CHAPTER 3

ERP-Based Endophenotypes: Application in Diagnosis and Neurotherapy

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INTRODUCTION

In a narrow sense brain neuromodulation includes methods of transcranial Direct Current Stimulation (tDCS) and neurofeedback. These two methods are based on knowledge regarding underlying neurophysiological processes. It is obvious that before doing any neuromodulatory approach on a client we need to know how his/her cortex is self-regulated and how

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information is processed in the cortex. A recently emerged branch of neuroscience, called *neurometrics,* helps in answering these two questions.

According to E. Roy John, the founder of this field, neurometrics is

> *a method of quantitative EEG that provides a precise, reproducible estimate of the deviation of an individual record from norm. This computer analysis makes it possible to detect and quantify abnormal brain organization, to give a quantitative definition of the severity of brain disease, and to identify subgroups of pathophysiological abnormalities within groups of patients with similar clinical symptoms.*
>
> ***(John, 1990)***

Several normative EEG-based databases exist (NxLink, introduced in John, 1977; Neuroguide, described in Thatcher et al., 1999; Brain Resource Company presented in Gordon, Cooper, Rennie, Hermens, & Williams, 2005). These databases were very helpful in defining neuronal correlates of some brain dysfunctions such as ADHD (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009), traumatic brain injury (Thatcher et al., 1999), and dementia (Prichep et al., 1994).

One of the parameters measured in these databases is EEG power in a certain frequency band. Spectral characteristics of spontaneous EEG used in all normative databases include absolute and relative EEG power in different frequency bands, at different electrode sites, as well as measures of coherence between EEG recorded from pairs of electrodes. Spontaneous EEG in a healthy brain represents a mixture of different rhythmicities which are conventionally separated into alpha, theta, and beta rhythms. Recent research shows that each of these rhythmicities is generated by a specific neuronal network: posterior and central alpha rhythms are generated by thalamo-cortical networks, beta rhythms appear to be generated by local cortical networks, while the frontal midline theta rhythm (the only healthy theta rhythm in the human brain) is hypothetically generated by the septo-hippocampal neuronal network (for a recent review see Kropotov, 2009). In general terms, spontaneous oscillations reflect mechanisms of cortical self-regulation implemented by distinct neuronal mechanisms.

EVENT-RELATED POTENTIALS (ERPs)

Another important aspect of brain functioning is the response of the brain to stimuli, and actions evoked by those stimuli. This electrical brain response is measured by event-related potentials (ERPs). Technically, ERPs are obtained by simple averaging of all EEG epochs in many

sequentially presented trials in a single subject and for a single electrode. Consequently, ERPs can be considered as voltage deflections, generated by cortical neurons that are time-locked to specific events and associated with stages of information flow in specific cortical areas.

It should be stressed here that ERPs, even in a simple behavioral paradigm, are generated by multiple neuronal sources. The sources are associated with ERP components which, in practice, are defined by their positive or negative polarity, latency, scalp distribution, and relationship to experimental variables (Duncan et al., 2009). Research during the past 50 years has separated several ERP components such as mismatch negativity, N400, error-related negativities, different types of P300, etc.

The guidelines for the use of ERPs in clinical research are presented in a recent paper by a group of distinguished researchers in the field (Duncan et al., 2009). The methodological issues emphasized in the paper are as follows: (1) minimizing eye movements in order to get a signal-to-noise ratio as high as possible; (2) measuring components defined as "the contribution of the recorded waveform of a particular generator process, such as the activation of a localized area of cerebral cortex by a specific pattern of input." Components can be disentangled by means of experimental manipulation if they are differentially sensitive in amplitude and latency to different manipulations (Donchin et al., 1986).

THEORETICAL CONSIDERATIONS

As we know from research in neuroscience, behavior is determined by multiple brain systems playing different roles in planning, execution, and memorization of human sensorimotor actions. These brain systems in turn are determined by genes and their complex interactions with each other and the environment. So, in contrast to genotype, behavior can be considered as a phenotype of a subject. In the past, psychiatry mainly relied on behavior. Recently, however, a concept of endophenotype was introduced in psychiatry (Gottesman & Gould, 2003). Endophenotypes are heritable, quantifiable traits (such as EEG power in specific frequency bands, or components of event-related potentials) that index an individual's liability to develop or manifest a given disease or behavioral trait. Endophenotypes represent simpler clues to genetic mechanisms than the behavioral symptoms. The whole idea of introducing this concept is based on the assumption that a more accurate psychiatric diagnosis can be made using knowledge about brain systems (such as the executive system) and

brain operations (such as action selection and action monitoring). The term comes from the Greek word *endos,* meaning "interior, within". In another words, endophenotype denotes a measurable component along the pathway between phenotype and genotype). An example of a physiological endophenotype could be given by a late positive fluctuation (the P3b waveform) of ERPs elicited in the oddball paradigm in response to target stimuli. This waveform appears to reflect the context updating (Donchin, 1981) and can be considered as an index of working memory.

In this chapter we present a theory according to which the brain is divided into several functional systems, playing different roles in organization of behavior: sensory system, affective system, executive system, memory systems, and attentional networks (Kropotov, 2009). Each of these brain functional systems can be considered as a set of overlapping neuronal networks, each performing a specific computation associated with a distinct psychological operation.

Neuronal elements in a neuronal network receive multiple inputs and transfer them into action potentials. The transfer operation performed by a neuron (output versus input) represents a non-linear relationship described by a sigmoid function. Similarly, the transfer function of a neuronal net as a whole also can be described by the sigmoid function presented in Figure 3.1(a). The shape of this function means that: (1) the neuronal network is poorly activated by a low input because the inputs in the majority of neurons do not exceed thresholds; (2) the neuronal network changes activity almost linearly to a moderate input; (3) the activation of the neuronal network reaches a plateau at higher levels of input — a so-called "ceiling" effect.

We can further suggest that the performance of the system is defined by the ability of the system to react to a small change in the input. Mathematically, the performance of the system is defined by the first derivative dO/dI (Figure 3.1b). The first derivative is represented by a so-called inverted-U shape. In psychophysiology it is known as the Yerkes–Dodson Law (Curtin, 1984).

