QEEG, ERPs in ADHD Assessment, Diagnosis & Treatment
by Kropotov Juri D.
Saint Petersburg, Russia
Introduction
Definition

- **HBI (Human Brain Index) methodology** is a set of standardized methods for recording, processing and comparing parameters of spontaneous and evoked EEG in healthy and diseased populations.
- **The theoretical part** of the methodology was developed at the Institute of Experimental medicine and the Institute of the Human Brain of RAS in Saint Petersburg, Russia (e.g. Kropotov, 2009).
- **The experimental part** of the methodology was developed in collaboration with Norwegian University of Science and Technology and Saint Olav’s Hospital in Trondheim, Norway (e.g. Brunner et al., 2011-2013; Ogren et al., 2011-2013).
- **The clinical part** of the methodology was developed in collaboration with Brain and Trauma Foundation in Switzerland (e.g. Mueller et al., 2011-2013).
- **The clinical testing** of the methodology was done in Department of neuropsychology of University of Krakow in Poland (e.g. Pachalska et al., 2012-2013).
In June 2013 in Saint Petersburg we had a user meeting in which people from 10 countries were present.
HBImed is a Swiss-based company that implemented HBI methodology into clinical practice.
QEEG and Event Related Potentials (ERPs) are biological markers reflecting different functional features of the brain

- Spontaneous EEG indicates modes of \textit{cortical self-regulation}.
- ERPs indicate \textit{stages of information flow} in the brain.
- These functional features are \textit{independent}, so that some brain dysfunctions might be associated with specific impairment in only one domain.
Suppose a boy comes to your door. His behavior looks like typical ADHD. Recent neuroscience research shows that there are several reasons why he behaves in this way:

- a patient might have a focus in his cortex, which without any overt symptoms of epilepsy may impair information processing and, consequently, may mimic attention deficit (see Aldenkamp, Arends, 2004);
- a patient might have a lack of overall cortical activation due to dysfunction of the ascending reticular system of the brain stem (Sergeant, 2000);
- a patient might have genetically determined hyperactive frontal lobes (Anokhin et al., 2004);
- a patient might have dysfunction of the prefrontal-striato-thalamic system due to structural abnormality (Castellanos et al., 1996); or increase of dopamine reuptake dopamine transporters in the striatum (Krause et al., 2003);
- a patient might have hypo-activation of the pre-supplementary cortex which is compensated by increase of motoric activity of the patient (Simmonds et al., 2007);
- a patient might have dysfunctioning in the anterior gyrus cingulus which may produce anxiety, emotional instability and hyperactivation (Albrecht et al., 2008).
Knowing brain dysfunction associated with symptoms the choice of treatment can be:

- medication using a dopamine reuptake inhibitor (such Ritalin) (Wilens, 2008),
- or medication using a noradranaline reuptake inhibitor (such as Straterra) (Garnock-Jones et al., 2009),
- or the patient can respond well to neurofeedback (Fox et al., 2005),
- or the optimal treatment can be transcranial Direct Current Stimulation (Kropotov et al., 2002),
- or the patient may simply respond to GABA agonists which “shut down” his cortical focus.
Definition

Event related potentials (ERPs) are scalp recorded voltage fluctuations that are time-locked to an event.

The event can be a stimulus presentation followed by 1) assessment operations (such as estimation of color or shape of the visual stimulus), by 2) executive operations (such as selection of appropriate response), as well as by 3) affective or memory operations.

The event can also be a motor or other type of subject’s response.

19 channel EEG in a healthy subject performing a cued GO/NOGO task. The first stimulus presentation in a trial is marked by red vertical line. Time marks (seconds) are on the top.
Signal-to-noise ratio

The ERP amplitude is usually smaller than the amplitude of background EEG so that it’s quite difficult by a naked eye to separate the ERP waveform from the ongoing EEG oscillations. In other words the ERP/EEG ratio (or the signal-to-noise ratio) in a single trial is rather small. To increase the ratio, EEG fragments are averaged over a large number of trials. The signal-to-noise ratio of the averaged ERP increases as the square root of the number of trials.

