Day Two:
“We Have Data...”

Siegfried Othmer, PhD
EEG Institute
ILF Synchrony Training

Siegfried Othmer, PhD
EEG Institute
A look at how we got here

First started looking at ILF Synchrony in 2016. The motivations:

1. The midline was largely absent from our protocols
2. The front-back axis is the most important in the Default Mode
   • Developmental considerations
3. Jeff Carmen was doing good work on the midline
   • Effectively at ILF frequencies!
4. David Kaiser was training the front-back relationship to good effect
   • In the Alpha Band (actually, “Thalpha”)
5. Les Fehmi was doing whole-brain synchrony training in alpha
   • That was impinging on the front-back axis as well
ILF or Alpha band training was the issue

- Could we even do ILF synchrony training?
- The problem: The reference is active in synchrony training, and we had no electrically inactive place to put it.

Here are the slides from the 2016 Summit
Is it artifact, sourced by the reference, or is it our signal?

• This question needed to be settled with an actual trial of the training, for which we needed the necessary software...

Our existing synchrony protocol only extended down to 1.8 Hz

Now that we have ILF synchrony, what questions does that leave?

• How does ILF synchrony fit in with alpha band and gamma synchrony?
• How does it fit in with differential ILF?
• How does it shift priorities with respect to PIR?
• How does that shift priorities with respect to David’s protocols?
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PIR Sensor

Independent rationale:

• Inherently complementary to EEG/ILF/ modalities
• Hemodynamic response ties into activation dynamics
• No clinical decision-making
• Facilitates early insertion
• Could serve the purpose of monitoring changes during parameter optimization
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Priorities with respect to David Kaiser DMN training

- The ILF Synchrony training should come before anything is done with the DMN protocol
  - The general training should precede the specific
- The case can be made that the ILF Synchrony training should even be done before the SKIL QEEG, so that the focus will be on whatever is left to be done
  - No point in measuring the obvious
Modulation of intrinsic brain connectivity by implicit (i.e., covert) infra-low frequency neurofeedback

Dobrushina Olga R, Vlasova Roza M, Rumshiskaya Alena D, Litvinova Liudmila D, Mershina Elena A, Sinitsyn Valentin E, Pechenkova Ekaterina V
Modulation of intrinsic brain connectivity by implicit (i.e., covert) infra-low frequency neurofeedback

Dobrushina Olga Ra,b, c, Vlasova Roza Ma,d, Rumshiskaya Alena Da, Litvinova Liudmila Dæ, Mershina Elena Aa, e, Sinitsyn Valentin Ea, Pechenkova Ekaterina Va, f

a Radiology Department, Federal Center of Treatment and Rehabilitation, Ivankovskoe 3, 125367 Moscow, Russia
b International Institute of Psychosomatic Health, Neglinnaya 14-1, 107031 Moscow, Russia
c Research Center of Neurology, Volokolamskoe shosse, 80, 125367 Moscow, Russia
d Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA
e Medical Research and Educational Center, Lomonosov Moscow State University, Lomonovoovsky prospect, 27, 119192 Moscow, Russia
f The Research Institute of Neuropsychology of Speech and Writing, Burakova ul. 27, corp. 3, 105118 Moscow, Russia
Modulation of intrinsic brain connectivity by implicit (i.e., covert) infra-low frequency neurofeedback

• Objective: Identify the networks engaged in the execution of implicit (covert) neurofeedback. Since within-session rsfMRI was ruled out, evaluate proximate pre-post-session assessments.

• Study design: 52 volunteers were randomized to a single session of ILF or sham neurofeedback. Resting state fMRI data were acquired immediately before and after the session, in order to observe training process-induced changes
Pre-post single-session ILF fMRI connectivity changes

• Increased connectivity within the proposed neurofeedback contour after the ILF NF session
• iLOC: inferior lateral occipital cortex
• RDLPFC: right dorsolateral prefrontal cortex
• vStriatum: ventral striatum
• dStriatum: dorsal striatum
Control group:

• In the control group, another set of three connections was altered after a sham-NF session.

