New tools for diagnosis and modulation of brain dysfunction

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Suppose a boy comes to your door. His behavior looks like typical ADHD: he is extremely inattentive, impulsive and hyperactive. He performs poorly in continuous performance tasks. Recent research in neurophysiology of ADHD shows that there are several reasons why the boy behaves in this way:

1) a patient may have a focus in his cortex , which without any overt symptoms of epilepsy impairs information processing and, consequently, mimics attention deficit (see Aldenkamp, Arends, 2004);
2) a patient may have a lack of overall cortical activation due to dysfunction of the ascending reticular system of the brain stem (Sergeant , 2000);
3) a patient may have genetically determined hyperactive frontal lobes (Clarke et al., 2003);
4) a patient may have dysfunction of the prefrontal-striato-thalamic system due to structural abnormality (Silk et al., 2009; Busch et al., 2005; Castellanos et al., 1996); or increase of dopamine reuptake dopamine transporters in the striatum (Krause et al., 2003)
5) a patient may have hypoactivation of the premotor cortex of the brain, which is compensated by increase of motoric activity (Simmonds et al., 2007);
6) a patient may have dysfunctioning in the anterior gyrus cingulus which produces anxiety, emotional instability and hyperactivation (Albrecht et al., 2008).

By knowing which brain dysfunction is associated with symptoms of ADHD a clinician can suggest the individualized treatment. The choice of treatment can be either a medication using a dopamine reuptake inhibitor (such as Ritalin) (Wilens, 2008), or a medication using a noradrenaline 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 “shuts down” the epileptic focus..

Recent research shows that the above mentioned dysfunctions are associated with specific patterns in spontaneous and evoked electrical potentials, recorded from the head by multiple

surface electrodes. Recent research also proves that these spontaneous and evoked electric potentials provide reliable brain markers of the brain function and dysfunction.

Neurometrics as adjunct to Psychometrics. Psychologists rely on Psychometrics to gauge personality, pathology, motivation, learning difficulties. But despite built in lie scales, split half designs and a host of other clever statistical manipulations psychometric measurements are still represented by behavioral data gained from self or other report.

A recently emerged science, called Neurometrics, relies on measuring the underlying organization of the human brain's electrical activity. According to E. Roy John, an outstanding American neurobiologist who coined this name in 1970s, Neurometrics is "a method of quantitative EEG that provides a precise, reproducible estimate of the deviation of an individual record from normal. This computer analysis makes it possible to detect and quantify abnormal brain organization, to give a quantatitive definition of the severity of brain disease, and to identify subgroups of pathophysiological abnormalitites within groups of patients with similar clinical symptoms" (John, 1990).

Entrepreneurs began to take notice of the potential of Neurometrics in the late 1980s. Three commercial systems were sequentially registered in 1988 (Neurometric Analysis System, based on the University of New York normative data, published in John et al., 1977), in 2004 (Neuroguide Analysis System, based on the University of Maryland normative data, published in Thatcher et al., 1998), in 2005 (BRC Software Product, based on the normative data collected internationally in several laboratories, published in Gordon et al., 2005). Each of these devices represent software which is capable of comparing a subject's EEG data to a normative database thus giving clinicians a tool for measuring the patient's variance from normal.

Normative databases in EEG. There are many normative neuroscience databases which include CT, MRI, PET and other datasets. However quantitative EEG and event related potentials normative databases play a critical role among many others in clinical practice because of the following reasons.

1) We are entering a new era of psychiatry and neurology. Long awaited, the fifth revised edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) will become the main reference for psychiatrists and neurologists upon its release in 2012. Primary focus of the new revision is to classify brain disorders according to their biological markers – endophenotypes. The new approach assumes that a psychiatric diagnosis is made not only from behavior, but also from the knowledge of which brain system is impaired. The only dynamical (at millisecond time scale) parameters of the brain function are provided by EEG and MEG

(Magnetoencephalogram). At the moment, MEG machines are too expensive, while EEG machines being inexpensive currently remain of the primary choice for clinicians.

2) We are facing a renaissance of EEG. On the one hand, the renaissance is associated with obtaining new knowledge regarding neuronal mechanisms of generation of alpha, theta and beta oscillations in spontaneous EEG as well as regarding functional meaning of different waves in event related potentials (for review see Näätänen, 1992; Luck, 2005).

