Individualized Neurofeedback in ADHD: Reflecting different Aetiologies?

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Personalized Medicine in Psychiatry?

- Limited effects of stimulant medication in ADHD (NIMH-MTA) and antidepressants (STAR*D)

- **Personalized medicine**: Right treatment, for the right person at the right time as opposed to ‘Blockbuster’ approach
  - From homogeneity to heterogeneity
  - 10\textsuperscript{th} year anniversary of the Human Genome Project (2011): Implications for psychiatry?
  - Focus on ‘endophenotypes’ or ‘biomarkers’
  - EEG: cost-effective, well researched, widely available

- Paradigm shift? Neuromodulation
  - Pharma-Industry suspended most of its CNS R&D budgets (Miller, 2010)

- EEG based neurofeedback and predictors for treatment outcome
Paradigm shift?

- Coverage of terms in scientific articles over the years related to drug treatment in Depression and ADHD
Paradigm shift!

- Coverage of terms in scientific articles over the years related to Neurofeedback, Neuromodulation, rTMS and DBS
Über das Elektrenkephalogramm des Menschen.

Von
Professor Dr. Hans Berger, Jena.
(Mit 17 Textabbildungen.)
(Eingegangen am 22. April 1929.)
Progression of EEG from waking to Sleep

Cortical EEG

Multi-unit activity at Thalamic relay nc.
Progression of EEG from waking to Sleep

Cortical EEG

Multi-unit activity at Thalamic relay nc.
EEG Vigilance model

For an overview see book chapter Arns, Gunkelman, Olbrich, Sander & Hegerl (2010)
Concept of EEG Vigilance
Depression: Rigid Vigilance Regulation

- EEG Vigilance regulation in Depression

Hegerl et al. (2011)
EEG Vigilance Regulation in ADHD

Attention Deficit / Hyperactivity Disorder
- Hyperactive subtype
- Combined subtype
- Inattentive subtype

Vigilance Autostabilisation Syndrome
(e.g. hyperactivity, sensation seeking, talkativeness)

Cognitive Deficits
(e.g. impaired sustained attention)

Unstable Vigilance Regulation (trait-like)
Group averaged data: ADHD

- Results from computerized EEG analysis or QEEG:
  
  - **Increased absolute Theta** *(Bresnahan, Anderson & Barry, 1999; Chabot & Serfontein, 1996; Clarke, Barry, McCarthy & Selikowitz, 1998; Clarke, Barry, McCarthy & Selikowitz, 2001c; DeFrance, Smith, Schweitzer, Ginsberg & Sands, 1996; Janzen, Graap, Stephanson, Marshall & Fitzsimmons, 1995; Lazzaro et al., 1999; Lazzaro et al., 1998; Mann, Lubar, Zimmerman, Miller & Muenchen, 1992; Matsuura et al., 1993)*
  
  - **Increased absolute Delta:** *(Bresnahan et al., 1999; Clarke et al., 2001c; Kuperman, Johnson, Arndt, Lindgren & Wolraich, 1996; Matsuura et al., 1993)*
  
  - **Decreased absolute Beta** *(Callaway, Halliday & Naylor, 1983; Dykman, Ackerman, Oglesby & Holcomb, 1982; Mann et al., 1992; Matsuura et al., 1993)*

- **Data from 250 unmedicated children with ADHD (BRC):**

![Absolute ‘Theta’ EEG power](image1)

![Relative ‘Beta’ EEG power](image2)
Does EEG predict treatment outcome?

Arns et al., 2008

P = .335
P = .038
P = .051

False negative errors on CPT

*
Does EEG predict treatment outcome?
Arns et al., 2008

Does EEG predict treatment outcome?
Arns et al., 2008
ADHD: EEG Vigilance dysregulation

- ADHD-subgroup characterized by lower EEG Vigilance
  - EEG vigilance model (Sander et al., 2010)
  - Many studies reporting excess (frontal) theta and alpha
  - Increased absolute Delta (stage C): Bresnahan et al., 1999; Clarke et al., 2001c; Kuperman, Johnson, Arndt, Lindgren & Wolraich, 1996; Matsuura et al., 1993

- Symptoms are a direct result of unstable vigilance regulation (deficits in sustained attention, distractibility) and auto-stabilization behavior (e.g. hyperactivity, “sensation seeking”)

- Responders to stimulant medication (Sander et al., 2010; Arns et al., 2008)
- Non-responders to antidepressants and rTMS (Arns et al., 2009; 2012)
- These sub-groups do respond to stimulant medication in Depression (Suffin & Emory, 1995; DeBattista et al., 2010) and Manic Depression (Bschor et al., 2001; Hegerl et al., 2010; Schoenknecht et al., 2010)

- Personalized Medicine in practice: QEEG informed Neurofeedback
Neurofeedback


4-day Neurofeedback course: NVvP, FGZP, VGCT, K&J, OG, LVE & BCIA accredited
http://www.brainclinics.com/neurofeedback-rtms-workshops
Neurofeedback: EEG Conditioning

- Classical conditioning of the EEG was first reported by Durup & Fassard in 1935 and Loomis, Harvey & Hobart in 1936.

