Neurofeedback and qEEG-
Personalized Medicine

Deborah R. Simkin, M.D.
Clinical Assistant Professor
Emory University School of Medicine

Joel Lubar, PhD
Professor Emeritus
University of Tennessee
CAM – Neurofeedback

Part 1
1. History of surface NF, especially as it pertains to ADHD and seizures
2. Studies of Surface NF
3. Enduring Effects
3. Controversies
4. Personalized Medicine - Use of qEEG to determine subtypes for ADHD.

Part 2. Next lecture
5. NF protocol determination and responders to medications
6. AAP approval NF for ADHD
7. Surface NF in regards to autism
8. Role of NF and qEEG in view of the new NIMH Research Domain Criteria (RDoC)
9. Conclusions
History

• From a historical viewpoint, surface NF is based on 2-4 electrodes.
• Originally Surface NF did not employ the use of Quantitative EEG

• There are three types of NF that employ the use of qEEG:
  1. Real time Z score NF
  2. Low Resolution Electromagnetic Tomography (LORETA NF)
  3. Functional magnetic resonance imaging (fMRI) neurofeedback’s

• Surface NF involves measuring the amplitude of neurons directly beneath the electrode where 95% of the neurons arise from a distance of 6 cm and all frequencies are mixed together at each electrode.

• However, LORETA uses three-dimensional source localization applied to human qEEG in which the mixture of frequencies under each scalp electrode are unscrambled and linked to three-dimensional sources in the interior of the brain with accuracies of approximately 1 cm in many situations.
History

- LORETA NF uses a different kind of qEEG NF analysis that provides an estimation of the location of the deep underlying brain generators, called modules or hubs (e.g.,
  - the anterior cingulate, insula, fusiform gyrus) and networks of the patient’s EEG activity within a frequency band.

- It allows the clinician to translate qEEG data into a three-dimensional figure that corresponds with and looks like the images in fMRI that are associated with disease states.

- It requires more labor-intensive preparation, because an electrode cap with 19 electrodes must be applied in every session, but it can shorten the length of treatment. Coherence training can include multiple areas.

- More on this in a later talk
- First- How did we get here?
History

Review:

- Delta-slow wave – (sleep) - up to 4 Hz
- Theta- inattention and drowsiness - 4-8 Hz
- Alpha - relaxed and attentive (8-12 Hz)
- Beta-active/attentive (12-30 Hz)
- Gamma - (25-100 Hz) - Usually 40 Hz

- NF is based on operant conditioning
History of Surface NF-operational conditioning

• First description of EEG by Berger, 1929

• First use of EEG alpha blocking response which followed classic Pavlovian conditioning, 1941

• Sterman first to use operational conditioning-while recording events with an EEG in cats in 1969
History of NF

- Sterman, 1969
- Operational Conditioning with Cats-Cat was connected to EEG to record what happened during operational conditioning

- Traditional conditioning where a lever is pushed and food comes into a bowl=now cat presses lever when hungry.

- Next, a new element was introduced to the experiment: a tone. If the cat pressed the lever while the tone was on, the dose of chicken broth and milk would not be delivered.

- The cat had to wait for the tone to stop before it could press the lever and get the reward.

- Sterman observed that while the cat was waiting for the tone to stop, it entered a unique state of consciousness.

- It remained absolutely still, though extremely alert, anticipating when the tone would stop.
History of NF

• Accompanying this motor stillness, a specific rhythmic frequency of 12Hz to 15Hz over a specific part of the brain was seen (which he called the sensorimotor frequency or SMR).

• Sterman wanted to see if he could teach the cat how to produce that specific frequency at will.

• No lever was used, instead, if the cat produced a half second of the SMR frequency, he were given a shot of the broth and milk.

• Cat would produce in anticipation of broth and milk

• Over time the cats learned how to produce the frequency at will.
History NF

• Operant conditioning-
• NF can provide a reward for the appearance of a particular electrical event in the brain.
• The electrical pattern soon begins to appear in anticipation of the reward, leading to increased frequency of appearance of that electrical pattern.
• In a similar way in humans, if a dot appears on the screen during an NF session with each occurrence of a particular targeted EEG pattern or rhythm, the rhythm eventually continues to occur in anticipation of the dot appearing.
Types of Surface NF Protocols for ADHD

• Sensorimotor Rhythm (SMR)

• Theta Beta Rhythm (TBR)

• Slow Cortical Potential (SCP)

• Due to controversies surrounding Low Energy Neurofeedback System (LENS), which uses passive radiofrequency electromagnetic stimulation with eyes closed, and Hemoencephalographic Neurofeedback (HEG), which provides feedback about cerebral blood flow, these techniques will not be reviewed here.