3) On the other hand, the renaissance is associated with the development of new methods of analysis. These methods (e.g. the decomposition of EEG and evoked responses into independent components, LORETA - Low Resolution Electromagnetic Tomography) were initiated in laboratory settings only ten years ago (see Makeig et al., 1996; Pascual-Marqui et al., 1999).

There is an urgent need to introduce these new methods into clinical practice. Unfortunately, none of the existing normative databases uses the newly developed technologies. This flaw of the current databases is resolved in a new database built up on the methodology developed in the Human Brain Institute (HBI) of the Russian Academy of Sciences and the Institute for Experimental Medicine of the Russian Medical Academy of Sciences. The methodology is presented in series of papers and summarized in the book recently published by Academic Press (Kropotov, 2009). The database named HBI (Human Brain Index) reference database is now used in many scientific centers in Europe and the USA.

EEG endophetotypes of brain disorders. In this paper we focus on the most common and, undoubtedly, the most controversial, disease – Attention Deficit Hyperactivity Disorder. The first theoretical attempt to introduce endophenotypes as neuroscience based markers of ADHD was done by Xavier Castellanos and Rosemary Tannock in 2002. The authors proposed three endophenotypes that would correspond to the causes of ADHD: 1) a specific abnormality in reward-related circuitry that leads to shortened delay gradients, 2) deficits in temporal processing that result in intra-subject internal variability, 3) and deficits in working memory (Castellanos, Tannock, 2002).

In practice, several attempts were made to discriminate ADHD population from healthy subjects. These attempts explore various imaging techniques including PET, MRI and fMRI. Here we discuss only studies in the field of EEG. In general terms, spectral characteristics of EEG are considered as good indicators of metabolic activity in the cortex. An excessive slow activity and a lack of beta activities in local EEG indicate low metabolic activity of the underlying cortical area (Cook et al., 1999).

EEG spectra in ADHD. The most commonly-used form of EEG analysis in studies of ADHD has been the calculation of absolute and relative power estimates. The research in this field is enormous. Just search for the key words “ADHD and EEG” gives 667 papers from 1970 to the present time. In this paper we mentioned only the most critical papers.

Chabot and Serfontein (1996) reported EEG differences in 407 ADHD children compared to a normative database. Children with ADD had an increase in absolute and relative theta, primarily in the frontal regions and at the frontal midline. Clarke et al. (1998) carried out the first study of EEG differences between children with different DSM-IV types, comparing 20 ADHD combined type, 20 ADHD inattentive type and 20 control subjects, using an eyes-closed resting condition. The ADHD groups had increased power levels across all sites in absolute and relative theta, and reductions in relative alpha and beta. In a follow-up study with larger independent subject groups Clarke et al. (2001) found ADHD children to have increased absolute and relative theta, and decreased relative alpha and beta, and these effects differentiated ADHDcom from ADHDin.

Bresnahan et al. (1999) was the first study to investigate the EEG profiles of adult AD/HD subjects, using 3 age groups: children, adolescents and adults, with age- and sex-matched controls. The results indicated that absolute and relative theta activity remained elevated through adolescence into adulthood.

Ratio coefficients The ratio between power in different frequency bands has been used to evaluate changes in the EEG that occur due to normal maturation (Matousek and Petersen, 1973) and as a measure of cortical arousal (Lubar, 1991). Matousek et al. (1984) found that the theta/alpha ratio was a good predictor of group differences between children with MBD, ADD and control subjects. Janzen et al. (1995) reported that children with ADHD had a higher theta/beta ratio than control subjects. Monastra et al. (1999) calculated a theta/beta ratio from 482 individuals aged 6–30 years old and showed that the theta/beta ratio was higher in AD/HD subjects than control subjects. Clarke et al. (2001) found that both the theta/ alpha and theta/beta ratios can differentiate between groups of normal children and children with AD/HD. Further, the ratio distinguished adults who met AD/HD criteria from those with some symptoms of the disorder who failed to meet those criteria (Bresnahan and Barry, 2002), indicating some specificity for this marker in ADHD. Sensitivity of the inattentive index (theta beta ratio) was found to be 86%, and specificity - 98% (Monastra et al., 1999).