- Reported pairing light to auditory stimulus and habituation.

- First experimental studies on conditioning of the alpha blocking response in the 1940's (Jasper & Shagass, 1941; Knott & Henry, 1941)

L'ÉLECTRENCÉPHALOGRAMME DE L'HOMME.

OBSERVATIONS PSYCHO-PHYSIOLOGIQUES RELATIVES À L'ACTION DES STIMULI VISUELS ET AUDITIFS

Par G. Durup et A. Fessard

Vol. XIX, No. 3 JUNE, 1936

ELECTRICAL POTENTIALS OF THE HUMAN BRAIN 1

BY ALFRED L. LOOMIS, E. NEWTON HARVEY AND GARRET HOBART
Clinical applications?

- Classical conditioning (Stevens & Stevens, 1960) and operant conditioning of epileptic activity difficult and no sustained effects (Fetz & Wyler, 1973; Wyler et al., 1974).

- Operant conditioning of SMR: Anticonvulsant effects (Sterman et al., 1969; 2010)

- First reports of improved sleep (Sterman et al., 1970)

- First clinical application of T/B Neurofeedback in ADHD (Lubar & Shouse, 1976) and SCP Neurofeedback in ADHD (Heinrich et al., 2004).
Efficacy of Neurofeedback Treatment in ADHD: the Effects on Inattention, Impulsivity and Hyperactivity: a Meta-Analysis

Martijn Arns, Sabine de Ridder, Ute Strehl, Marinus Breteler and Anton Coenen

Effect Size (Hedges' D)

Inattention
Impulsivity
Hyperactivity
Efficacy of Neurofeedback Treatment in ADHD: the Effects on Inattention, Impulsivity and Hyperactivity: a Meta-Analysis

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Effect Size (Hedges' D)

<table>
<thead>
<tr>
<th></th>
<th>Inattention</th>
<th>Impulsivity</th>
<th>Hyperactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ritalin</strong></td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
</tr>
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Faraone & Buitelaar (2010)
Long-term effect of Neurofeedback in ADHD?

Inattention

Hyperactivity

Arns & Kenemans (Under Review)
The Effects of QEEG-Informed Neurofeedback in ADHD: An Open-Label Pilot Study

Martijn Arns · Wilhelmus Drinkenburg · J. Leon Kenemans

• 21 patients including drop-outs, non-responders and responders
• Intake, outtake and every 10th session ADHD symptom checklist, PSQI, BDI
• Last Observation Carried Forward (LOCF)
• Responder: >50% decreased on Inattention and/or Impulsivity/Hyperactivity
• Neurofeedback protocol ‘personalized’ based on previous EEG subtypes (objective decision rules)
Results

• Response rate 76% (16/21)
• Non-Responders: 14%
• Drop-outs: 10%

• Worst case scenario: Response = 76%

• No child X adult interaction.
Effects on ADHD symptoms

All ‘Time’ effects $p < .001$

- **Inattention**
  - Pre-treatment
  - Halfway treatment
  - Post-treatment (LOCF)

- **Impulsivity/Hyperactivity**
  - Pre-treatment
  - Halfway treatment
  - Post-treatment (LOCF)

- **Sleep Quality (PSQI; N=17)**
  - Pre-treatment
  - Halfway treatment
  - Post-treatment (LOCF)

- **Depression score (BDI; N=13)**
  - Pre-treatment
  - Halfway treatment
  - Post-treatment (LOCF)
Effects of QEEG informed Neurofeedback in ADHD

Comparison of the within group ES from Neurofeedback in ADHD meta-analysis (grey) and QEEG-based based neurofeedback (black) with their 95% confidence intervals.

Arns, Drinkenburg & Kenemans (2012)
Pre- and post-ERP changes

- Most studies demonstrate normalization of ERP’s

Kropotov et al. (2005; 2007); Heinrich et al. (2004); Wangler et al. (2011)

Arns, Drinkenburg & Kenemans (2012)
Concluding...

• Slow iAPF: Endophenotype for non-response to treatment, related to cerebral perfusion
• ‘Impaired vigilance regulation’ sub-group (excess frontal Theta and Alpha)
  – Respond to stimulant medication
  – Personalizing Neurofeedback to the specific subtype improves outcomes
  – Non-responders to antidepressant treatments

• What is the underlying etiology of this sub-group?
A Decade of EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis

Martijn Arns\textsuperscript{1,2}, Keith Conners\textsuperscript{3}, and Helena Kraemer\textsuperscript{4,5}

- Theta/Beta ratio not reliable as a diagnostic tool
- Sign. Time effect related to control groups
- Further supporting decreased sleep duration?