So, the neural network is characterized by two parameters: level of activation (that is, the input signal which drives the system), and the responsiveness of the system (reaction of the system to a small change in the input). In neurophysiological studies these two parameters are usually named *tonic* and *phasic* activities respectively. We speculate that, for the brain, tonic and phasic activities have two different functional meanings, the first associated with the state and the second with the response. For

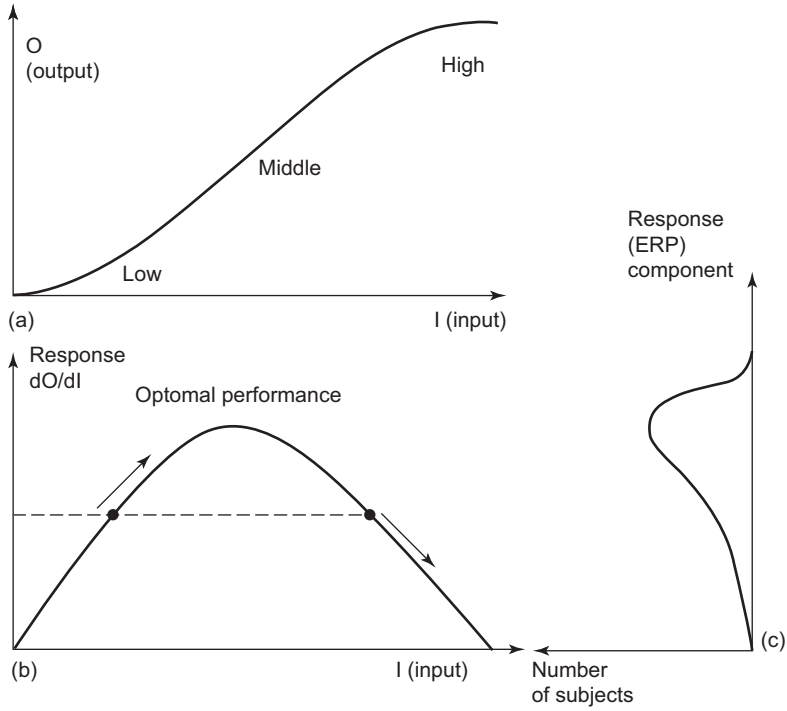

Figure 3.1 Reactivity of neuronal network. (a) Schematic representation of the dependence of the overall activity of a hypothetical neuronal network on the input driving the system. (b) Schematic representation of the dependence of the response of the system on its input. The response is defined as a reaction of the system to a small and elementary increase of the input. (c) Distribution of subjects over reactivity of the system. The distribution is closer to the Gausisan, in which smaller amplitudes correspond to poor performance.

example, for the attentional network the tonic activity can be associated with non-specific arousal, while the phasic activity can be associated with selective attention. We presume that the reactivity of a certain functional network is reflected in a distinct ERP component. So, when we measure an ERP component in a population of subjects the distribution of the subjects over the component would be expected to look like that depicted in Figure 3.1(c). Indeed, the majority of the population of healthy subjects would have the component with amplitude around an average level and only few would have the component deviant from normality thus forming a normal or log-normal distribution.

In reality, response of a neuronal network consists of reactions of excitatory and inhibitory neurons that produce potentials of different polarities.

Moreover, the neuronal reaction evolves in time in a hierarchically organized network. The process of shaping the component is determined by a complex interaction between feed-forward and feed-back pathways interconnecting lower and higher level layers of the network.

NEW METHODS IN ERP ANALYSIS

Recently, the practical application of ERPs was accelerated by introducing new mathematical techniques for ERP analysis. One of these techniques is independent component analysis (ICA). ICA is a decomposition technique which is regarded as a solution of the "blind source separation (BSS)" problem (James & Hesse, 2005). ICA decomposes data such that the resulting component activities have minimal mutual information. The mutual information is considered as a measure of statistical independence of the components (Congedo et al., 2008).

It should be stressed here that the concept of statistical independence goes far beyond statistical orthogonality. Independence implies that two or more variables are not only orthogonal (uncorrelated), but also that all higher order moments are zero. In this respect the ICA differs from principal component analysis (PCA), which assumes only statistical orthogonality (Bugli & Lambert, 2007). From a more practical point of view, another advantage of ICA is that this approach can be applied to low density EEG data (Makeig et al., 2002). In research involving ERPs, ICA has been applied for separating the observed signals into both physiologically and behaviorally distinct components.

There are at least three different methods of applying ICA to ERP analysis which deal with different input and output datasets, and which allow different questions to be addressed: (1) the input data for the first method represent single-trial ERP epochs from a single subject: the ICA components are defined either separately for each subject, with subsequent cluster analysis (Makeig et al., 2004; Zeman, Till, Livingston, Tanaka, & Driessen, 2007), or for all trials in all subjects (Debener, Makeig, Delorme, & Engel, 2005; Mehta, Jerger, Jerger, & Martin, 2009); (2) the input data for the second method are averaged ERPs recorded in response to many stimulus types and many task conditions (Makeig et al., 1999); and (3) the input data for the third method are from averaged ERPs recoded in a few task conditions, but for many subjects (Liu et al., 2009; Olbrich, Maes, Valerius, Langosch, & Feige, 2005).

HBI REFERENCE DATABASE

In this chapter we introduce a methodology that was recently implemented in the HBI (Human Brain Index) reference database. The database includes 19-channel EEG recordings of more than 1000 healthy subjects in resting conditions with eyes open and eyes closed as well as in six task conditions. Subjects were recruited from students of St Petersburg State University (recordings were made by I. S. Nikishena), the staff of the Institute of the Human Brain of Russian Academy of Sciences (recordings were made by E. A. Yakovenko), students of the Norwegian University of Science and Technology, Trondheim (recordings were made by S. Hollup), and healthy subjects from Chur, Switzerland, recruited by Dr Andreas Mueller (recordings were made by E. P. Tereshchenko, I. Terent'ev, and G. Candrian). The investigation was carried out in accordance with the Declaration of Helsinki, and all subjects provided informed consent. The tasks were specifically developed for recording components associated with visual and auditory processing, facial emotion recognition, working memory, engagement (GO) and disengagement (NO-GO) operations, mathematical- and speech-related operations, and novelty reactions.