• Low Resolution Electromagnetic Tomography (LORETA), Z score training and functional Magnetic Resonance Imaging (fMRI) neurofeedback will be covered in another lecture.
History of NF

- Both Sterman and Lubar utilized Operant Conditioning
- First use of **Sensorimotor Rhythm Training** over sensory motor cortex to decrease seizures was done by:
  - Sterman, 1972 in animals and
  - Lubar, 1976 in humans.
History of NF-SMR

- Lubar-first to use NF on hyperkinetic child in 1976
  Placed 2 electrodes at C3 and C4
  Trained up Sensorimotor EEG rhythm= Beta (12-14Hz) so (theta) 4-8 Hz was no longer present
  qEEG was not utilized yet
  Result-increased attention and decreased seizures

Called Sensorimotor Rhythm (SMR)

ABA design
History of NF-SCP

• **Contingency Negative Variation or Slow Cortical Potentials (SCP)** demonstrated by McAdams, 1966

  CNP is not based on amplitude of a given band (like SMR or TBR) but rather the polarity of the slow EEG content-surface positivity or surface negativity

  Seizures =surface negativity

  CNP is a type of event related potential in which slow wave activity (.02-2Hz) exhibits a negative shift in anticipation of an expected event (waiting for a green light to change)
Slow Cortical Potential – SCP (0.02-2Hz)

• (-) SCP (dec. in CNP) = cortical excitation of underlying networks (seizures) or deficiency in regulation of brain resources (behavioral inhibition)

• Based on this:
  • SCP NF used in drug refractory seizures (Rockstroh, et al, 1993) and
  • Heinrich, et al, 2004-first to use protocol based on Contingent Negative Variation (CNP) for ADHD by increasing SCP (or inc. CNV)

SCP, TBR and SMR NF decreases seizures and is used to treat ADHD
Lubar-1st to use qEEG

• Began using qEEG to differentiate ADHD from NL (1991)
• ADHD individuals with excess theta (4-8 HZ) and decreased Beta (13-30 HZ) at Fz, FCz or Cz
• Trained down theta and trained up beta at C3 and C4
• Lubar called this the **Theta/Beta protocol or Ratio (TBR)**
  
  (Arns, Conners and Kraemert, 2012)

  (Linden, et al, 1996)

First to use TBR for ADHD with qEEG in comparison to wait list

Result-increased attention and decreased impulsivity
Studies on ADHD-


None in metaanalysis used qEEG

Six studies included randomization and 3 non-randomized studies compared NF to Medication

In all studies, only 12% were on medication

Three studies used semi-active control group (not known to affect ADHD)

2 studies =computerized attention training group and 1 study =EMG biofeedback

One study used a group therapy control group

Mean ES for measures of inattention was 0.72, hyperactivity/impulsivity 0.70, all ADHD symptoms 0.62, and all problems (ADHD or otherwise) 0.57.
Studies of ADHD

Of the 12 RCTs, only 4 studies utilized a sham-NF design

Of these 4 studies none of them examined the validity of the sham’s inertness and they all used unconventional NF protocols that are not typically used in the field

Re-calculating the aforementioned ESs, without these 4 sham-controlled studies:

- Inattention 0.81 (vs. 0.72),
- Hyperactivity/impulsivity 0.73 (vs. 0.70),
- All ADHD problems 0.71 (vs. 0.62),
- And any problems (ADHD or otherwise) 0.68 (vs. 0.57). (Arns et al, 2009, Hurt et al, 2014)
Studies on ADHD-ES Meta analysis, Arns, 2009

