Symposium: EEG Based Personalized Medicine

Ulrich Hegerl
Martijn Arns
In memoriam Dieter Bente

- In memoriam published in 1984
- A senior and founding member of IPEG
- One of his main research themes was ‘EEG Vigilance’ which he conceptualized in 1964

The most proper way of keeping *Bente* in kind remembrance as well as keeping his way of thinking and his scientific activity alive may well be to accept this challenge by critically re-evaluating it.

H. Künkel, Hannover
Vigilance Regulation and response to psychostimulants in affective disorders - Ulrich Hegerl

EEG-based assessment of vigilance regulation in major depression and cancer-related fatigue - Sebastian Olbrich

The change of prefrontal QEEG cordance as a predictor of response to antidepressant treatment - Martin Brunovsky

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study - Martijn Arns
Research report

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study

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Is Pharma Running Out of Brainy Ideas?

Recent cutbacks raise concerns about the future of drug development for nervous system disorders.
Personalized Medicine in Psychiatry

- Efficacy of current pharmaceutical treatments seem maximal (AD 40%; Ritalin 70-90%)
  - Efficacy of newer drugs (i.e. TCA vs. SSRI) are not dramatically improved, mainly improved side effect profile
  - Limited long-term effects of stimulant medication (MTA trial)
  - Several pharmaceutical companies (GSK, AstraZeneca) will no longer develop psychiatric medications (Miller, 2010)
  - Current DSM-based treatment approach not valid!

- Personalized medicine: Right treatment, for the right person at the right time as opposed to ‘Blockbuster’ approach

- Assumes heterogeneity rather than homogeneity within a psychiatric disorder!

- No EBM Personalized Medicine application in psychiatry yet…
Thinking from the Neurobiological Phenotype (i.e. EEG) rather than from behavior

- **EEG Vigilance: Labile or Rigid vigilance regulation**
  - Relation to behavior but not a linear correlation

- **EEG Phenotypes:**
  - I.e. Low Voltage EEG genetically linked to HTR3B, CRH-BP, GABA-A receptor genes (Enoch group).
  - Alpha peak frequency linked to COMT gene (Bodenmann et al., 2009)

- Integrative approach
The increase in theta/beta ratio on resting-state EEG in boys with attention-deficit/hyperactivity disorder is mediated by slow alpha peak frequency

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- APF matures with age and can vary between 5-14 Hz and fixed frequency bands do not accommodate deviating APF’s (Klimesch, 1999)
- Theta/Beta ratio calculated using:
  - Fixed Frequency bands (4-7.5 Hz / 12.5-25 Hz)
  - ‘Individual’ frequency bands (Based on IBIW method from Doppelmayr et al., 1998).
  - ADHD and control group matched on age
Theta/Beta ratio using **Fixed** frequency bands: Significant effect, $p = .038$

Theta/Beta ratio using **Individual** frequency bands: NO significant effect

A. Eyes open

B. Eyes closed

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[Graphs showing theta/beta ratios for ADHD and controls in eyes open and eyes closed conditions.]
Does EEG predict treatment outcome?

- ‘Frontal slow’: Decreased false negative errors: Inattention
- ‘Frontal alpha’: decreased false positive errors: Impulsivity.

Thinking from the neurobiological phenotype instead of behavior

Use multiple measures: Integrative approach
Treatment prediction in Depression

- First report of prognostic use by Roth et al. (1957)
  - Barbiturate induced changes (delta increase) predicted long term outcome to ECT (3-6 mo.)
- Other well investigated Biomarkers in depression:
  - Neurophysiology:
    - LDAEP: Hegerl, Gallinat & Juckel, 2001
    - EEG Cordance: BRITE-MD trial -> Brunovsky
    - EEG Vigilance: -> Hegerl
    - EEG Alpha Asymmetry: Bruder et al. 2001
  - Neuropsychology:
    - Improved Neuropsychological performance
  - Genetics:
    - BDNF, COMT, 5-HT genes, results inconsistent.
- All studies using single measure, no integrative studies
Methodology

- Sample of 31 patients, 25 had complete data
- Open-label non-randomized
- Subject prescribed with an SSRI/SNRI/TCA

Demographics and clinical characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Age</td>
<td>42.8 (14.2)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7/18</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.2 (3.1)</td>
</tr>
<tr>
<td>HAM-D-17 baseline</td>
<td>20.2</td>
</tr>
<tr>
<td>HAM-D-17 week 8</td>
<td>11.2</td>
</tr>
<tr>
<td>SSRI/SNRI/TCA</td>
<td>14/8/2*</td>
</tr>
</tbody>
</table>
Analysed data

- QEEG: Eyes Open / Closed EEG (Delta, Theta, Alpha, Beta; Fz, Cz, Pz)
- ERP: Auditory oddball, Continuous Performance Test (n-back): Fz, Cz, Pz
- DNA: Cheek swab sample:
  - BDNF (Brain Derived Neurothrophic Factor)
  - COMT (Catechol-O-Methyl Transferase)
  - Grouping of homozygote genotype with lowest prevalence (COMT V/V; VM vs. M/M; BDNF: M/M; V/M vs. V/V)
- Multiple regression models with absolute change in HAM-D (wk. 8) as dependent variable.
Cognitive measures

- Total memory score: $R^2 = .263$

Fig. 1. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and verbal memory performance.
ERP measures

- Oddball N100 @ Pz amplitude: $R^2 = .369$

Fig. 2. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment N1 amplitude as measured in an Auditory Oddball task.
EEG Measures

- Theta power @ Fz: $R^2 = .236$

Fig. 3. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment absolute Theta power measure during the rest EEG eyes closed task.
Genetics

- COMT: $R^2 = .318$:
- COMT Met/Met positive predictor for treatment outcome.

Fig. 4. Individual COMT genetic variants against change in HAM-D score.
Integrative model

Table 2
Model parameters integrative model.

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>SE</th>
<th>t-statistic</th>
<th>p</th>
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<tbody>
<tr>
<td>Step 2 Baseline HAM-D</td>
<td>-0.179</td>
<td>.181</td>
<td>-0.988</td>
<td>.334</td>
</tr>
<tr>
<td>N1 amplitude at Pz</td>
<td>-1.581</td>
<td>.381</td>
<td>-4.145</td>
<td>.001</td>
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<tr>
<td>Verbal memory performance</td>
<td>0.300</td>
<td>.0100</td>
<td>2.994</td>
<td>.007</td>
</tr>
</tbody>
</table>

\[ R^2 = .602. \]
Conclusions

- Integrative model explained most of the variance.
  - Different predictors have different predictive validity (overlap between N100 ampl and verbal memory was only 3%!)
  - No added value of genetics and EEG in this model.
  - Baseline HAM-D was a covariate but non-significant.
  - Increased Frontal theta marker:
    - Decreased frontal theta? (Suffin & Emory, 2005; Knott et al., 1996)
    - Increased theta in anterior cingulate? (LORETA studies: Pizzagalli et al., 2001 - AD; Narushima et al., 2010 - rTMS)
  - Predictive validity of main class (AD) or subclass (SSRI, SNRI, TCA)?
  - Small sample size: Pilot study
iSPOT-A and iSPOT-D

Replication in a larger sample:

- iSPOT trial: international Study for Optimized Treatment response in Depression and ADHD
- Largest international trial on Personalized Medicine in Depression (N=2000) and ADHD (N=500) using medication
Thank you for your attention!

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