Exclusion criteria were: (1) an eventful perinatal period; (2) presence of head injury with cerebral symptoms; (3) history of neurological or psychiatric diseases; (4) history of convulsion; and (5) current medication or drugs. Inclusion also required normal mental and physical development, as well as average or better grades in school.

GO/NO-GO TASK

Here we provide details of the two-stimulus GO/NO-GO task that was developed to study sensory and executive functions in the human brain. Three categories of visual stimuli were selected: (1) 20 different images of animals, referred to later as "A"; (2) 20 different images of plants, referred to as "P"; (3) 20 different images of people of different professions, presented together with an artificial "novel" sound, referred to as "H + Sound". All visual stimuli were selected to have similar size and luminosity. The randomly varying novel sounds consisted of five 20 ms fragments filled with tones of different frequencies (500, 1000, 1500, 2000, and 2500 Hz). Each time a new combination of tones was used and the novel sounds appeared unexpectedly (probability of appearance: 12.5%). Stimulus intensity was about 75 dB SPL, measured at the patient's head.

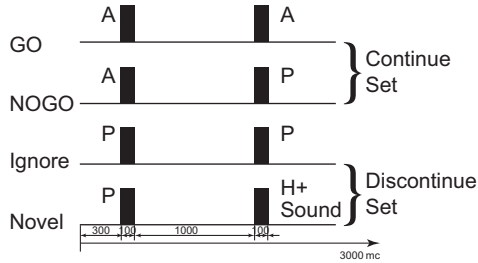

Figure 3.2 Schematic representation of the two-stimulus GO/NO-GO task. From top to bottom: time dynamics of stimuli in four categories of trials. Abbreviations: A, P, H stimuli are "Animals", "Plants", and "Humans". GO trials are when A−A stimuli require the subject to press a button. NO-GO trials are A−P stimuli, which require suppression of a prepared action. GO and NO-GO trials represent "Continue set" in which subjects have to prepare for action after the first stimulus presentation (A). Ignore trials are stimuli pairs beginning with a P, which require no preparation for action. Novel trials are pairs requiring no action, with presentation of a novel sound as the second stimuli. Ignore and Novel trials represent "Discontinue set", in which subjects do not need to prepare for action after the first stimulus presentation. Time intervals are depicted at the bottom.

The trials consisted of presentations of paired stimuli with inter-stimulus intervals of 1 s. Duration of stimuli was 100 ms. Four categories of trials were used (see Figure 3.2): A−A, A−P, P−P, and P−(H + Sound).

The trials were grouped into four blocks with 100 trials each. In each block a unique set of five A, five P, and five H stimuli were selected. Each block consisted of a pseudo-random presentation of 100 pairs of stimuli with equal probability for each stimulus category and for each trial category. Participants practiced the task before the recording started. Subjects rested for a few minutes after each 200 trials. Subjects sat upright in a comfortable chair looking at a computer screen. The task was to press a button with the right hand to all A−A pairs as fast as possible, and to withhold button pressing to other pairs A−P, P−P, P−(H + Sound) (Figure 3.2).

According to the task design, two preparatory sets were distinguished in the trials (Figure 3.2). They are: "Continue set", in which A is presented as the first stimulus and the subject is supposed to prepare to respond; and the "Discontinue set", in which P is presented as the first stimulus and the subject does not need to prepare to respond. In a "Continue set" A−A pairs will be referred to as "GO trials", A−P pairs as "NO-GO trials". In a "Discontinue set" P−P pairs will be referred to as "Ignore trials" and P−(H + Sound) pairs as "Novel trials" (see Figure 3.2).

The subject responses were recorded in a separate channel on the amplifier. Averages for response latency and response time variance across trials were calculated for each subject individually. Omission errors (failure to respond in GO trials) and commission errors (failure to suppress a response to NO-GO trials) were also computed for each subject separately.

In gathering data EEG was recorded from 19 scalp sites, bandpass filtered between 0.53 and 50 Hz and digitized at a rate of 250 samples per second per channel. The electrodes were applied according to the International 10–20 system. The EEG was recorded referentially to linked ears, allowing computational re-referencing of the data (re-montaging). For decomposing ERPs into independent components, the EEG computationally was re-referenced to the common average montage. EOG was recorded from two electrodes placed above and below the right eye. All electrode impedances were below 5 Ohms.

To standardize data collection procedures across the four laboratories, the same protocol was used: (1) EEG was recorded with a 19-channel electroencephalographic PC-controlled system, the "Mitsar-201" (CE 0537) manufactured by Mitsar, Ltd (www.mitsar-medical.com); (2) electrodes were applied using caps manufactured by Electro-cap International, Inc. (www.electro-cap.com/caps.htm); (3) the tin recessed electrodes contacted the scalp using ECI ELECTRO-GEL; (4) stimuli were presented on similar 17 inch computer screens which were positioned 1.5 meters in front of the subjects and occupied the same range of the visual field (3.8°); (5) images of stimuli as well as the stimuli presentation protocols were standardized; (6) all trials were presented using "Psytask", a computer code written by one of the authors (VAP); (7) subjects were recruited according to the same inclusion/exclusion criteria (see paragraph "Subjects" above).

Eye Movement Correction

Eyeblink artifacts were corrected by zeroing the activation curves of individual ICA components corresponding to eye blinks using methods similar to those described in Jung et al. (2000) and Vigário (1997). Comparison of this method with an EOG regression technique is described by Tereshchenko, Ponomarev, Kropotov, and Müller (2009). In addition, epochs with excessive amplitude of filtered EEG and/or excessive faster and/or slower frequency activity were automatically marked and excluded from further analysis. The epoch exclusion thresholds were set as

follow: (1) 100 μV for non-filtered EEG; (2) 50 μV for slow waves in the 0−1 Hz band; and (3) 35 μV for fast waves filtered in the band 20−35 Hz.