Figure 3.
This figure shows the grand mean ES for the controlled studies compared to the within-subject effect sizes for all studies for all 3 core symptoms. Note that the ES for the controlled studies are slightly smaller, which could be due to the fact that many controlled studies used a "semi-active" control group. Furthermore, given the 95% confidence intervals the ES for inattention, hyperactivity and impulsivity are significant for both comparisons.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Conditions</th>
<th>n</th>
<th>Age</th>
<th>Measure</th>
<th>Instrument</th>
<th>NF Site</th>
<th>Treatment</th>
<th>Mean # Sessions</th>
<th>Notes</th>
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<td>10</td>
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<td>Waiting list control</td>
<td>13</td>
<td>11.1</td>
<td>Hyperactivity</td>
<td>BASC</td>
<td>C3 or C6</td>
<td>Beta/Theta</td>
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<td>C3 or C6</td>
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<td>CA</td>
<td>RCT Waiting list control</td>
<td>15</td>
<td>10.2</td>
<td>Hyperactivity</td>
<td>BASC</td>
<td>C3</td>
<td>Beta/Theta</td>
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<td>9.61</td>
<td>Hyperactivity</td>
<td>BASC</td>
<td>FCP-Cz-Pz</td>
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<td>SCP</td>
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**Table 1**

This table shows an overview of all studies used in the meta-analysis. The study numbers correspond to the same numbers in the figures and the references.

A total of 476 subjects were included based on prospective controlled studies and 718 subjects for studies employing a pre- post-test design.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Conditions</th>
<th>n</th>
<th>Age</th>
<th>Measure</th>
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<th>NF Site</th>
<th>Treatment</th>
<th>Mean # Sessions</th>
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<td>C3-Fz or C4-Pz</td>
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<td>Hyperactivity</td>
<td>DSM-IV RS</td>
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<td>Beta/Theta</td>
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<td>11</td>
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<td>9.2</td>
<td>Hyperactivity</td>
<td>DSM-IV RS</td>
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<td>USA</td>
<td>Multisite naturalistic pre-/postdesign</td>
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<td>Impulsivity</td>
<td>TOVA</td>
<td>C3, C4</td>
<td>Beta/Theta</td>
<td>198</td>
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</table>

**Notes:**

SCP = Slow Cortical Potentials; SMR = Sensorimotor EEG Rhythm; RCT = Randomized Controlled Trial; DSM-IV RS = DSM-IV Rating Scale (Lauth & Schlotke). * The original Kaiser & Ottmer sample consisted of 1089 subjects, however Means and SDs were only available for N=530 (Kaiser, personal communication.)
Studies on ADHD-Arns 2009

• Problems with studies

   For studies that did not randomize, parents asked for medication or NF-so some bias may have occurred.

   Small N in some of the studies

   No follow at the time (but since then other studies have had follow up-(see enduring effects).

   No double proven blind placebo controlled studies- (see controversies)

   However, none of the studies considered subtypes of ADHD based on qEEG
• Studies on ADHD-Arns, 2009-
• Monastra’s study (2002) was not included because it had a higher effect size which was probably due to
• 1. participants receiving a Comprehensive Clinical Care program and
• 2. because it only included subjects with an increased theta/beta ratio (a particular subtype), thereby potentially selecting those subjects who could benefit most from neurofeedback treatment (and not representative of all ADHD subjects) leading to higher ES as compared to the other studies
• **Importance of this led to personalized medicine discussed latter.**
• Studies on ADHD-Arns, 2009
• The study by Gevensleben et al was the most methodologically sound study at the time.
  • It included randomization, a large sample size and a multi-center approach.
  • This study showed a medium ES for hyperactivity (ES=0.55) and a large ES for inattention (ES=0.97).
Studies on ADHD


All demonstrated significant improvements in attention, hyperactivity or impulsivity as compared to controls.
Enduring effects

- Steiner, et al., 2011 F/U at 6 months demonstrated that NF students maintained the same medication dosage but
- Students getting cognitive training and control groups had statistically significantly increases in meds (9 mg, p=.002 and 13 mg, p=<.001)
- At 6 months to 2 years (Gani, et al., 2008, Gevensleben, et al., 2010, Leins, et al., 2007, Strehl, et al., 2006) demonstrated that effects did not fade over time and impulsivity and hyperactivity effects continued to improve.
- See next graphs-bar to right is controls
Fig. 2. Within subject Hedges’ D ES for 3 randomized studies who have performed 6 month and 2 year follow-up data for inattention (left) and hyperactivity (right). For Post-Treatment and 6 month follow-up the ES for the control group from the Gevensleben et al. (2010) study has been plotted as a comparison for non-specific effects across time. For the comparison at 2 years follow-up the ES of 7–10 yr. vs. 14–17 yr. children has been plotted as an indication of improvements of ADHD symptoms related to aging from Erhart et al. (2008). Note that for all studies the effects of neurofeedback tend to increase with time, most specifically for hyperactivity. (Error bars are Variability of the ES.)
Figure 15.1 The effects of neurofeedback over time for three controlled studies for inattention (left) and hyperactivity (right). The study by Heinrich et al. performed 3 months follow-up and the other two studies performed 6 months follow-up. Note that the effects of neurofeedback tend to improve further over time (as opposed to the effects of medication, which are not sustained when the medication is stopped).