Event Related Potentials in ADHD. Since the early 1970s (e.g. Satterfield et al., 1972; Buchsbaum and Wender, 1973; Saletu et al., 1973) ERP studies have revealed much about

information processing in ADHD. Some of these studies focused on tasks testing functioning of the auditory and visual attention systems, with others examined so-called executive functions.

Typical paradigms used in ERP studies of ADHD include auditory or visual selective attention tasks, combined-modality selective attention tasks, two or 3 tone oddball tasks, S1-S2 tasks, go-nogo tasks and stop-signal tasks. Literature search on the two keywords “ADHD and Event Related Potentials” in PubMed gave 382 papers published within period from 1970 to the present time.

Here we focus only on the late positive complex in the visual modality in ERPs studies. The visual P3 component has been reported to differentiate clinical from control children. For example, P3 amplitude was reduced in ADHD subjects in an letter sequence oddball task (Holcomb et al., 1985), in easy and hard versions of a letter oddball task, with larger differences being evident in the hard task (Lubar, 1991), during classification and oddball tasks (Robaey et al., 1992), and during several CPT studies (Klorman et al., 1979; Overtoom et al., 1998) and other visual selective attention tasks (Jonkman et al., 1997).

In recent years there has been a shift of focus away from attention-based accounts of ADHD deficits, towards ‘executive functions’ (e.g. Barkley, 1997). Within this context, the focus has been on the psychological process of inhibition, and its role in the behavioural manifestations of ADHD. Specific paradigms believed to access this process, such as the go-nogo task and the stop-signal task, have been utilized.

ERPs recorded during inhibitory processing typically contain a negative component approximately 200 ms after the onset of the inhibition-evoking stimulus, which is believed to reflect a frontal inhibition process (Kopp et al., 1996). Research with the oddball task suggests deficits in inhibitory processing in ADHD. For example, a reduced frontal N2 peak in ADHD compared to control subjects was found, indicating an atypical frontal inhibition process in ADHD (Johnstone and Barry, 1996). Similar results have been reported in inhibition-specific tasks. Using the stop-signal task with an auditory stop signal, frontal N2 amplitude to the stop stimulus was dramatically reduced in ADHD (Pliszka et al., 2000).

Here we present some results of our own multi-centre study that was done within the frames of the COST B 27 initiative. This initiative was sponsored by the European Commission Research Foundation and included 5 countries: Switzerland (Andreas Mueller and his group), Austria (Michael Doppelmayr and his group), Norway (Stig Hollup and his group), Macedonia (Jordan Pop-Jordanov and his team), and Russia (Juri Kropotov and his lab). In particular, the study included recordings of 150 ADHD children (24 girls) of age from 7 to 12 years old. Below the results of comparison between two age matched groups of healthy subjects (taken from the

HBI reference normative database) and ADHD children recorded under the same task conditions. All subjects and patients participated in the same two stimulus GO/NOGO task.

Seven independent components, constituting 87% of the signal, were separated from collection of ERPs recorded in response to GO and NOGO stimuli. Four of them are presented in Fig. 1. As one can see only one component significantly (with the size effect of 0.43) discriminates the ADHD group from the control healthy group". This component is generated in the premotor cortex. Its reduction in ADHD reflects functional hypoactivation of the premotor area in the inhibitory control in children with attention deficit.

