Update on the Theory and Practice of Infra-Low Frequency Neurofeedback

Clinical Summit, Los Angeles, May-June 2019
Siegfried Othmer

Copyright, The EEG Institute, 2019
Agenda for Day One: Past and Present

• Update on the results of research on ILF NF
• Review of the Theoretical Understanding of ILF NF
  – The basis for moving forward on protocol development
• The present challenge: Synchrony training
We have data!

• Analysis of our collective CPT data
• Analysis of EEG Institute CPT data
• Results of pilot study on 251 ADHD children and adolescents
• Results of a study on frontal lesions in traumatic brain injury
• Controlled study of ILF NF with HRV as control
QIK CPT Data Analysis for the Network

Last year we showed comprehensive data from over a decade:

• Segregated by age category: 6-10; 10-20; 20-70+
• Segregated by time: 2006-end 2013; 2014-2017
• This yielded ‘improvement factors’ on the order of 2 for the discrete errors
• This did not yield a good sense of the clinical significance
Performance comparison, post-2013 with pre-2014

<table>
<thead>
<tr>
<th></th>
<th>6 through 9</th>
<th>10 through 19</th>
<th>20 through 70</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commission Errors</td>
<td>1.12</td>
<td>1.18</td>
<td>1.09</td>
<td>1.13</td>
</tr>
<tr>
<td>Omission Errors</td>
<td>0.97</td>
<td>1.03</td>
<td>1.03</td>
<td>1.01</td>
</tr>
<tr>
<td>Outliers</td>
<td>0.96</td>
<td>1.11</td>
<td>1.22</td>
<td>1.10</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.98</td>
<td>0.99</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>Variability</td>
<td>0.97</td>
<td>1.02</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

The significant improvements are high-lighted
**EEG Expert QIKtest Pre-Post Comparison**

**Commission Errors | 6-9 all | 2014**

# Errors at the Median decline from 30 to 15
How meaningful are the changes observed in the discrete error distribution?

We can use our norming data to assign a mental age to the median score for each distribution.

We can then express the training-induced changes in terms of equivalent mental age.

The median score is the best choice to characterize the distribution as a whole.
Improvements in terms of equivalent mental age

Improvements in Implicit Mental Age: All Categories, 6-9 age range

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>VARIABILITY</td>
<td>6.6</td>
<td>7.6</td>
</tr>
<tr>
<td>REACTION TIME</td>
<td>7.3</td>
<td>8</td>
</tr>
<tr>
<td>OMISSION ERRORS</td>
<td>6.2</td>
<td>8.5</td>
</tr>
<tr>
<td>COMMISSION ERRORS</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>
Improvements in terms of equivalent mental age

**Improvement in Implicit Mental Age:**
*All Categories: Age Range: 10-19*

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variability</td>
<td>10.4</td>
<td>11.8</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>12.1</td>
<td>12.6</td>
</tr>
<tr>
<td>Omission Errors</td>
<td>10.3</td>
<td>13.8</td>
</tr>
<tr>
<td>Commission Errors</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>
Improvements in terms of equivalent mental age

Improvement in Implicit Mental Age: Total Age Range

- **VARIABILITY**
  - Pre-training: 11.9
  - Post-training: 13.4

- **REACTION TIME**
  - Pre-training: 12.0
  - Post-training: 12.9

- **OMISSION ERRORS**
  - Pre-training: 11.7
  - Post-training: 17.2

- **COMMISSION ERRORS**
  - Pre-training: 13.0
  - Post-training: 19.3

Legend:
- Post-training
- Pre-training
Improvements in terms of equivalent mental age

Improvement in Implicit Mental Age:
Total Age Range: EEG Institute

VARIABILITY
- Pre-training: 13.8
- Post-training: 16.8

REACTION TIME
- Pre-training: 14.5
- Post-training: 16.5

OMISSION ERRORS
- Pre-training: 18.5
- Post-training: 30

COMMISSION ERRORS
- Pre-training: 15.5
- Post-training: 27
Analysis of EEG Institute CPT data by John Putman
Accuracy, pre-score < 100  (N = 155)