METHODOLOGY OF DECOMPOSITION OF COLLECTION OF ERPs INTO INDEPENDENT COMPONENTS

The goal of independent component analysis (ICA) is to utilize the differences in scalp distribution between different generators of ERP activity to separate the corresponding activation time courses (Makeig, Bell, Jung, & Sejnowski, 1996). Components are constructed by optimizing the mutual independence of all activation time curves, leading to a natural and intuitive definition of an ERP component as a stable potential distribution which cannot be further decomposed into independently activated sources.

In the present study ICA was performed on the full ERP scalp location × time-series matrix. ERPs were constructed in response to the second (S2) stimuli in a time interval −100 and +1000 ms after the second (S2) stimulus presentation. The ICA of the ERPs was made separately for Continue sets and Discontinue sets The number of training points was computed as follows: Number of subjects (297) × Number of categories of trials (2) (GO/NO-GO for Continue set, Novel/Ignore for Discontinue set) × Number of 4 ms time intervals (250 samples/s × 1.1) = 163,350. This number is much larger than that required to obtain good quality decomposition: $20 \times 19^2 = 7220$ (Onton & Makeig, 2006).

Assumptions that underlie the application of ICA to individual ERPs are as follow: (1) summation of the electric currents induced by separate generators is linear at the scalp electrodes; (2) spatial distribution of components' generators remains fixed across time; (3) generators of spatially separated components vary independently from each other across subjects (Makeig et al., 1996; Onton & Makeig, 2006).

Briefly, the method implemented is as follows: 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 19 × T matrices and U is 19 × 19 matrix. S(t) are maximally independent. In our work matrix U is found by means of the

Infomax algorithm, which is an iteration procedure that maximizes the mutual information between *S*.

According to the linear algebra,

$$P = U^{-1}S,$$

where U^{-1} is the inverse matrix of U (also called mixing matrix), and the ith column of the mixing matrix represents the topography of i-independent component; S_i represents time course of the i-independent component. The ICA method (Makeig et al., 1996) was implemented in the analysis software written by one of the authors (VAP). The topographies and activation time courses of the components were tested against the corresponding results obtained by means of "InforMax" software in EEGLAB, a freely available interactive Matlab toolbox for processing continuous and event-related electrophysiological data (http://sccn.ucsd.edu/eeglab).

The topographies of the independent components are presented as topographic maps, while time courses of the components (also called "activation time courses") are presented as graphics with time corresponding to the x-axis. In this paper the "power" of the components is characterized by a variance $\mathrm{VAR_i} = \sum\sum(U_{ij}^{-1}S_{ik})^2/(N_{samp}N_{chan})$ where N_{samp} = number of time points and N_{chan} = number of channels. The topographies are divided by the square root of the variance of the corresponding components, while the normalized activation curves are multiplied by the square root of the variance.

METHODOLOGY OF DECOMPOSITION OF INDIVIDUAL ERPs INTO INDEPENDENT COMPONENTS

The essence of neurometrics is a comparison of individual EEG parameters with normative data. In our approach there is a need for decomposing an individual's ERPs into independent components by means of the spatial filters extracted for the collection of "normal" ERPs. It is done as follows: The ith independent source S_i can be found as

$$S_i = U_{zi}P,$$

where U_{zi} is matrix U in which all rows are zeroed except the ith row.

According to linear algebra,

$$P_i = U^{-1}S_i = U^{-1}U_{zi}P.$$

In our work, we used this filter for decomposing individual ERP difference waves into the independent components.

The sLORETA (standardized low resolution tomography) imaging approach was used for locating the generators of the ICA components extracted in this study (ICs). The free software is provided by the Key Institute for Brain–Mind Research in Zurich, Switzerland (www.uzh.ch/keyinst/loreta.htm). For theoretical issues of this method see Pascual-Marqui (2002).

Amplitudes of the components were computed for each condition and each subject separately. Student's *t*-test was used for assessing statistical significance of deviation of the ICs from the baseline, as well as for assessing statistical significance of the difference between conditions. To assess the strength of a component in one condition (for example, NO-GO) in comparison to another condition (for example, GO) the effect size was calculated as $d = M_1 - M_2/SD$ where *M1* and *M2* are mean values of the component in conditions 1 and 2, and *SD* is the pooled standard deviation (Cohen, 1988).

Using the above-mentioned technology, we are able to decompose individual ERPs into distinct components. Comparison with the database can be easily made by computing z-scores for each time interval and for each component separately.

INDEPENDENT COMPONENTS IN GO/NO-GO TASK

From 19 components separated by ICA those that corresponded to horizontal and vertical eye movements were excluded from further analysis. Among the remaining components only those with highest values of variance (altogether constituting more than 90% of the signal variance) were analyzed. To estimate the reliability of the ICA decomposition we used a split-half method. All subjects participating in the study were separated into two groups, either odd or even, according to the number at which they appeared in the database. This separation gives an equivalent age and gender distribution in both groups. ICA was applied to the array of ERPs computed to the second stimulus for the two subject groups, as well as for the Continue and Discontinue task conditions. Topographies and time courses of the resultant ICs were compared with each other. The measure of similarity of components is given by two correlation coefficients obtained separately for topographies and time courses.

Visual inspection of the extracted components shows that some ICs computed for Continue and Discontinue sets are quite similar. The

components that do not differ between the two preparatory sets are presented in Figure 3.3.

In our two-stimulus paradigm design, the second paired stimuli have one thing in common: they all include brief presentations of visual stimuli. So, if our null hypothesis is correct, and the ICA enables us to decompose ERPs into functionally meaningful components, then there must be components that are common to Continue and Discontinue sets, and that reflect stages of visual information flow. We indeed were able to separate at least three set-invariant components which (according to their time course and localization) reflect sequential stages of visual information processing in the occipital−temporal−parietal networks.

