The NIMH-Funded OSU Randomized, Double-Blind, Sham-Controlled Pilot Feasibility Trial of Neurofeedback for Pediatric ADHD - Complete Results.

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OSU Grand Rounds
November 16th, 2011
Presentation Plan
1. Why Additional Txs Are Needed for Pediatric ADHD
2. What is Neurofeedback (NF)?
3. Current Research Status of NF for ADHD
4. NIMH-OSU NF Study Team
5. Background
6. Hypotheses (N=4)
7. Sample, Design & Method
8. Successful Results
9. Unexpected Results
10. Conclusions & Recommendations
11. The Collaborative NF Project
Acknowledgments

- Research supported by National Institute of Mental Health Award R34 MH080775 & Award UL1RR025755 from the National Center for Research Resources (OSU Center for Clinical & Translational Science)

- Free use of SmartBrain NF equip. supplied by CyberLearning Technology, LLC. (Domenic Greco, Ph.D., President)

- Dr. Greco & Ms. Lindsay Greco trained staff in use of equipment & monitored Tx fidelity

- Alan Pope, Ph.D. consulted during study development
1. Why Additional Txs are Needed for Pediatric ADHD?

1. Best documented, most successful & most widely used Tx = stimulants:

a) Methylphenidate (Ritalin, Concerta, Metadate, Focalin & Daytrana)

b) Amphetamine (Adderall & Dexedrine)

c) Robust effects in grp data, w/ placebo-controlled effect sizes (Cohen’s d [-.2=small effect, 0.5 =med. 0.8= large]) from 0.7 to 1.5 on parent & teacher ratings of attention & beh. (e.g., Arnold, 2004)

d) Atomoxetine (Strattera) & Guanfacine XR (Intuniv), FDA-approved non-stimulants, effect sizes in a slightly lower but overlapping range
2. **Main Problem = Individual patient response rate less than satisfactory:**

   a) **e.g., NIMH Multimodal Tx Study of Children with ADHD (MTA, *MTA Cooperative Group, 1999*)**
   579 7-9 yr-olds rigorously dx with ADHD randomly assigned to several Tx conditions

   b) **MTA data re-analyzed (Swanson et al, 2001)** to determine % with satisfactory outcome or near normalization ( “mean rating of $\leq 1.0$ on ADHD sxs on a 0-3 metric after 14 mths of Tx”):
   - Carefully crafted med. management by study staff success rate = 56%
   - Community-care comp. success rate = 25%

3. **Unknown % families refuse to try approved meds** even though might benefit satisfactorily
4) Another established Tx = beh. modification:
   a) Carefully crafted, intensive beh. mod. + well-managed med. boosted % near-normalization to 68% (*Swanson et al, 2001*)
   b) However, even this premium combination Tx (not usually available in most communities) still left ~ 1/3 with less than completely satisfactory results

5. ~ 1/3 of children w/ ADHD don’t fully benefit from optimal established Txs & unknown proportion won’t even consider most effective Tx (meds) = major public health issue

6. Therefore, additional alternative or complementary Txs are greatly needed
2. What is Neurofeedback (NF)?

- **Definition:** Trains brain, via classical & operant conditioning, to change its physiological activity to improve performance by providing it w/ real-time video/audio info re its electrical activity (EEG)

- **Rationale for Use:** Attempts to modify certain EEG rhythms (brainwaves) thought to be associated w/ ADHD including $\uparrow$ beta-rhythms, either sensorimotor (12-15 hertz [Hz]) or higher (15–18 Hz) & $\downarrow$ theta rhythms (4-8 Hz)
3. Current Research Status of NF for ADHD


- All studies had sig. reductions in ADHD sx
d

- Mean Effect Sizes (ES, Medication ES ~1.0):
  - All ADHD sx = 0.66 (medium)
  - Inattentive sx = 0.74 (medium)
  - Hyp/Imp. Sx = 0.70 (medium)