ERP is obtained by averaging the raw EEG fragments which are time locked to the stimulus.
Red line – visual stimulus presentation.
A: EEG fragments measured at O1 at a healthy subject in three trials with visual stimulus presentation (no response was required).
B: ERPs at O1 in the same subject in response to visual stimulus presentation obtained by averaging different number of trials (10, 25, 50 and 200 trials).
C: amplitude and time scales are the same for A and B
Independent Component Analysis (ICA) for extraction ERP components
• ERPs are a sum of potentials generated in different cortical areas (sources) at different time intervals.

• The main task of ERP research is to decompose raw ERPs into functionally meaningful (latent) components.
Input matrix P for ICA
Mathematical basis: finding unmixing matrix

- The input data are the collection of individual ERPs arranged in a matrix $P$ of 19 channels (rows) by $T$ time points (columns) in which $T$ is a product of $N$ (number of subjects) and number of time intervals in the epoch of analysis for the two task conditions. The ICA finds an “unmixing” matrix ($U$) that gives the matrix $S$ of the sources (ICs) when multiplied by the original data matrix ($P$),
  \[ S = UP \]
- where $S$ and $P$ are 19x$T$ matrices and $U$ is 19x19 matrix. $S(t)$ are maximally independent.
- There are several algorithms for finding matrix $U$. In our studies we applied the **Infomax algorithm** and the **Joint Diagonalization** approach.
BSS based on cross-covariance structure modeling

- Steps:
  - (1) the set of covariance matrices is calculated using the initial data $X$: the sample of individual ERPs;
  - (2) if covariance matrices have a common structure, the matrix $W$ that performs approximate joint diagonalization of these matrices can be found;
  - (3) the mixing matrix $A = W^{-1}$ is calculated; (4) the signals $S = WX$ are estimated.
Long-term test-retest reliability of latent components

(Jan Brunner et al., 2011)
Test-retest reliability of ERP components

- ERPs were recorded twice with time interval between recordings from 2 to 12 months.
- For amplitude the good reliability (ICC >0.8) is archived by both methods of scoring, peak or FA.
- The excellent reliability (ICC >0.9) for latency is to a larger degree dependent on the use of FA approach.
Finding the functional meaning of the latent components

Changing the task sets

(Kropotov, Ponomarev, 2014)
Experimental design of the main task (Exp1).

A. – Examples of visual stimuli; B. – timing of stimuli in the trial; C. - sequences of stimuli in Match, Mismatch, Ignore trials (examples). The screen was kept blank white except stimulus presentation. The subject has to respond to the target (two matching animals) as fast and as precise as possible.
Expected sensory related effects in five experiments

A. - Schemes of experiments. Green – GO trials. Red – NOGO trials. Blue – Ignore trials. Black – Novelty trials. B. - Category effect. Left - the schematic difference waves for the corresponding component for the first stimulus (Discontinue – Continue) and for the second stimulus (Mismatch – Match) are presented for each experiment in yellow color. Right – the pattern of the difference wave amplitude (Y-axis) in the five experiments (X-axis). C. - Comparison to WM effect. Left - the schematic difference waves for the corresponding component for the first stimulus (Discontinue – Continue) and for the second stimulus (Mismatch – Match) are presented for each experiment in light pink color. Right – the pattern of the amplitude of the difference wave in the five experiments. D. - Action-related effect. Left - the schematic difference waves for the corresponding component for the first stimulus (Discontinue – Continue) and for the second stimulus (Mismatch – Match) are presented for each experiment in light blue color. Right – the pattern of the amplitude of the difference wave in the five experiments.
Estimation of the optimal number of the components

A. $BIC$ (Y-axis) as a function of number of components (X-axis). Arrow indicates the minimum of the function that correspond to the optimal number of latent components. 