One of the components was localized in the occipital lobe and consisted of a sequence of positive (with peak latency of 100 ms), negative (150 ms) and positive (240 ms) fluctuations resembling previous findings of the visual N1 wave (see, for example, Hillyard & Anllo-Vento, 1998; Näätänen, 1992; Paz-Caballero & García-Austt, 1992).

The other two visual components were localized over the temporal-parietal junction in the left and right hemispheres and consisted of a sequence of positive (with peak latency of 120 ms), negative (170 ms), and positive (240 ms) fluctuations. These two ICs appear to correspond to bilateral occipito-temporally distributed N170 waves described in numerous studies on ERP correlates of object processing (Itier & Taylor, 2004). The N170 wave is reliably larger for faces than to any object category tested (Itier & Taylor, 2004a,b). Although the exact neuronal generators of this wave are still debated, this wave may reflect structural visual encoding (Rossion et al., 2003).

Our recent study with stroke patients who experienced hemispatial neglect in the visual field contralateral to the area of damage (Kropotov, Brunner, in preparation) showed severe impairment of the P 240 fluctuation of the component. This fact enables us to suggest that the above-mentioned components generated in the left and right temporal-parietal junctions are associated with detecting salience of the visual stimulus.

The remaining independent components are set dependent and are analyzed separately for each preparatory set. In order to associate the components with some functional meaning GO and NO-GO conditions were contrasted for the Continue set, while Novel and Ignore conditions were contrasted for the Discontinue set.

The components that are specific for Continue set are presented in Figure 3.4. According to sLORETA they are localized to the middle

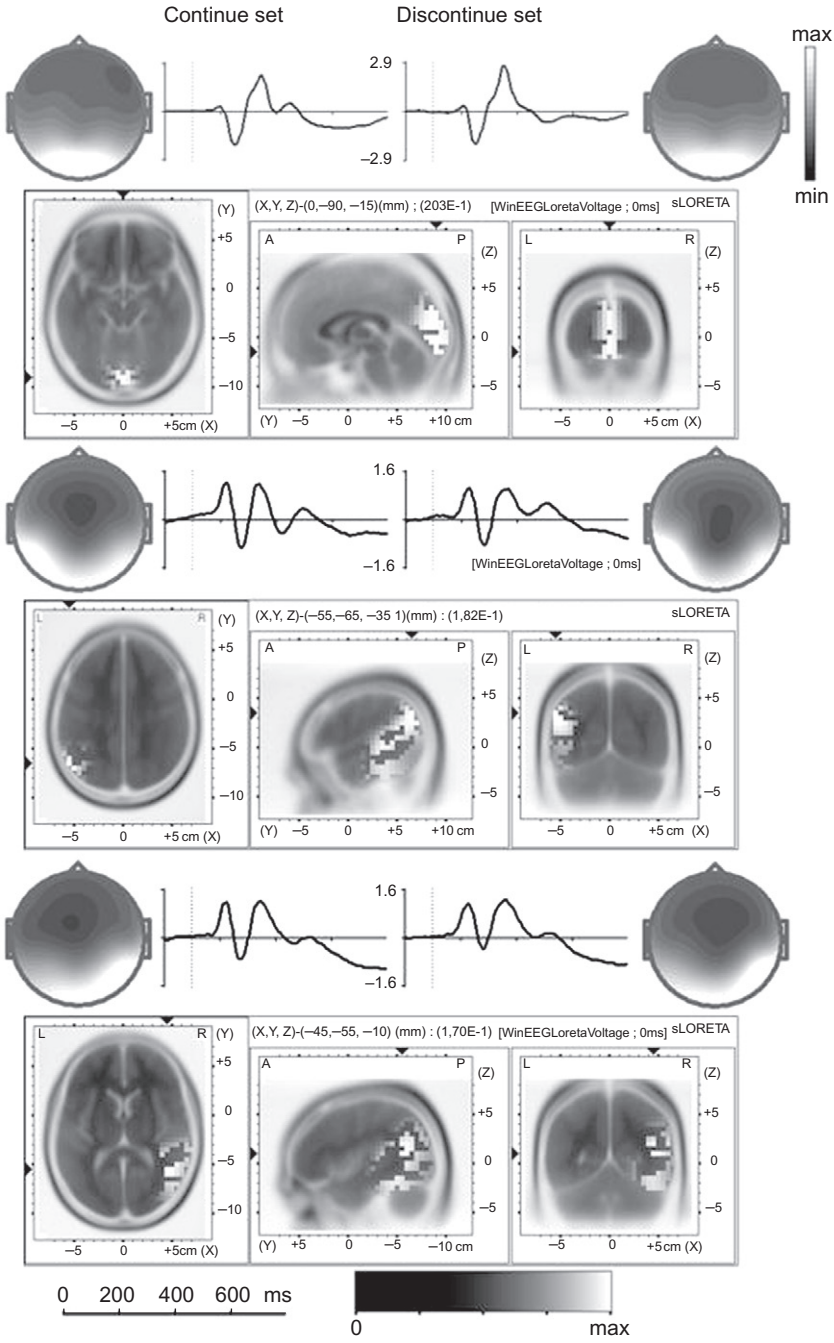

Figure 3.3 Occipitally and temporally generated components are similar for Continue and Discontinue sets. At the left is the topography and on the right the time course of the components. Below each pair of graphs is the sLORETA imaging of the component.