- 4 studies showed neurophysiological changes specifically associated w/ NF
Only 3/10 RCTs used blinding & sham-NF designs (deBeus et al 2010; Perreau-Linck et al 2010; Lansbergen et al 2010)

Only 2 of those 3 underwent peer-reviewed publication (Perreau-Linck et al 2010 & Lansbergen et al 2010) but both small N & neither able to show superiority of NF over sham-NF (deBeus et al 2010, a book chapter, did show NF superiority)

Promising…but need for a definitive large, multi-site, DB, sham-controlled randomized study, w/ long-term FU, of pediatric ADHD

Additionally, studies varied in # of Txs (20-40) & frequency (1-4X /wk); so not clear how many Txs are needed nor how frequently they should be given
ANY Tx

1. SPECIFIC TX EFFECT DUE TO ACTIVE INGREDIENT IN TX
2. NON-SPECIFIC Tx effects due to just being in Tx.
3. Patient’s past experiences.
4. Patient choosing that Tx.
5. +/- expectations about Tx.
7. Improvements on assessments due to practice.
8. Regression to mean.

Science tries to control 2-8 & isolate the Specific Tx Effect by:
1. Randomization: Randomly assigning S’s into a Tx or a non Tx grp to control for S differences & Tx preference bias.
2. Blinding: Disguising Tx & control grps (e.g., placebo pill) s S’s, raters (parents/teachers) & experimenters don’t know who is getting Tx to control for expectancy biases (+ve & -ve views about Tx or no-Tx).
3. Equal attention: to control group to equalize non-specific Tx effects (e.g., attention by experimenters, practice paying attention, sitting still, inhibiting responses).
4. NIMH OSU NF Study Team

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5. Background

- 2008 NIMH funding to explore feasibility of a randomized, double-blind, sham controlled pilot trial, & determine optimal session frequency, duration & explore efficacy of NF vs. sham-NF for a larger trial

Importance of Study

1. ~1/3 of children w/ ADHD don’t fully benefit from optimal established Txs & an unknown proportion won’t even consider most effective Tx (meds), we need additional Txs

2. Many already using NF & companies marketing as Tx for pediatric ADHD but, due to research limitations, not clear variance of outcomes due to specific effects, (i.e., training of EEG rhythms) or nonspecific effects (e.g., placebo)
6. Primary Hypotheses (N=4)

1. **Feasibility of DB Sham-Controlled Design:**
   a) High study completion rate
   b) Child & parent post-hoc guess Tx assignment (active NF vs. sham NF) ≤ chance alone (50%)

2. **Feasibility of 2 vs. 3 Tx’s/wk (2 components):**
   a) **Palatability/Compliance Hyp:** After random assignment to 2X vs 3X wk Tx families will prefer 3X/wk as shown @ Tx 24 by attendance, satisfaction ratings & choice of Tx frequency
   b) **Exploratory Outcome Hyp:** On tables/graphs of clinical outcomes, 3X/wk similar to 2X/wk when randomly assigned for 24 Tx’s
3. **Necessary # of Tx’s:**
   - Max. benefit evident by 24 Txs as shown on tables/graphs of clinical & neuropsych. outcome variables for 40 Tx

4. **Exploratory Outcome Hypothesis:**
   - > pre-post Tx improvement for NF grp vs. sham-NF group as shown on tables/graphs of clinical & neuropsych. outcomes

This was a FEASIBILITY NOT AN EFFICACY STUDY looking at practical research issues of NF Tx of pediatric ADHD before applying for funds to examine a larger efficacy study
7. Sample, Design & Materials

- 39 unmedicated 6-12 yr-olds rigorously dx with DSM-IV:TR ADHD
- Twice-randomized:
  a) Active NF (n>24) vs. sham NF (n>12)
  b) 2 vs. 3 X/wk Tx freq (>12 active, >6 sham NF)
- 40 Tx’s: @ Tx 24 choice to stay with initial or change freq
- NF = SmartBrain Technology: Sony PS & MS Xbox videogames; Interface modulates input to videogame hand-controller based on EEG
- ↓theta & ↑beta via single CZ placement
Active NF = Game controller responsiveness (speed & vibration = feedback) contingent on real-time EEG