B. Estimation of how well the signal is explained by the number of components. Percentage of the signal (Y-axis) explained by the number of components (X-axis). Arrow indicates the percentage of the signal power of the latent components which were selected for further analysis.
The latent components

A. Topographies of components. B. Time course for Continue (green), Discontinue (red) trials and the difference Discontinue-Continue (grey). C. Time course for Match, GO (green) and Mismatch, NOGO (red) trials and the difference Mismatch-Match (grey). D. s-LORETA images. Arrows at times t1 (130 ms), t2 (140 ms), t3 (250 ms) are as in Fig 3. The gray horizontal bars below the curves indicate the p<0.01 statistical significance of the difference wave. Note that because of ambiguity of component’s amplitude the Y-axis is in Conventional Units. The relative power of the components is presented in Table 3.
The latent component differences in five experiments.

A. Topographies of components. B. Difference for the first stimulus Discontinue – Continue. C. Difference for the second stimulus Mismatch – Match. D. and E. Mean values and 95% confidence intervals computed for the two time windows (left – the first time window, right – the second time window) for the first (D) and second (E) stimuli. Only subplots with statistically significant effects are shown. Colors of subplots correspond to the category effect (yellow), comparison to WM effect (light pink), action-related effect (light blue), attention effect (white),
Finding the functional meaning of the latent components

*Intracranial recordings*

*(Kropotov, 2009)*
Brain nodes of cognitive control

- The brain structures activated in the cognitive control paradigms include:
  - Temporal-parietal,
  - Prefrontal
  - Basal ganglia-thalamic anatomical area
Implantation of electrodes in stereotaxic neurosurgery
Responses to GO and NOGO cues in the human brain

Local field potentials of the human ventrolateral thalamus (A) and post-stimulus time histograms depicting responses of a thalamic neuron (B) to GO and NOGO stimuli in the cued GO/NOGO paradigm (adapted from Kropotov et al., (C) schematic representation of direct and indirect pathways supposedly participating in action initiation (GO) and action suppression (NOGO). During initiation of action (GO condition) it is hypothesized that GO-selective neurons in the parieto-frontal circuits activate a distinct neuronal population of in the striatum giving rise to the direct pathway. Consequently, neurons in GPi will be inhibited and the motor thalamus will be disinhibited. During suppression of action (NOGO condition) NOGO-selective neurons activate a different neuronal population in the striatum giving rise to indirect pathway. Consequently, the GPe neurons will be inhibited, the GPI/SNR neurons will be inhibited that in turn will inhibit the thalamic neuron.
USSR State Prize in science, Moscow, 1985
Finding the functional meaning of the latent components

Correlating with parameters of neuropsychological domains

(Brunner et al., 2014)
Decomposing frontal lobe functions into three domains (Stuss model)

- We need the frontal lobes when task becomes complex and non-routine, have novel demands or potentially conflicting responses might be generated. Stuss (1995) has proposed to fractionate the frontal lobe functions into three anatomically and functionally independent processes: **energization, monitoring, and task setting**.

- **Energization** refers to “the process of initiation and sustaining any response” (Stuss 2005). Energization is different from motivation, fatigue or drowsiness which have more general effect on task performance. Energization is a facilitating process that boosts other executive sub-components, especially those necessary for making decisions and initiate responses.

- **Monitoring** is "the process of checking the task over time for quality control and the adjustment of behavior. Monitoring is necessary in order to handle the mismatch between the current state of affairs and what is required.