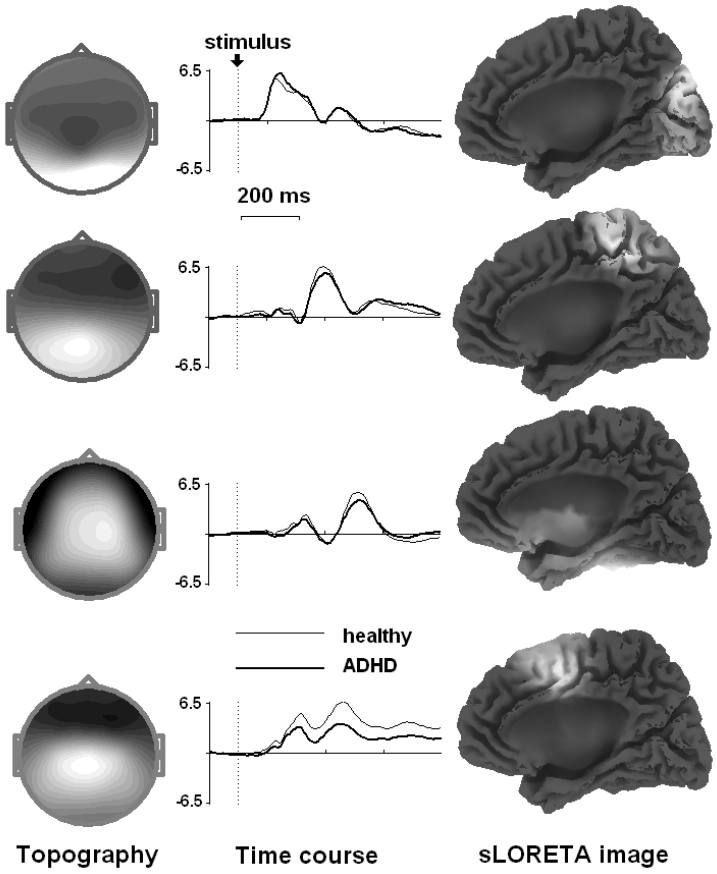

Fig. 1 Independent components of ERPs in response to NOGO cues in ADHD and healthy children.

Neurofeeedbak in ADHD. 50 years of using psycho-pharmacology for treatment of brain disorders brought some dissatisfaction and controversy. One part of the controversy is associated with side effects induced by regular consumption of psychoactive drugs. For example in ADHD, the most common side effects of psychostimulants include headaches, abdominal pain, appetite suppression, irritability, insomnia, and hypertension. The other part of the controversy is associated with a failure to find a genotype for a certain disease. Recent attempts

of medical genetics have indicated that ADHD as most of psychiatric disorders does not follow a simple Mendelian rule and that no single gene could not be attributed to a single disorder.

This led some scientists to introduce the concept of endophenotypes as biological markers of disease that are non-molecular but closer to the genotype than behaviorally defined classification of diseases. One of such endophenotypes of ADHD is shown in Fig. 1. It represents functional hypoactivation of the premotor cortex of ADHD children during NOGO trials. This ERP-based endophenotype fits the increased theta activity and decreased beta activity over central-frontal regions observed in studies of spontaneous EEG oscillations in ADHD population.

Nowadays we know at least three different interventions that would activate frontal-central areas of the cortex. They are: psychostimulants, neurofeedback and Transcranial Direct Current Stimulation.

Historically, the fact that 30% of ADHD population can not be treated by psychostimulants motivated researchers to search for alternative forms of treatment. The rationale for EEG biofeedback was derived from substantial neurophysiological research and QEEG assessment in ADHD population. One of the leading scientists in this field, Barry Sterman in his review (Sterman, 1996), indicated that “variations in alertness and behavioral control appear directly related to specific thalamocortical generator mechanisms and that such variations are evident in distinctive EEG frequency rhythms that emerge over specific topographic regions of the brain”. He hypothesized that neuropathology (such as ADHD) could alter these rhythms and that EEG feedback training directed at normalizing these rhythms may yield sustaining clinical benefits.

Retrospectively, based on extensive research during the last decade we now recognize the existence of QEEG sub-types in ADHD and understand the need of different neurofeedback protocols to correct QEEG abnormalities in ADHD sub-types, but historically some of the protocols at the first years of neurofeedback era were obtained empirically. Most of the protocols use the conventional EEG in the frequency range higher than 0.1 Hz, while EEG at lower frequencies was used in studies of a German group at the University of Tuebengen (Strehl et al., 2005).

Neural circuits are pruned from the womb on – some reinforced by repetitive patterns (mothers voice, smell of food etc) and others dropped from the connecting network. Life’s experience shapes and progressively refines brainwave circuits so that like finger- prints, brain waves are unique. But there are similarities on which a QEEG data base relies. For example neural signatures of developmental processes that have been disrupted have a similar pattern.

Dyslexics will show lower amplitude of “task beta” in the language circuits used for reading for example and Depression is associated with high amplitude of alpha in the left prefrontal cortex. .

A QEEG is likely to be a Psychologist’s best partner in looking through this window to the brain, as the equipment becomes, as was the case with computers, cheaper, smaller and easier to use. Courses in the theory and practice of neurotherapy are increasingly common in the United States and Europe. The Society for Applied Neuroscience is organizing an Masters degree for professionals who wish to add this therapy to their practice.