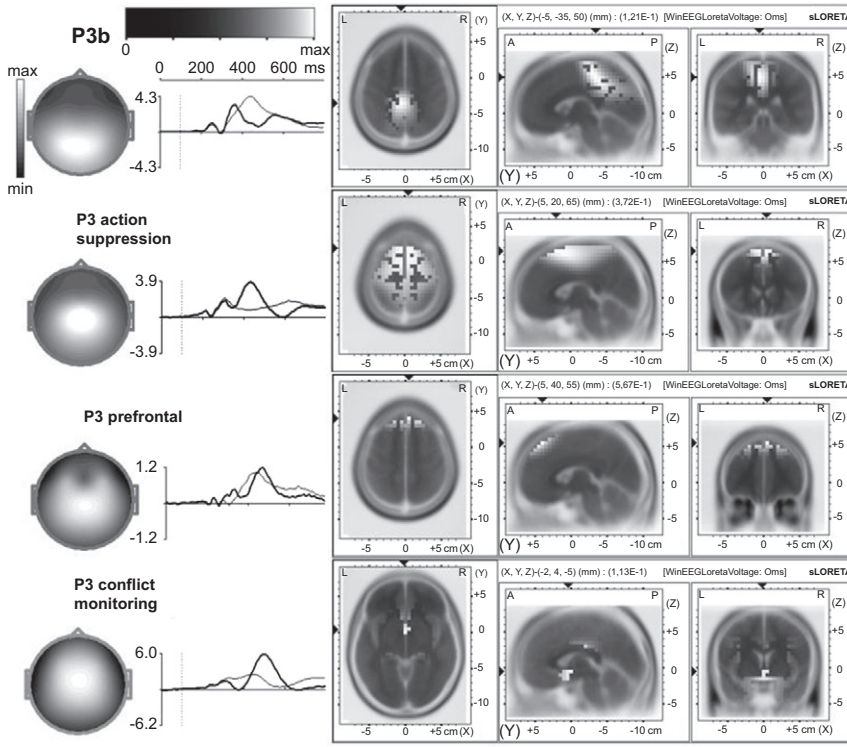

Figure 3.4 Independent components specifically generated in Continue set – Executive components. From left to right: topography, time course separately for GO (thin line) and NO-GO (thick line) conditions, and sLORETA imaging.

parietal cortex, supplementary motor cortex, frontal eye fields of the frontal lobe, and the anterior part of the cingulate cortex.

Our ICA data show that the P300 GO wave (elicited in response to GO cues) consists of at least two ICs with similar peak latencies (around 340–350 ms). The largest IC is a parietally distributed positive component, and the smallest is a frontally generated component. According to sLORETA the large component is generated in Brodmann areas 5 and 7 of the parietal cortex, while the smaller component is generated over the BA 8.

The parietal P300 component has similar time course for GO and NO-GO conditions up to 280 ms and deviates substantially at 340 ms with effect size of 1.5. The frontal P300 component was observed with almost the same amplitude but with slightly different latencies for GO and NO-GO conditions. It appeared that the parietal (BA 5 and 7) and frontal

(BA 8) areas were activated by both GO and NO-GO cues during at least the first 280 ms.

These ERP data fit well with recent fMRI (functional magnetic resonance imaging) studies showing that visual images of task-relevant stimuli are topographically represented both in parietal and frontal cortical areas (for a recent review see Silver & Kastner, 2009). The parietal P300 component dominates during a 300–400 ms time window in GO condition in comparison to NO-GO condition. The peak latency (around 340 ms) and topography (parietal distribution) of this component fit the corresponding parameters of a conventional P3b wave which is elicited in oddball paradigms in response to rare targets (for review see Polich, 2007). This component is quite similar to the parietal component extracted by ICA on an array of individual ERPs computed for healthy subjects and schizophrenic patients performing a one stimulus GO/NO-GO task (Olbrich et al., 2005).

Several functional meanings of the P3b components were suggested (for recent reviews see Polich, 2007). The most influential of them relates the component to the updating of working memory (Donchin, 1981). However, this was loosely defined at the psychological level, and was not associated with a neurophysiological circuit or cellular mechanism. Consequently it was criticized (Verleger, 1988). In intracranial recordings (Clarke, Halgren, & Chauvel, 1999; Kropotov & Ponomarev, 1991) the P3b-like waves were found in various cortical and subcortical structures, indicating a widespread distribution of the P3b component.

Analysis of independent components in our work shows that the late positive wave to NO-GO cues includes two ICs. The first component has a central distribution with peak latency of 340 ms, which is 60 ms shorter than the mean latency of response, and it is completely absent in response to GO cues. According to sLORETA imaging, this component is generated over the premotor cortex (Brodmann area 6). This component appears to correspond to subdurally recorded potentials found over pre-supplementary motor cortex in GO/NO-GO tasks in epileptic patients in response to NO-GO cues (Ikeda et al., 1999). The involvement of this part of the cortex in motor inhibition was demonstrated by the fact that direct stimulation of the pre-supplementary motor cortex in epileptic patients inhibited ongoing, habitual motor actions (Ikeda, Lüders, Burgess, & Shibasaki, 1993). A recent meta-analysis of fMRI studies in GO/NO-GO tasks demonstrates that the Brodmann area 6 is one of the

most commonly activated areas of the cortex (Simmonds, Pekar, & Mostofsky, 2008), thus supporting the involvement of this area in response selection and response inhibition. We associate the centrally distributed P340 NO-GO-related IC separated in our study with inhibition of a prepared motor action in response to NO-GO cues.

The second NO-GO-related IC identified in the study has a more frontal distribution in comparison to the P340 motor suppression component. This second component peaks at 400 ms, corresponding to the mean latency of response to GO cues. It should be stressed here that, when contrasted to GO cues, this component exhibits a strong negative peak at 270 ms. This negative part of the IC may be associated with the NO-GO N270 component commonly found as a difference between ERPs to NO-GO and GO cues and coined as the N2 NO-GO (Bekker, Kenemans, & Verbaten, 2005; Pfefferbaum, Ford, Weller, & Kopell, 1985). This N2 NO-GO peaks before a virtual response, it has been associated with response inhibition (Jodo & Kayama, 1992) and conflict monitoring (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). The wave has been inconsistently localized in various cortical areas including the anterior cingulate cortex (Bekker et al., 2005), the inferior prefrontal and left premotor areas (Kiefer, Marzinzik, Weisbrod, Scherg, & Spitzer, 1998), the medial posterior cortex (Nieuwenhuis et al., 2003), and the right lateral orbitofrontal areas (Bokura, Yamaguchi, & Kobayashi, 2001). Our sLORETA imaging supports source localization of the component in the anterior cingulate cortex.