- **Task setting** “requires the ability to set a stimulus-response relationship, which would include formation of a criterion to respond to a defined target with specific attributes, organize the program (schemata) to complete a specific task” (Stuss 2005).
Grand average ERP waves and independent components of cognitive control

- Grand average ERP waves and independent components for the group of healthy subjects (n = 193) in the visual cued Go/NoGo task.
- (a) Schematic representation of the task. Images of animals (A) and plants (P) are presented in pairs with the subject task to press a button as fast and precise as possible to A-A pairs (Go condition), to withhold from pressing to A-P (NoGo condition) and to ignore trials started with P. Below - timing of the stimuli in the trials.
- (b) ERP waves at Fz, Cz and Pz in GO, NOGO and Ignore conditions. The CNV wave is a negative fluctuation preceding the second stimulus and mapped (c) at time (1) just before the second stimulus.
- (c). Maps of CNV, GO and NOGO waves taken at their extremes as indicated by arrows in (b).
- (d). The proactive components: IC CNV early and IC CNV late. Left – topography. Right – time course. Time scale as in (b). Y-axis – standard units. (e) The reactive components: IC NOGO early and IC NOGO late,
Decomposing P3 NOGO into two independent components

- P3 NOGO wave is decomposed into two independent components with different topographies and different latencies.
- They correlate with different executive functions.
Correlations between neuropsychological domains and IC´s.

<table>
<thead>
<tr>
<th></th>
<th>Energization</th>
<th>Monitoring</th>
<th>Task setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC P3 NoGo early</td>
<td>.78*** (.69***)*</td>
<td>.21 (.18)</td>
<td>.32 (.38)</td>
</tr>
<tr>
<td>IC P3 NoGo late</td>
<td>.32 (.24)</td>
<td>.56 ** (.54**)</td>
<td>.30 (.13)</td>
</tr>
<tr>
<td>IC CNV early</td>
<td>-.25 (-.07)</td>
<td>.01 (.00)</td>
<td>-.03 (.00)</td>
</tr>
<tr>
<td>IC CNV late</td>
<td>-.72*** (-.80****)</td>
<td>-.42* (.42*)</td>
<td>-.71*** (-.71****)</td>
</tr>
</tbody>
</table>

- Correlation coefficients between the neuropsychological domains of Energization, Monitoring and Task Setting and IC´s. In parentheses are the partial correlation coefficients when corrected for Full scale IQ.
Index of the energization domain correlates with IC P3 NOGO early and CNV late (Brunner,... Kropotov, 2014)

(a) On the scatter plot X-axis – individual index of energization, Y-axis – individual amplitude of the IC P3 NOGO early. Each dot corresponds to a healthy subject. (b, c, d) Map with mapping scale, time course (X-axis - time after stimulus in ms, Y-axis – the averaged back projected component) and sLORETA image of the component. Gray area on (c) depicts the time window for averaging the amplitude of the component. (e, f, g, h) the same as (a, b, c, d) but for IC CNV late.
Index of the monitoring domain correlates with the IC P3 NOGO late (Brunner, Kropotov, 2014)

(a) On the scatter plot X-axis – individual index of monitoring, Y-axis – individual amplitude of the IC P3 NOGO late. (b, c, d) Map with mapping scale, time course and sLORETA image of the component. Gray area on (c) depicts the time window for averaging the amplitude of the component.
ERPs: comparing groups of patients with ADHD (N=94), OCD (N=53) and Schizophrenia (N=100) to the healthy control group (N=258).

Age limits: 17 to 50 y.o.

In collaboration with the Open University, England (Dr. Antonio Martins-Mourao)
Latent components: unspecific decrease in all three disorders

- **SPN** – stimulus preceding negativity elicited in response to cue and reaching maximal negativity before the imperative stimulus at temporal electrodes.
- **P3b** – parietally distributed component in response to the target (GO) stimulus.

![Graphs showing SPN and P3b](image)
Latent components: specific decrease in schizophrenia

- **CNV** – Contingent Negative Variation elicited in response to cue and reaching maximal negativity before the imperative stimulus at central electrodes.
- **P3 cue** – parietally distributed component in response to the cue stimulus.
- **N170** – sensory-related temporally distributed component elicited in response to visual stimulus.
Latent components: specific increase in OCD

- P3 GO – centrally distributed positive fluctuation to target (GO) stimulus.
Latent components: differentiating OCD from schizophrenia

- **P3 energization** – a component in response to NOGO stimulus, generated in the pre-supplementary motor cortex.
- **P3 monitoring** – a component in response to NOGO stimulus, generated in the anterior cingulate cortex.
Scatterogramm of the two ERP independent components in ADHD (young children)

Note two types of ADHD: Type 1 – sensory processing deficit – “non-responders”. Type 2 – enerization deficit (responders to Ritalin).