Sham NF = identical to active NF except interface module pre-programmed to give random feedback not contingent on EEG

NF devices independently pre-programmed by off-site consultant w/ no contact w/ Ss or data

Major assessments @ pre-Tx, Tx 24, post-Tx, & 2-mo FU: of ADHD sx's, functional impairment, IQ, achievement, social skills, EEG, Tx satisfaction, blinding, & neuropsych. tests. ADHD sx's every 6 Tx’s
8. Successful Results
Hyp. #1: Feasibility Of Double-blind, Sham-controlled Design

- 34 (87%) finished all 40 Tx’s (5 dropouts)
- Guesses at Tx 40:
  - Children:
    Correct = 32%  Incorrect = 32%  DK = 35%
  - Parents:
    Correct = 24%  Incorrect = 47%  DK = 29%
  1/3 didn’t know; those who thought they knew were wrong more often than right
- High study retention & child/parent guesses ≤ chance indicate **blinding is feasible**
Hyp. #2: Feasibility of 2 Vs. 3 Tx/Wk

a) Adherence/Palatability

- Attendance @ Tx 24: 2X/wk = 17/19, 3X = 19/20

- Parent & Child Satisfaction Rating
  0 (Very Dissatisfied)- 7 (Very Satisfied); 4=neutral)

  - Overall:
    2X/wk = 5.36±1.36    3X/wk = 5.36±1.68

  - Active NF:
    2X/wk = 5.21±1.82,    3X/wk = 5.62±1.27

  - Sham NF:
    2X/wk = 5.40±1.07    3X/wk = 5.08±1.73
Choice of Freq. (Option to Switch at Tx 24):
2X → 3X/wk = 43.7%  
3X → 2X/wk = 22.2%

Freq. choice @ Tx 24 indicates more families preferred 3X/wk but satisfaction high for both freqs
b) Exploratory Outcome Hypothesis:

- **Swanson, Nolan & Pelham-IV (SNAP-IV) 18**
  DSM-IV ADHD Sxs M Parent Ratings (0-3 metric) for Tx Freq. 2 vs. 3X/Wk @ Tx 24
b) **Exploratory Outcome Hypothesis. (cont.):**

- **SNAP-IV 18 DSM-IV ADHD Sxs M Teacher Ratings (0-3) for Tx Freq. 2 vs. 3X/Wk @ Tx 24**

- SNAP-P/T ratings indicate **Tx 2X & 3X/wk have similar outcomes**
Hyp. #3: Necessary # of Tx’s:

- SNAP 18 DSM-IV ADHD Sxs M Ratings by Parent for Active NF Through Tx 40

Maximal benefit was shown by Tx 24
Successful Results Summary

1. Demonstrate feasibility DB with sham-NF in a RCT, 87% retention for 40 Txs & 92% for 24 Txs

2. Find that blinding technology works

3. Examine feasibility of NF Tx 2X vs. 3X/wk. Families preferred 3X/wk but outcomes similar for both freqs, allows family preference/study logistics to determine Tx freq. for larger RCT

4. Examine response curve over 40 Txs & find maximal effect attained by Tx 24

5. Examine safety: No severe adverse effects, proportionate b/w active & sham Txs
9. Unexpected Results: Parent Rating 18 ADHD Sx
Parent Rating 9 Inattentive Sx

![Graph showing inattentive symptoms over vnum for treatments A and C.](image-url)
Parent Rating 9 Hyp/Imp Sx
Teacher Rating 18 ADHD Sx

![Graph showing teacher ratings for ADHD symptoms over vnum. The x-axis represents vnum ranging from 0 to 50, and the y-axis represents adhd_all ranging from 0 to 3. Two lines are plotted: one for trt A (solid red line) and one for trt C (dashed black line).]
Stroop Errors

vi_err_m

Session

group A C
CPT Reaction Time Variability

![Graph showing reaction time variability over sessions for groups A and C.](image-url)
CPT Omission Errors