8 significant declines in score in first 20 sessions: ~5%

Improvement in mean standard score from 81.9 – 99.0

Improvement in mean percentile score from 12th to 47th
EEG Institute CPT data; analysis by John Putman

Performance pre-score <100  (N=91)

8 significant declines in score in first twenty sessions: 9%

Improvement in mean standard score from 89.4 – 99.0

Improvement in percentile score from 24th to 47th
The bar chart above illustrates the # Omission Errors before and after an intervention. The chart shows a comparison between the total number of omission errors (blue bars) and the number of errors that were less than 100 (orange bars) for two groups: Om pre and Om post.

<table>
<thead>
<tr>
<th>Om</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=271</td>
<td>10.3</td>
<td>5.3</td>
</tr>
<tr>
<td>N=92</td>
<td>22.9</td>
<td>9.0</td>
</tr>
</tbody>
</table>
Commission Errors

Mean Commission Errors
N= 271

Pre-training 16.4
Post-20 sessions 9.3
Improvement factor 1.8
Therapeutic effect of Infra-Low-Frequency Neurofeedback (ILF NF) training on Children and Adolescents with Attention Deficit Disorder

Dr. Adam Alfred¹, Andrea Blunck², Dr. Bernhard Wandernoth³ and Dr. Horst Schneider³

¹Praxis für Kinder- und Jugendpsychiatrie, München und Prien
²EEG Info, Schweiz
³BEE Medic GmbH, Singen
Presented at the 63rd Annual Meeting of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN)
March 28-30, 2019 in Freiburg, Germany
Study Objectives

- Goal was to see whether neurofeedback is practical in a large psychiatry practice with high patient turnover
- This was not an efficacy study, or even a clinical effectiveness study
  - Neither was still in question among the participants
- Practicality was to be established comprehensively, in the context of financial constraints, scheduling constraints, and pharmacological as well as other therapeutic alternatives
Multi-center observational study

- Praxis für Kinder- und Jugendpsychiatrie Dr. Alfred, München
- Praxis für Kinder- und Jugendpsychiatrie und Psychotherapie Thilo Palloks, München
- Privat- und Neurofeedback Praxis Klaus Werner Heuschen, München
- Praxiszentrum Chiemsee, Praxisgemeinschaft Palloks/Dr. Alfred/Heuschen, Prien
Multi-center observational study

• 25 NFB-trained Therapists
  • Using 16 Cygnet systems
• 251 Patients with clinically validated diagnosis of ADHD
  • 196 tested with QIKtest pre-post
  • 43 cases have pre-post symptom data
• Age 7 – 21 years
• Survey period: 2016 - 2017
## Results – Continuous Performance Test (CPT)

Comparison of four parameters of Attention and Impulse Control before and after NFB

<table>
<thead>
<tr>
<th></th>
<th>N= 196</th>
<th>Pre (T₀)</th>
<th>Post (T₂)</th>
<th>Diff.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>̅𝑥𝑥 Reaction Time (RT)</strong></td>
<td></td>
<td>457 ± 88 ms</td>
<td>436 ± 85 ms</td>
<td>-21 ms</td>
<td>&lt;.0001*¹</td>
</tr>
<tr>
<td><strong>̅𝑥𝑥 Variability of RT (VAR)</strong></td>
<td></td>
<td>122 ± 31 ms</td>
<td>104 ± 30 ms</td>
<td>-18 ms</td>
<td>&lt;.0001*¹</td>
</tr>
<tr>
<td><strong>̅𝑥𝑥 Omission Errors (OM)</strong></td>
<td></td>
<td>9.6 ± 15.1</td>
<td>5.0 ± 9.3</td>
<td>-4.6</td>
<td>&lt;.0001*²</td>
</tr>
<tr>
<td><strong>̅𝑥𝑥 Commission Errors (COM)</strong></td>
<td></td>
<td>19.1 ± 17.2</td>
<td>9.0 ± 9.0</td>
<td>-10.1</td>
<td>&lt;.0001*²</td>
</tr>
</tbody>
</table>