• Problems with DBPC studies

• “Given that NF is based on operant conditioning principles, it is crucial that the active treatment be based in with principles of learning and conditioning principles” (Arns, 2014)
Controversies

1. Use of unconventional neurofeedback protocols:
   - Lansbergen, et al, 2011 used qEEG based protocols with 2 channel training, and

2. Auto thresholding—where child is always rewarded whether active learning is taking place or not—Lansbergen, 2011, Arnold, 2012
Controversies

• Five recent DBPC studies did not find a difference between sham neurofeedback:
  • Lansbergen, et al, 2011,
  • DeBeus and Kaiser, 2011,
  • Arnold, et al, 2012,
  • Perreau-Linck, et al, 2010,
  • van Dongen-Boomsma, 2013)
Controversies

3. Partial non-contingent feedback on a variable ratio or random-reinforcement-DeBeus, Lansbergen and Perreau

“Imagine a child with ADHD who already spends a lot of time playing computer games and is now placed in front of a display that purportedly is going to help but he is in the sham group. The child becomes engaged by the display, tries to make it occur more frequently, and in the process is releasing dopamine in both the dorsal and ventral attention networks and from dopamine-producing regions within the brain such as the nucleus accumbens and related areas.

The display elicits an unconditioned response of increasing EEG activation in many areas including the one in which the sensor has been placed, such as FZ or CZ, resulting in more beta and less theta. Sometimes when a burst of beta activity associated with decreased theta activity occurs at the location where the sensor is placed, reinforcement is delivered.”

Joel Lubar (Simkin, et al 2014)
Controversies

• This same type of reinforcement, used in the gambling industry, is the most powerful reason why casinos make billions of dollars.
• As a result, the child in the sham conditioning group often has an activated EEG, tries hard to get the noncontingent reinforcement, which is sometimes contingent, and shows improvements in several ADHD indices such as rating scales and perhaps even academic performance.
“It has been repeatedly stated that, because an operant conditioning of a particular EEG pattern reinforcement is usually delivered after 0.5 to 1 second of the production of that pattern, the EEG recording can be marked every time reinforcement is delivered in both the experimental and sham control group.

In the sham group, a simple correlation can be run between the percentage time that the reinforcement was contingent and the degree to which the measured EEG parameters changed in the desired direction along with all of the appropriate before and after measures. It would not be surprising that, even if there was a 20% contingency in the sham group, powerful learning effects might occur. As a result it is impossible to develop a sham in which reinforcement never coincides with the EEG pattern that is being trained in the experimental group.”

Joel Lubar (Simkin et al, 2014)

A Collaborative Neurofeedback Group has been formed to address this issue (Arnold, Arns, Conners, deBeus, Hirshberg, Kerson, Krarmer, Lofthouse, Lubar, McBurnett and Monastra, 2013)
Controversies

4. Providing reinforcement (80%) too high so that no learning occurs because it is too easy—Lansbergen, 2011, and van Dongen-Boomsma, 2013)

5. Complicated feedback—instead of simple auditory or visual feedback, exciting sony play stations (DeBeus, 2011, Arnold, 2012) or movies (Lansbergen, 2011) were used.

Made it hard to differentiate when feedback occurred due to entertainment or treatment.
Controversies

• 6. Recent meta analysis by Sonuga-Barke, et al, 2013 was negative to NF but Arns and Strehl, 2013 criticized the analysis due to not focusing on standard protocols, selection of control conditions and change of medication status not being taken into account.
PERSONALIZED MEDICINE-Treatment Matching

- Use of qEEG to determine subtypes:
  - A. Used to determine specific protocol to be used with NF
  - B. Used to determine who will respond to medicines
  - C. In line with NIMH new Directive-Research Domain Criteria (RDoC)

- It was Monastra’s study (2002) where it only included subjects with an increased theta/beta ratio (a particular subtype) that led clinicians to think about personalized medicine
Use of qEEG subtypes to determine NF protocols

A. Sherlin, et al, (2010) pointed out that when pre-qEEG data is evaluated in, for instance, a study involving pre-selection of participants based on abnormal theta/beta ratios for ADHD (Monastra, 2002):

- the ES for inattention was 2.22 and hyperactivity was 1.2.

