immediate consultation of the clinicians involved in the study, and would of course be reported to the IRB, which also has annual reviews. Participants will be informed at their next regular appointment about any serious adverse event or pattern of severe adverse events that might change the risk-benefit ratio, and the IRB's direction will be sought regarding possible modification of consent forms.

3. Potential Benefits of the Proposed Research to the Participants and Others.

The participants may potentially benefit directly from the study treatment, which has been reported by others to help ADHD. They and all patients with ADHD will benefit from the advance in knowledge about treatment of the disorder. In addition, the participants will have a psychiatric evaluation by a child psychiatrist or child psychologist as well as careful treatment monitoring without charge.

4. Importance of Knowledge to be Gained

ADHD is a significant public health problem, a chronic disorder conservatively affecting 3-8% of school children and 2-4% of adults. No treatment is completely satisfactory. The best documented treatment, stimulant medication, gives optimal results in only half of patients, has worrisome nuisance side effects, and has not been documented to be effective beyond 2 years. If NF can provide another effective treatment option either alternatively or adjunctively, ***especially if shown to have enduring effects,*** it would significantly improve the treatment of ADHD. This study is necessary to determine whether NF has a specific persisting benefit that would justify its expense and difficulty. Therefore the knowledge to be gained could be of tremendous importance. Even if NF turns out to be ineffective, the knowledge would be valuable. Because NF is already accepted by many of the public, lack of significant specific benefit would be important in preventing needless/useless diversion of expense and effort and delay of effective treatment. But if it could be shown to have statistically and clinically significant specific benefit, it would facilitate efficient incorporation into established practice, ***coverage by insurance, and widespread availability.***.

Risk-Benefit Ratio. The experimental treatment is minimal risk, the expense and inconvenience of 45 visits is minimized by reimbursement, and in general, risks and discomforts are minimal to nil. The benefits for society (including the participants) are great: preparing to find whether this safe treatment for ADHD works. The benefits may also be considerable for the individual participants if the treatment works, either immediately during the study or after the study as the treatment becomes established. In summary, the benefits of this study greatly outweigh the minimal risks, both for the participants and certainly for society, which would benefit greatly from development of a safe treatment and the knowledge whether or not this one works, thus making a favorable risk-benefit ratio.

Women and Minority Inclusion in Clinical Research

Female Representation and Sex Ratio - ADHD affects predominantly boys in a ratio of 3:1 to 9:1 in clinical samples (Arnold, 1996). Therefore it would be difficult to recruit enough girls to provide a definitive answer to a possible sex difference in treatment response. Oversampling of girls, to be balanced and scientific, would have to involve rejecting 3 of 4 or 2 of 3 available male applicants randomly, unduly delaying timely completion of the study. Even if it were practical to recruit the same number of girls as boys, making any scientific sense of the comparison would require doubling the sample size. Further, there is no evidence of a sex difference in treatment response (Arnold, 1996) as long as both sexes are diagnosed the same (same criteria and same subtype). A far larger sample than the one proposed here (579 participants), failed to find significant differential treatment effect by sex with 4 kinds of treatment (MTA Cooperative Group, 1999). In particular, there is no reason to expect a sex-differential response to NF, given that the inclusion criteria will select for the biomarker believed to indicate those likely to respond regardless of sex. Therefore recruiting extra girls is not likely to yield new information. There is evidence that girls may differ in proportion of different subtypes of ADHD (Arnold, 1996), but if the subtype makes a difference in response, that is the real issue, not gender. Further, oversampling of girls could be scientifically counterproductive by making the sample less representative of the children who are actually treated for ADHD. The published data were from predominantly male samples routinely found in the clinical population. In light of the available data and literature, the best strategy seems to be to recruit eligible children in the sex ratio found in the ADHD clinical population (which makes the sample representative of ADHD), analyze the results on the assumption that sex makes no significant difference in treatment response, then heuristically compare the means for boys and girls to see if there is any hint of a difference that would justify mounting a larger study focused on sex differences in response.

Minority Representation. The only minority available in considerable numbers in central Ohio is African-American, about 12-20%, depending on whether only Franklin County is counted or all areas close enough in travel time to participate in studies. The other recruitment site, in North Carolina, has an ethnic composition of 11% African American and 6% Latino. The available literature offers little to no suggestion of a possible racial/ethnic difference in possible treatment response to this or other treatments for ADHD. The hint of ethnic differences in some other disorders is likely explained by socioeconomic correlates (Vargas and Rand, 1999: Williams, 1997). Any ethnic effect is far outweighed by individual differences in treatment response within each ethnic group. There had been some suggestion in unpublished data that African-Americans might be more sensitive to stimulant drug effects (same effect at lower doses), but no evidence that they have less (or more) benefit as a group. However, in a much larger sample (the 579-participant MTA), one of the PIs found a robust placebo-controlled response to methylphenidate among African-Americans, similar to that found in Caucasians, with similar optimal doses, and a response to addition of behavioral treatments at least equal to that of Caucasians (Arnold et al, 2003). Most of the same problems in oversampling girls apply also to oversampling minorities. Again, the best strategy for this study seems to be to recruit regardless of race/ethnicity, analyze the results as if race and ethnicity make no difference on treatment response, and then heuristically compare the racial/ethnic groups to find any hint of differences that would warrant a larger study focused on such differences. We will aim to recruit minorities at rates at least representative of our research catchment areas.

In summary, in regard to gender and minority representation, checking for differences in response to this treatment is a later step. For this new treatment strategy, the first step is to document a specific effect. If it has significant benefit, the next step would be to look for differences in response by gender or race/ethnicity.

The expected gender and ethnic composition of the sample, based on local demographics, sex ratio of the disorder, and prior experience in recruiting ADHD samples, is shown on the attached designated form.

Inclusion of Children in Research Involving Human Participants.
All of the participants in this study will be children because that is the usual age of first diagnosis of ADHD. The sample must be children because efficacy may be moderated by developmental age so that results in adults could be misleading.

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