*¹ Student’s t-test  
*² Wilcoxon signed rank test
Results of CPT expressed in terms of Equivalent Mental Age

Improvements in *Equivalent Mental Age*

<table>
<thead>
<tr>
<th></th>
<th>Post-training</th>
<th>Pre-training</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>12.3</td>
<td>10.2</td>
</tr>
<tr>
<td>VAR</td>
<td>12.8</td>
<td>10.0</td>
</tr>
<tr>
<td>OM</td>
<td>10.3</td>
<td>8.9</td>
</tr>
<tr>
<td>CO</td>
<td>15</td>
<td>8.5</td>
</tr>
</tbody>
</table>
Results – Symptom Tracking

• After the NFB intervention 97% of the patients had an improvement in symptoms that once were perceived as stressful.
• Only 3% of the patients claimed no noticeable improvement of the symptoms.
Results – Symptom Tracking

- After the NFB therapy, patients (n=43) rated the severity of various ADHD-specific symptoms.
- These were found to be significantly reduced!
- Example (the three cardinal symptoms for ADHD):

<table>
<thead>
<tr>
<th>Severity of Symptoms</th>
<th>Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inattention</td>
<td>T₂ 5.4 ± 2.2</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>T₀ 8.3 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>T₂ 4.6 ± 2.5</td>
<td>.012</td>
</tr>
<tr>
<td></td>
<td>T₀ 8.1 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Impulsivity</td>
<td>T₂ 6.1 ± 2.5</td>
<td>.018</td>
</tr>
<tr>
<td></td>
<td>T₀ 7.4 ± 1.8</td>
<td></td>
</tr>
</tbody>
</table>

Statistics by Wilcoxon signed rank test.
Appraisal

• There were only two dropouts from the study over its duration (< 1%)

• 87% of parents and teachers surveyed expressed satisfaction with the outcome
  – Taking costs in time and money, as well as the availability of alternative treatments, into account

• Management appraisal:
  – “Parents are satisfied; therapists are happy; the accountants are satisfied; and the management burden is light.”
Pilot study on veterans with TBI/PTSD

- Principal Investigator: Judy Carlson in Hawaii
- Four cases of concussion involved in pilot study
- All declared fully disabled by the VA:
  - PTSD, headaches, sleep issues, attention, quality of life
- PTSD scale, military version, declined below clinically significant values in all four cases in twenty sessions
  - Average decline in score > 40 points
  - 10 point improvement is regarded as clinically significant
Neurofeedback in patients with frontal brain lesions: a randomized, controlled double-blind trial

Annaheim C, Hug K, Messerli M, Simon Y, Stumm C, Hund-Georgiadis M,
REHAB Basel, Basel, Switzerland

Results:

After 20 sessions of either NF or sham-NF, the NF-group showed a trend towards a larger improvement in the Frontal Assessment Battery and the phasic alertness task. In a subgroup of patients with predominantly frontal brain lesions, these improvements were significantly higher in the NF-group than the sham group.
Frontal Assessment Battery

Improvement demonstrated with a large effect size of 2.7
Task of Attentional Performance

Improvement demonstrated with a large effect size of 1.0
Controlled study of effect of Neurofeedback at Infra-Low Frequencies on Infra-Slow Oscillations of Brain Potentials

Vera A. Grin-Yatsenko, Sergey A. Evdokimov, Olga Kara, Mark Gregory, and Juri D. Kropotov