Session

group A C

wmfn

1 2 3 4 5
Achievement - WRAT

![Graph showing WRAT achievement with vnum on the x-axis and wrat_wr_le on the y-axis. The graph compares group A and group C.](image-url)
Moderator Analyses:
ADHD Combined vs. Inattentive Type

![Graph showing comparison between ADHD Combined and Inattentive Type groups across different vnum values.]
Moderator Analyses: EEG Theta-Beta Ratio; Parent-rated ADHD

![Graph showing EEG Theta-Beta Ratio and Parent-rated ADHD]
Mediator Analysis: ADHD Sxs
Improvement Correlation with Theta-Beta Ratio Reduction: $r = -0.05$
Pre-Post EEG: Active vs. Control
(Full Theta/Beta)
Why Not Same Effects as Other RCTs?
- 5 Possible Explanations

1. Invalid sample
   a) ADHD Diagnosis
   b) Severity
   c) EEG pattern (theta-beta ratio)

2. Randomization Failure

3. Invalid Tx

4. “Sham” not truly inactive

5. Our Tx less effective vs. past studies controls inadequate
#1: Invalid Sample

- ADHD Dx by standard procedures by doctoral clinician & structured interview
- Severity criterion: 1.5 item mean on 0-3 sx's rating
- EEG theta-beta ratio varied from published

<table>
<thead>
<tr>
<th>OSU Sample Theta-Beta age 6-12</th>
<th>Monasatara ADHD-I</th>
<th>Monasatara ADHD-C</th>
<th>Monasatara Normal Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.62</td>
<td>8.48 *</td>
<td>7.70 *</td>
<td>3.03 *</td>
</tr>
<tr>
<td>6.78 **</td>
<td>6.63 **</td>
<td>2.67 **</td>
<td>age 6-11</td>
</tr>
<tr>
<td>4.49 *</td>
<td>5.55 *</td>
<td>2.06 *</td>
<td>age 6-11</td>
</tr>
<tr>
<td>3.80 **</td>
<td>5.55 **</td>
<td>1.97 **</td>
<td>age 12-15</td>
</tr>
</tbody>
</table>

* Monastra, 1999;  **Monastra, 2001
#2: Randomization Failure

<table>
<thead>
<tr>
<th></th>
<th>Active n=26</th>
<th>Control n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Years)</strong></td>
<td>9.0 (SD 1.5)</td>
<td>8.7 (SD 2.1)</td>
</tr>
<tr>
<td><strong>Gender (Male)</strong></td>
<td>22 (84.6%)</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td><strong>Prior Meds (Yes)</strong></td>
<td>15 (57.7%)</td>
<td>7 (53.8%)</td>
</tr>
<tr>
<td><strong>ADHD Dx (Combined)</strong></td>
<td>17 (65.4%)</td>
<td>9 (69.2%)</td>
</tr>
<tr>
<td><strong>SNAP-P (Total)</strong></td>
<td>1.9 (SD 0.5)</td>
<td>1.8 (SD 0.4)</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theta</td>
<td>25.5 (SD 7.2)</td>
<td>23.3 (SD 2.4)</td>
</tr>
<tr>
<td>Ratio Theta : Full Beta</td>
<td>5.02 (SD 2.02)</td>
<td>4.66 (SD 1.91)</td>
</tr>
<tr>
<td>Ratio Theta : Beta 2</td>
<td>3.6 (SD 0.9)</td>
<td>3.4 (SD 0.7)</td>
</tr>
<tr>
<td><strong>CGI-S</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 (11.5%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>4</td>
<td>20 (76.9%)</td>
<td>9 (75.0%)</td>
</tr>
<tr>
<td>5</td>
<td>3 (11.5%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

1 n=11
2 n=12
#3: Invalid Tx

- Tx fidelity monitored by 3 in-person visits for training & monitoring, teleconferences, review of videotaped Tx sessions & downloaded data from Smartbox interfaces by equipment supplier.