Taking in account involvement of the anterior cingulate cortex in a hypothetical conflict monitoring operation (Botvinick, 2007; Schall, Stuphorn, & Brown, 2002; van Veen & Carter, 2002), we associate the P400 frontal-central IC selected in our work with conflict monitoring. Indeed, in the two-stimulus paradigm used here the subject develops a behavioral model: to press a button in response to two "animals" (A−A). When the second stimulus is a "plant" appearing after first "animal" (NO-GO condition), this stimulus does not fit the behavioral model (a conflict), and this conflict seems to activate neurons in the anterior cingulate cortex that monitor this conflict situation.

The components that are specific for the Discontinue set are presented in Figure 3.5. They include a component generated in the primary auditory cortex. It has a negative part with a latency of 120 ms which corresponds to the conventional auditory N1 component which has been found in numerous studies previously (for review see Näätänen, 1992).

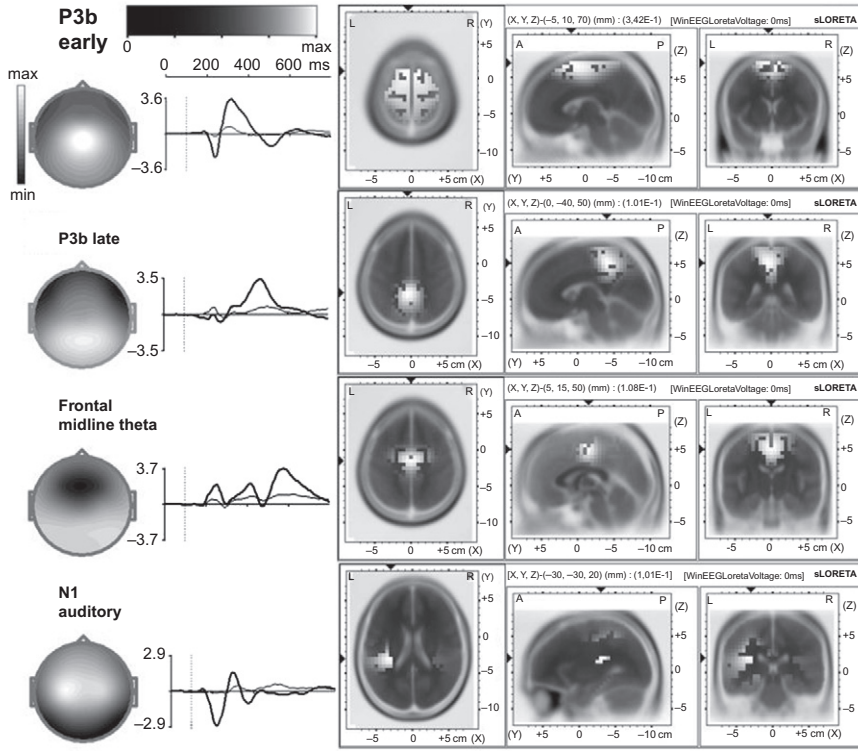

Figure 3.5 Independent components specifically generated in Discontinue set novelty-related components. From left to right: topography, time course separately for Ignore (thin line) and Novel (thick line) conditions, and sLORETA imaging.

The second novelty component has a central distribution with a positive fluctuation peaking at 220 ms, corresponding to the novelty component found in previous studies by using conventional current density mapping (Escera et al., 1998), by principal component analysis (Dien, Spencer, & Donchin, 2003), and by IC analysis performed on single-trial EEG epochs (Debener et al., 2005).

Two models were suggested to explain the functional meaning of the novelty P3a: an attention-switching model (Escera, Yago, & Alho, 2001) and a response inhibition model (Goldstein et al., 2002). In the attention-switching model the novelty P3 reflects involuntary switching of attention to deviant events that distract the subject from a primary task. In the response inhibition model, it is assumed that the detection of a deviant event leads to context updating and, after proper identification of the stimulus, to suppression of response that was activated by the deviance detection. In our work

using sLORETA imaging, this component is generated in the premotor cortical area, which supports the response inhibition model. Indeed the topography of this component is similar to the topography of the P3 suppression component separated from the collection of NO-GO and GO ERPs (see discussion of executive components above).

The third component has a parietal distribution with a positive wave peaking at 360 ms. It fits quite well with the topography and time course of the parietally distributed component (P3b) observed in our present work in response to GO and NO-GO cues. The late parietal part of the electrical brain response to novel stimuli was reported in previous studies (Escera et al., 1998, 2001).

Our work confirmed the previous attempts at separating novelty-related components and enabled us to dissociate a new component. This component was found to be generated in the mid-cingulate cortex and consists of a burst of theta waves with a frequency of 6.25 Hz. The frequency and location of this theta burst corresponds to the parameters of the "frontal midline theta" rhythm (Inanaga, 1998). The functional meaning of the frontal midline theta rhythm in humans is not clear, however some evidence associates it with an orienting response (Dietl, Dirlich, Vogl, Lechner, & Strian, 1999) and with allocation of cognitive resources by an attentional system (Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007). It should be noted here that application of principal component analysis enabled some authors (Dien et al., 2003) to localize the novelty P3 in the anterior cingulate cortex.

APPLICATION OF ERP/ICA METHODOLOGY FOR ADHD – RESPONSE INHIBITION

We use the above-mentioned methodology for analysis of ERP data in an ADHD population when compared to norms. According to Russel Barkley, the core of the disorder is impairment of response inhibition (Barkley, 1997). If this hypothesis is correct, then we should see a decrease of the independent component associated with action suppression in an ADHD population. Here we present the results of our study with a group of ADHD children of ages 8 to 12. We compared independent components presented above between this group and a group of healthy subjects of the same age taken from the HBI database. We found that two out of 11 independent components were significantly reduced in the ADHD population, with relative large effect size (Figure 3.6). The first of these

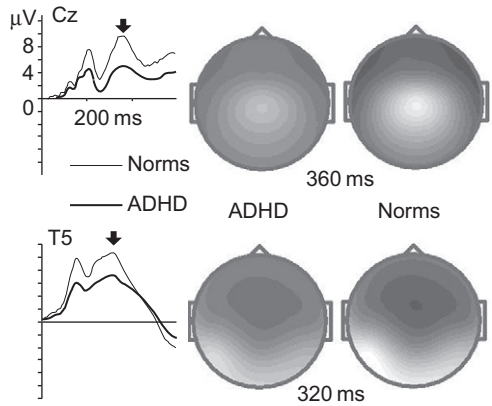

Figure 3.6 Reduction of central and left temporal independent components in ADHD. Number of ADHD patients is 94, number of control subjects, 69. Top: time courses and topographies of independent components obtained on 19 channel ERPs by spatial filtration. Thick line: ADHD; thin line: healthy subjects.

two components (Figure 3.6, top) appears to be associated with action suppression (see discussion above regarding the executive components) whereas the second component is associated with detecting salience of the stimulus (see discussion of the sensory components).