Theta/Beta ratio (with SD) 6-18 yrs.

\begin{itemize}
\item N=1062
\end{itemize}
Sleep duration and Sleep restriction

- Sleep duration for children decreased across the last 100 years (Matricciani, Olds & Petkov, 2012; Meta-analysis N=690,747 children) and shorter sleep duration associated with obesity (Magee & Hale, 2012)
- Sleep restriction in healthy children results in impaired attention (Fallone et al., 2001; 2005; Sadeh et al., 2003; Beebe et al., 2008) and increased Theta (Beebe et al., 2010)
- ‘Recovery’ of sleep restriction takes more days than actual sleep restriction!
- Sleep restriction as an explanation for increased incidence of ADHD and increased obesity rates?
ADHD and sleep

• Many sleep-related problems affecting sleep duration and sleep efficiency are more prevalent in ADHD e.g.:
  – 20% prevalence of breathing disorders/sleep apnea (Silvestri et al., 2009)
  – 26% restless legs syndrome (Konofal et al., 2010; Silvestri et al., 2009)
  – 70-80% sleep onset insomnia (SOI) characterized by delayed circadian phase (van der Heijden et al., 2005; 2007; van Veen et al., 2010).

• Treat these as ‘Sleep Phenotypes of ADHD’? (Miano, Parisi & Villa, 2012)
  – Treatment of sleep apnea (adenotonsillectomy) resulted in substantial improvement on attention and ‘ADHD behavior’ (Huang et al., 2007).
  – Treatment of restless legs syndrome by LDOPA improved sleep and dramatic improvements in ‘ADHD behavior’ (Walters et al., 2000). Patients were unresponsive to Stimulants.
  – Chronobiological treatments for SOI in ADHD: LT Melatonin (Hoebert et al., 2009) and early morning bright light (Rybak et al., 2006)
EEG Vigilance subgroup in ADHD

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Cognitive Deficits
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Unstable Vigilance Regulation

Sleep problems

Arns & Kenemans (under review)
Neuroscience & Biobehavioral Reviews
Neurofeedback and Sleep

- SMR Neurofeedback (during waking!):
  - Decreases sleep latency, increases total sleep time and sleep efficiency (Cortoos et al., 2010; Hoedlmoser et al., 2008; Sterman et al., 1970)
  - Increased number of sleep spindles (Sterman et al., 1970; Hoedlmoser et al., 2008)
  - Neurofeedback improves sleep in ADHD (Arns 2011)
SMR Neurofeedback

• All TB NF studies have also included the SMR band in their beta band!

• SMR NF:
  – Increases sleep spindle density during sleep (Sterman et al., 1970; Hoedlmoser et al., 2008)
  – Decreases sleep latency, increases total sleep time and sleep efficiency (Cortoos et al., 2010; Hoedlmoser et al., 2008; Sterman et al., 1970)

• SMR NF impacts on the SOI in ADHD?
SMR Neurofeedback

- All TR NF studies have also included the SMR beta band!

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• SMR NF improves SOI in ADHD?
Sleep-spindle generation

- SMR Neurofeedback
- SCP Neurofeedback

Increased sleep spindle density

• SMR = training sleep spindle circuitry directly (frequency & location)
Sleep-spindle generation

- SMR Neurofeedback
- SCP Neurofeedback

Increased sleep spindle density

Sinha (2011)

Glu

Cortical Neuron

Glu

Thalamocortical Neuron

GABA

Reticular Neuron

- RAS Sensory Input

**Sleep-spindle generation**

- SMR = training sleep spindle circuitry directly (frequency & location)

- Cortical slow waves (< 1Hz) trigger sleep spindles (Amzica & Steriade, 1997; Marshall et al., 2006)

- SCP: Training this cortical ‘slow wave’ circuitry

- SCP, SMR (=TBR) impact on sleep spindle circuitry!

- **Shared mechanism** between different types of Neurofeedback
Conclusion

• Personalized Treatment can result in new insights regarding etiology of ADHD-subgroups

• ‘Impaired vigilance regulation’ sub-group
  – Respond to stimulant medication: ‘symptom suppression’
  – Non-responders to antidepressant treatments
  – Core-pathophysiology hypothesized to be sleep-onset insomnia and circadian phase delay (or other ‘sleep phenotypes’)
  – Treatments should aim at restoring sleep: melatonin, bright light, neurofeedback, LDOPA/Iron deficiency or Adenotonsillectomy.

• Slow iAPF: Endophenotype for non-response to treatment, related to cerebral perfusion

• Patience... normalization of neurophysiology and behavior takes time...
Thank you for your attention!

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