- Company president repeatedly confirmed Tx appeared to be administered accurately.

- So pretty confident Tx administration was valid.

- However, automatic thresholds & fast-paced videogame formats may not have been as effective as personalized manual adjustment of RF threshold, with slower-paced tasks, as favored by most NF experts.
#4: Invalid Sham

- Sham setup to give random feedback not contingent on child’s EEG

- What if it became, inadvertently, associated w/ child’s EEG & thus gave feedback?
  1. Child just happens to be in the correct theta/beta ratio when random feedback occurs
  2. Cued-learning - As S’s told when controller vibrates/you lose control/speed you need to pay more attention, random feedback could cue children into paying more attention

- No data from study/field to test these hypotheses
#5: Our Tx Ineffective or Past Studies Controls Inadequate

- Compare pre-post improvement of our active & sham conditions to pre-post improvement reported by others’ active conditions
  - If others’ active pre-post improvement is $>$, then our Tx less effective for some reason
  - If pre-post improvement is $\leq$ across studies, suggests unblinded control condition used by other studies may not be adequate
- Most commonly reported outcome across published studies was parent-rated inatt. sxs, so we used those for comparison
Ineffective OSU Tx vs. Ineffective Control in Other Studies

Pre-post ES for parent-rated ADHD Inattentive symptoms
Ineffective Tx OSU vs. Ineffective Control in Other Studies: % Improvement

Pre-post % improvement in parent-rated inattentive symptoms
10. Conclusion & Recommendations

- **Take-Home Message:**

  1. Successful in feasibility goals of demonstrating ability to run a DB sham RCT for pediatric ADHD
  2. Clinical outcomes merely exploratory & don’t contribute to settling issue of NF’s specific benefit
  3. Feasibility outcomes provide a base & justification for planning a large cooperative study
4. Large multisite DB sham-controlled RCT feasible & needed:

- Probably 3X/wk, 30 Tx
- Follow-up >6 mo.
- All stakeholders must be involved
- Collaboration among mainstream ADHD investigators & NF experts to
  - Decide technology
  - Agree on standard protocol, inclusion & exclusion criteria & primary Tx outcomes
11. The Collaborative NF Project

- **Our Main Goal:**
  Develop & obtain funding for a definitive multi-site, DB, sham-controlled RCT of NF for pediatric ADHD, designed so results (whatever they are) **acceptable** to both sides of the debate.

NFB Field

Mainstream ADHD Researchers
The Collaborative Team:

PI
Gene Arnold
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Site PIs

Nick Lofthouse, PhD
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Keith McBurnett, PhD
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Cynthia Kerson, PhD
ISNR Research Foundation

Helena Kraemer, PhD
Professor Biostatistics Psychiatry, Stanford (Emerita)

Joel Lubar, PhD
Professor Emeritus – UTK

Vince Monastra, PhD
Time-line:

03/10: Gene & Nick invited Roger, Larry & Russell Barkley to apply for a symposium on a review of NF for ADHD for 2010 ChADD (Children & Adults w/ ADHD) conference.

11/12/10: Atlanta, ChADD Conference, Atlanta, GA - “EEG Neurofeedback for ADHD: Review of the Science and New Findings” w/ positive reception by Dr. Barkley.

- Presenters agreed future larger study include major players from NF & ADHD fields for design & results (no matter what they are) to be acceptable to all
• 11/12/10 - 11/30/10: E-mails & phone calls to major players in NF & ADHD fields.
• 11/30/11: Initial meeting.
• 11/30/11 - 4/25/11: Weekly teleconferencing meetings to discuss goals & design for a grant application for a large multi-site randomized controlled study of NF for pediatric ADHD.
• 4/25/11: Letter of Intent (LOI) sent to NIMH.
• 06/24/11: NIMH response.
• 06/24/11 - Current: Revisions to LOI.
Thank you for your attention & questions