- Perhaps participants should be treatment matched based on the sub type in order to be more effective.
Use of qEEG subtypes-to determine NF protocols

• B. NF protocols using qEEG.
• Arns (2012)- Based on qEEG data one of 4 NF protocols selected:

1. *Frontocentral Theta/Beta* protocol- when excess theta was observed midline site at FZ, FCz or Cz where activity was maximal using Z scores, Theta dec/Beta inc protocol was used unless:

   a. Beta was in excess-in this case only theta was dec.

   b. Theta was nl but beta dec, then beta was rewarded
Use of qEEG and subtypes to determine NF protocol

• 2. *Frontocentral alpha* protocol-If there was excess frontocentral alpha (esp during eyes open or EO) then midline site where the activity was greatest was chosen and downtrained. If no excess beta or beta spindles, then beta was rewarded.

• 3. *Beta downtraining* protocol-If excess beta or beta spindles were present then site where maximal was selected-exact training frequency established from qEEG single Hz in zones and downtrained.
Use of qEEG and subtypes-to determine NF protocol

4. Low voltage EEG – If observed, SMR protocol was used (either rewarding SMR spindles with a .25 duration or SMR/theta at C3/C4. If dec alpha power was noted on Eyes Closed (EC), alpha uptraining was done at Pz with EC (Johnston, 2005)

5. If no clear qEEG deviations, and or if sleep problems were a main complaint, SMR was used on side where 12-15Hz activity was lowest.

In all protocols, EMG inhibits were employed where EMG (55-100Hz) had to be kept below 5-10 uV
Use of qEEG and subtypes-to determine NF protocol

• Results:

Fig. 1 Clinical effects over time for the total group of ADHD/ADD patients at pre-treatment, halfway treatment and post-treatment (averages plus SEM) for ATT and HI. All time effects were significant ($p \leq .001$)
Use of qEEG and subtypes-to determine NF protocol

Fig. 3 ES for the different studies mentioned in the introduction and the ES obtained from the current study, with on the left ES for ATT and on the right ES for hyperactivity. Note that ES for hyperactivity for this study was based on a combined HI scale.
Use of qEEG and subtypes

- ES for Attention was 1.78 and for Hyperactivity was 1.22
- Recent meta analysis of effects of stimulants medication in ADHD found ES 0.84 for Ritalin for ATT (Faraone and Buitelaar, 2009)
- In addition, an anterior individual alpha peak frequency (iAPF) was related to improvement of depressive symptoms.
- Slow anterior iAPF at baseline predicted poor treatment response on comorbid depressive complaints.
Use of qEEG and subtypes to determine NF protocol

Fig. 2 Improvement on comorbid depressive symptoms for the patients across time (time effects: $p = .003$; Left) and the significant correlation between the frontal iAPF and the percentage improvement in BDI scores ($p = .002$; $r = 0.851$; Right)
Use of qEEG and subtypes-to-determine NF protocol

• C. Other considerations:
  • Subgroup of ADHD patients characterized by a circadian rhythm delay, associated with delayed sleep onset, already present by age 3.
  • These patients have more theta and frontal alpha and they respond well to medication.
  • Use of SMR and SCP causes normalization of sleep.
  • Perhaps targeting these patients will cause a decrease in ADHD sx.
  • If so, NF could be stopped once sleep onset insomnia improves and perhaps less sessions would be required.
• Arns, Kenemans, 2012
Conclusions

1. Surface NF has shown to be important as an integrative approach to treating psychiatric disorders.

2. Early DBPCT studies that did not show effectiveness were often flawed due to a lack of treatment matching and poorly devised protocols, etc.

3. Quantitative EEG opens the door for the ability to determine specific NF protocols better suited to the patient.

Next talk - Personalized Medicine and use of qEEG to determine response to medications.

Third Talk - LORETA NF - poor man’s fMRI