• This subnetwork included decreasing connectivity between the RDLPFC and the iLOC bilaterally and increasing connectivity between the RDLPFC and the left thalamus.

Even in covert NF, the brain is trying to figure out what the game is. So even sham training is an active process.
Pre-post single-session ILF fMRI connectivity changes

• Increased connectivity between the language network and salience and visual networks after the ILF NF session
  • IFG: inferior frontal gurus
  • pSTG: posterior portion of the superior temporal gyrus
  • RPFC: rostral prefrontal cortex
  • aInsula: anterior insula).
Conclusions

• We found no significant within-network connectivity changes in post-EEG vs. pre-EEG sessions in the salience, language or visual networks.

• However, between-network connectivity significantly increased in the NF vs. sham-NF group, at post- vs. pre-session for both tested network pairs
  • \( p = .01 \) two-sided for salience and language networks
  • \( p = .006 \) for salience and visual networks
Commentary

• This research was both a daunting undertaking, given the complexity of fMRI studies under time constraints.

• A bold hypothesis was under test. A lot was staked on the proposition that single-sessions changes would be observable, first of all, and secondly remain available for inspection after the session.

• We are not dealing with small effects here. The changes are macroscopic, and they appear to be systematic—i.e., consistent across the cohort.

• The work was done with ‘healthy’ subjects, so presumably we are not dealing with the remediation of deficits here.
Observations

• Note that the linkages affected significantly by virtue of the training process, none were associated with the Default Mode Network!

• And yet our model has assumed that our primary appeal is to the Default Mode organization primarily, and Salience Network secondarily

Matters should perhaps be looked at differently:

• We have chosen to direct the training to resting state organization, and to the foundational core of our regulatory regime
  • That is the Default Mode in its low-frequency organization

• The consequences, of course, are brain-wide, and in no way directed or constrained by us
Effect of Infra-Low Frequency Neurofeedback on Infra-Slow EEG Fluctuations

Vera A. Grin-Yatsenko, Valery A. Ponomarev, Olga Kara, Bernhard Wandernoth, Mark Gregory, Valentina A. Illyukhina and Juri Kropotov
Pre-post ILF data

- Case of depression
- 20 session of ILF training
- Depression was remediated
- Benefits held over the one-year follow-up

EEG in 43-year-old male subject. EEG recorded with linked ear montage during VCPT performance. Bandwidth, 0.016 Hz – 0.5 Hz.
Pre-post ILF spectrum

- Logarithmic ordinate scale
- Low-frequency increase greater than x100

EEG power spectra at Fz in the same 43-year-old male subject before and after training.
Average change in ILF power

- Averaged over eight participants
- For all 19 standard sites
- Note increase in variability along with amplitude
- Deficited regions saw largest increase
- Hence smoother distribution

ILF bandwidth, 0.016–0.5 Hz
Whiskers represent a 95% confidence interval.
Conclusions:

• The changes in band properties are macroscopic
• They are consistent across the board with this population

• What are the expectations, if any?
The temporal structures and functional significance of scale-free brain activity

Biyu J. He1, John M. Zempel, Abraham Z. Snyder, and Marcus E. Raichle
FMRI spectral density

- Increases as we go to lower frequency in ILF regime
- Power-law distributed
EEG spectra

- Also power-law distributed
- Variable exponents in different regions
- Confirms fMRI data in ILF region
Comparison of rest and task conditions

• Black curve refers to resting state
“The effect of arousal state on power-law exponent was non-significant”
Pre-post ILF spectrum

- The change is in the expected direction for good regulation
- Power-law distribution
- The improvement extends down to the measurement limit of 0.016Hz
Infra-Low Frequency Neurofeedback in Depression: Three Case Studies