- Comparison of ILF NF against Heart Rate Variability training
- 17 participants

Results:
- Significant increase in spectral power in upper ILF regime in training group—as distinct from control group, where power decreased
- Positive changes in functional status reported for both groups
- Positive change in CPT performance in NF group
Power increase in ILF BF group vs decrease in control group

What’s expected? We saw power increase in upper ILF range in depression study.
## CPT Scores

<table>
<thead>
<tr>
<th></th>
<th>Neurofeedback cohort</th>
<th>Heart Rate Variability cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
</tr>
<tr>
<td>Commission Errors:</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Omission Errors:</td>
<td>60</td>
<td>20</td>
</tr>
</tbody>
</table>
Review of Theoretical Model

• We are training on the dynamics of Default Mode activity
• ...in interaction with the Salience Network
• …predominantly in the ILF regime
• …because the core regulatory functions are organized with a view toward persistence, toward stasis
• We are a predator species, organized to live out of resting states
The hemispheric divide

- The dominant cerebral architectural feature in mammalian species is the hemispheric divide
- Functional organization across that divide is one of our greatest challenges
- Hence brain instabilities are our greatest clinical challenge
  - Macro-instabilities
  - Subtlety of coordination---autonomic regulation
The front-back axis

• Coordinating input and output functions ranks as the second greatest challenge for the brain
• This is the primary burden of the Default Mode Network
  – In collaboration with the Salience Network
• Clinically, this may be the primary issue in our most challenging population—victims of early trauma
Resting state networks

From “The Restless Brain,”
by Marcus Raichle
Default Mode Network (Mantini)
Access point for:

- Bilateral inferior parietal lobule
- Posterior cingulate cortex

Access point for:

- Anterior medial prefrontal cortex
- Dorsal anterior cingulate cortex
Significant correlations in DN

This diagram supports the centrality of T4 as the common site in most of our placements.

Buckner (2008)
Legend

- LTC RTC  Left / Right Temporal Cortex
- dMPFC  dorso-Medial Pre-Frontal Cortex
- vMPFC  ventro-Medial Pre-Frontal Cortex
- IPL  Inferior Parietal Lobule
- PCC  Posterior Cingulate Cortex
- Rsp  Retrosplenial Cortex
- PHC  Para-Hippocampal Cortex
- LHC RHC  Left / Right Hippocampal Formation
Peaks in connectivity gradient…
The principal hubs of the Default Mode Network

Mantini

Functional Correlation Strengths


Principal linkages shown
Adding subsidiary linkages

Note predominance of right-side linkages
All Relevant Linkages:
Reflections on History

• There was a two-year period in which Sue was using inter-hemispheric placements almost exclusively

• Primarily:
  – T3 - T4
  – P3 - P4
  – Fp1 - Fp2

• Father to the thought: Can we combine the calming protocol with the inter-hemispheric placements?
Placement:
{T3-P3} – {T4-P4}
Placement:
\{T3-T4\} – \{P3-P4\}
Visualizing the Temporo-parietal protocol

• One can think of this protocol as combining the two posterior lateralized protocols
• One can equally well think of it as combining the two primary inter-hemispheric protocols
• Neither perspective has preference over the other
• The protocol covers both bases….
If this works in the posterior region, how do we involve the frontal hub?
The Three New Protocols:
The objectives and the driving principles

Objectives:
- Improved calming with the posterior placement
- Improved regulation of the front-back axis

Underlying principles: seeking balance and symmetry
- Preservation of lateral symmetry in protocol placement
- Serving both core objectives simultaneously:
  - Calming and Stabilizing
  - Add activating as a core objective
Our present challenge: Synchrony training

• Alpha band synchrony
  – Our first approach to front-back coordination
  – Following David Kaiser
    • synchrony or comodulation?

• ILF synchrony
  – The preferred approach to front-back coordination

• Gamma band synchrony
A brain suffering from neglect shows a loss of front-back coordination, i.e. comodulation, in the upper ILF range (from fMRI measurements)

From David Kaiser