Blue – Norms. Red – ADHD.
ERPs as predictors of response to pharmacological treatment
(Geir Ogrim, presentation at this meeting)
The cue GO independent component is decreased in the non-responders group

Left - the independent component for the group of responders (green) and non-responders (red) in comparison to the group of healthy controls (grey). X-axis – time after the onset of the first stimulus in ms. Y-axis amplitude of the component back-projected and measured at Pz.

Right – the sLORETA image of the cortical generators of the component. The scale is shown below.

Bottom – the map of the difference responders minus non-responders. The scale is shown on the right to the map.
The NOGO early independent component is decreased in the responders group.

Left - the independent component for the group of responders (green) and non-responders (red) in comparison to the group of healthy controls (grey). X-axis – time after the onset of the second stimulus in ms. Y-axis amplitude of the component back-projected and measured at Cz.

Right – the sLORETA image of the cortical generators of the component. The scale is shown below.

Bottom – the map of the difference responders minus non-responders. The scale is shown on the right to the map.
Effect of Ritalin in ADHD responders

Ritalin increases the NOGO early independent component generated over the Rolandic fissure.
ERPs in patients with stroke – measure of hypersensitivity

• In a neglect patient ERPs in two stimulus visual GO/NOGO task were recorded and compared with the HBI normative data.

• According to s-LORETA images electrodes were applied as shown in Fig.

• Duration of tDCS in one session 30-45 min.

• Number of sessions 20.

• Sham sessions were applied before application of tDCS.
ERP as indexes of improvement during neurofeedback (Kropotov et al., 2005)
Application of ERPs for monitoring effects of neurofeedback

- ADHD child sits in front of the VCR/TV set watching a movie which in turn is controlled by biofeedback signal: “the better is EEG, the better is a picture”.
Relative beta training

- Eighty-six children (ages 9–14) with ADHD participated in this study.
- Each session included 20 min of enhancing the ratio of the EEG power in 15–18 Hz band to the EEG power in the rest of spectrum with C3-Fz electrodes’ placements.
- On the basis of quality of performance during training sessions, the patients were divided into two groups: good performers and bad performers.


Relative beta power during a training session.
(A) Dynamics of the biofeedback parameter during a single training session in an ADHD boy.
(B) Mean values (averaged over 22 patients) of relative beta power at rest and training periods computed in 19 electrodes for a single session at the end of the training course.
Enhancement of NOGO component after relative beta training

- Grand average NOGO ERPs in the two-stimulus auditory GO/NOGO test for the group of good performers before and after 20 sessions of the relative beta training.
- Horizontal axis: time in ms; vertical axis: averaged scalp potentials recorded in different electrode locations (Fp1,Fp2,. . ., O1, O2). Thin line: ERPs taken before training; thick line: ERPs taken after 20 sessions of training.

The ability to increase beta during neurofeedback sessions leads to ERP enhancement over central frontal areas

- Comparison of ERPs differences induced by 20 sessions of neurofeedback in the groups of good (A) and bad (B) performers.
- At the left: grand average ERP differences for GO (thin line) and NOGO (thick line) stimuli taken for Fz location.
- At the right: maps of grand average ERP differences for GO and NOGO stimuli taken at 310 ms after stimulus. Mapping scale is presented in the middle.
ERP might be modified by ERP-based neurofeedback (Kropotov et al., 2009)
Neurofeedback training of ERP ICs in GO/NOGO task

Group average

Individual

P3b trained

Slow Positive Wave

a. 400 ms

b.

c.