Vera A. Grin-Yatsenko, Siegfried Othmer, Valery A. Ponomarev, Sergey A. Evdokimov, Yuri Y. Konoplev, and Juri D. Kropotov
Three cases of depression:

• 20 sessions of ILF
• Pre-post QEEG and VCPT analysis
• One-year follow-up
• Assessment instruments:
  1. Montgomery-Asberg Depression Rating Scale
  2. Beck Depression Inventory
  3. Hamilton Depression Scale
Case A

Eyes-Closed Data

Pre-post difference

Red, pre-treatment; Green, post-treatment; Blue, follow-up
Eyes-open data

Before | After | Difference

Case A

\[ \delta \theta \alpha \beta_1 \beta_2 \]

- Pre-treatment
- Post-treatment
- Follow-up
QIKtest Data Summary
2007-2017

Siegfried Othmer, PhD
EEG Institute
Review of cumulative QIKtest results after a decade of use

Quantifying the functional improvements achieved with ILF:
• At the group level – cumulative scores
• Segregated by age category
• By comparing early data to more recent data
  • 2007-2013 versus 2014-2017
• Test-retest error for total sample versus EEG Institute
Cumulative data for discrete errors

The most critical issues in the CPT are the discrete errors, omissions foremost among them.

Look at the incidence of each class of errors across the entire range being measured.
68,220 data points, from 68,220 tests: Commission errors
Commission errors:

EEG Expert QIKtest Pre-Post Comparison

- PRE
- PRE smoothed (+2 x 3)
- POST
- POST smoothed (+2 x 3)

Number of tests

NUMBER OF ERRORS (Tests pre/post 12212/12212)

x 2.4
Omission errors:

![Graph showing EEG Expert QIKtest Pre-Post Comparison with Omission Errors](image)

- PRE
- PRE smoothed (+2 x 3)
- POST
- POST smoothed (+-2 x 3)

Number of Tests vs. Number of Errors (Tests pre/post: 12212/12212)

- x1.8
Reaction time outliers:
Summary of ‘improvement factor’:

• In the range of more major dysfunction as indexed by the discrete error incidence, the improvement factors are as follows:
  • Commission errors: 2.4
  • Omission errors: 1.8
  • Outliers: 1.4
• This implies that with neurofeedback we can make significant inroads even with severe levels of dysfunction
Interpretation:

• The curves (smoothed for clarity) asymptote to stable values, indicating that comparable gains are achievable irrespective of the severity of the deficit.

*It appears that anyone capable of taking the test is likely to be able to benefit from the training*
Next, look at the same data near the ordinate axis where nearly everyone lives.
Median value goes from 12 errors to 6.3 (age range: 6-70, 2017)
Omission Errors, 6-70, 2017 (12,200)

Equipoise
• Observe that most of the population gain shows up in the zero-error bin
• This means that with respect to this measure, full normalization of function has been achieved
  • To the extent that can be determined in a single QIK-test
Median value of 4.25 goes to 1.75 omissions
• As in the case of omission errors, most of the benefit of training shows up in the zero-error bin
Median value declines from 2.7 to 1.3
Summary of improvement factors

The ratio of pre-training status to post-training status is as follows, as indexed by the median # of errors for the population:

• Commission Errors: 1.90
• Omission Errors: 2.43
• Outliers: 2.08
Improvement factors can be compared between the near-normal and the dysfunctional range

![Graph showing improvement factors for commission, omission, and outliers for near-normals and dysfunctional categories.](image)
Interpretation

• Those who function nearly in a normal manner improve comparably on all measures of discrete errors, in line with the assumption that there may well be a common underlying failure mechanism.

• Those who suffer from more severe levels of dysfunction exhibit a greater capability to improve on errors of commission versus errors of omission and outliers.

• This is to be expected, as a degree of functionality must exist in order for the person to exhibit impulsivity in the first place. In the case of omission errors, the more severely dysfunctional are more likely to be handicapped by factors of organicity that constrain their capacity for functional recovery.
Age Dependence:

The age range of 6-70 was divided into three subgroups:

• Children under ten years of age
• Adolescents under twenty
• Adults ranging from 20-70
6-9 years

# Errors at the Median decline from 30 to 15
10-19 yrs

# Errors at the Median decline from 18 to 8
20-70+ yrs

# Errors at the Median decline from 4 to 2.3
6-9 years
10-19 yrs
20-70+ yrs
6-9 yrs
cumulative
10-19 cumulative
20-70+ cumulative
6-9 years
10-19 yrs

x 1.176
20-70+ yrs
Age dependence:

• Observe that there is not a substantial age dependence except for the outliers, which apparently don’t respond to ILF training in the early years

• Substantial improvement is expected only for the discrete errors
Compare early to late data to track improvement or decrements traceable to protocol changes (or other factors)

• A suitable dividing line is the end of 2013, which yields roughly comparable sample sizes
• Also corresponds roughly to the introduction of HD
### 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>
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<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.
Performance Comparison, Post-2013 vs. Pre-2014

- Commission Errors
- Omission Errors
- Outliers
- Reaction Time
- Variability

6 through 9 10 through 19 20 through 70
An appraisal

• Improvement factors are compared between the more recent activity (2014-2017) and the early history of Cygnet (2007-2013).

• Substantial consistency of the results is observed over this ten-year time frame.

• There is a trend toward improved resolution of outliers in the mature age range, and of improved resolution of commission errors across the age range.
It is critical to know whether we might be losing a step on CPT normalization with our focus on the right hemisphere and the low frequencies.

The slight decline in scores of the youngest cohort will be something to watch in the future.

It could be due to a variety of factors.

We need to evaluate the contribution of ILF Synchrony to CPT normalization.
The QIKtest as a quality control instrument

Analysis of the CPT is a critical quality control for us:
1. at the level of the entire practitioner network
2. at the level of the individual practice, and
3. at the level of the individual client.
A look at the deficited population
Look at commission errors because these are data-rich:

• Here we are looking at the bottom half of the total population (actually the bottom 53%)
• Median score is 29 commission errors, pre-training
• Post-training, the median score is 13
  • Improvement factor is 2.2
• The median post-training score of the entire pool was 12
  • Improvement factor was 1.9

Hence, we have essentially achieved normalization of the deficited pool in twenty sessions
  • i.e., 13 errors at the median rather than 12)
Check for test-retest uncertainty

In order to focus on the well-functioning end of the distribution:

• We can truncate the sample at four commission errors or less
• What happens to these after the training?
• Compare the entire cohort with the results obtained at the EEG Institute
Total sample, subset of <5 commission errors

98th percentile @ 21 errors

+27% in zero error score
EEG Institute sample, <5 commission errors

98th percentile @ 12 errors

+76% in zero error score
Comparison

• The EEG Clinic data exhibits a shorter tail
• But is this partly because of the smaller sample size?
• Repeat the above comparison with a larger sample
Total sample, subset of <10 commission errors

80% of the pool is better off for the experience @ 20 sessions

11% of the pool declined in score

98th percentile @ 23 errors
EEG Institute sample, <10 commission errors

92% of the pool is better off for the experience.

6% of the pool declined in score.

98th percentile @ 14 errors.
Findings:

• Unsurprisingly, the results are better at the EEG Institute, with seasoned clinicians
  1. Higher success rate
  2. Greater progress per individual
  3. Fewer decrements in training
  4. Absence of long tail
  5. Quicker trip to the goal
A perspective:

Analysis of CPT is a critical quality control for us at the level of the entire practitioner network, at the level of the individual practice, and at the level of the individual client.

- Every large practice has the opportunity to compare its outcomes against the network as a whole and against the EEG Institute.
Episodic failure: the instability continuum
Conclusion:

• Discontinuities in brain function should be regarded as priorities in neurofeedback
  • They must be explicitly tested for

• The CPT should be seen as a necessary constituent of a neurofeedback practice