Note that ERP components were obtained by spatial filtration described above (see methodology of decomposition of individual ERPs into independent components). That means that any individual ERPs can be decomposed into independent components and any individual component can be statistically compared to normative data. The results of such comparison are presented in the scattergram in Figure 3.7.

The scattergram maps each individual's ERP independent components (circles – normal, triangles – ADHD) into the two-dimensional space with indexes of action inhibition and salience of the stimulus depicted at the *x*- and *y*-axis correspondingly. Two groups of the ADHD population can be separated: those with decrease of the action suppression component (might be associated with impulsive/hyperkinetic type of ADHD) and those with decrease of the salience detection component (might be associated with inattention type of ADHD).

ERPs AS INDEXES OF NEUROFEEDBACK EFFICACY

In a critique raised by Loo and Barkley it is stated that neurofeedback studies do not report pre- and post-qEEG differences since the EEG is

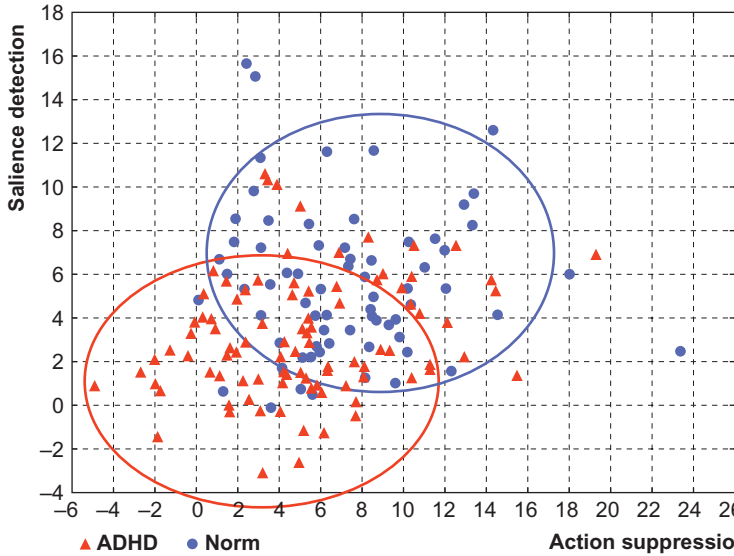

Figure 3.7 Scattergram of action suppression vs. working memory components in ADHD (triangles) and healthy subjects (circles). *X*-axis: amplitude of the action suppression component averaged over 100–700 ms time interval. *Y*-axis: amplitude of the working memory component averaged over 50–500 ms time interval.

the basis of treatment in neurofeedback (Loo & Barkley, 2005). One explanation of a few reports in the literature regarding post-pre spectra differences resides in a large variance of EEG spectra in theta, alpha, and beta frequency bands. There are several endophenotypes of EEG spectra in the normal and ADHD populations (Johnstone, Gunkelman, & Lunt, 2005). This heterogeneity leads to a large variance of EEG power taken for any frequency band. Consequently, changes induced by neurofeedback training usually are smaller than this inter-individual variance which makes the task of proving statistical pre-post QEEG difference rather difficult but not impossible providing an appropriate study design was selected (see Chapter 15 in this book).

However, ERPs parameters are more sensitive to neurofeedback training. In contrast to EEG spectra they reflect stages of information flow in the brain. When continuous performance tasks (such as GO/NO-GO) are implemented, ERPs are shown to be reliable markers of the executive system of the brain.

In our recent study (Kropotov et al., 2005) we used relative beta as a neurofeedback parameter for modulation behavior of ADHD children. The neurofeedback parameter was defined as a ratio of EEG power in a

beta frequency band (15–18 Hz) and EEG power in the remainder of the EEG band, i.e., in 4–14 Hz and 19–30 Hz frequency bands. The EEG was recorded bipolar from C3 and Fz electrodes in the standard 10–20 system. A typical training session included 20 minutes of relative beta training. The biofeedback procedure consisted of the following computations: power spectrum was calculated for a 1-second epoch every 250 ms using Fast Fourier Transformation. Visual feedback was provided by a bar against a background on a computer screen. The height of the bar followed the dynamics of the biofeedback parameter. The participant's task was to keep the bar above a threshold determined at the pre-training 2 minute interval.

In addition to the simple visual feedback, a so-called video mode was used. In this mode, the biofeedback parameter controlled the level of a noise generated by a separate electronic unit called a Jammer (the unit was designed specifically for this purpose in our laboratory). The amplitude of the noise was maximal if the biofeedback parameter was minimal, and decreased gradually up to zero while the parameter approached a threshold. The noise was mixed with the video-signal of a video-player and was fed to a TV-set. Thus the patient actually also controlled the quality of the picture on the screen by his/her brainwaves, i.e., when the biofeedback parameter was higher than the threshold, the picture on the screen was clear, otherwise the TV picture was blurred by the noise.

Usually during the first five to eight sessions, patients performed training in the simple visual mode with the bar to be able to get a feeling for the procedure. Then training in the video mode started. The patient was instructed about the rationale of the procedure, as well as about the dependence of the biofeedback signal on the brain activity and attention. Before the procedure, the patient tried to relax, decrease muscular tension, and maintain regular diaphragmatic breath. The patient was asked to assess his or her own internal state and feelings when the biofeedback parameter surpassed the threshold and to reproduce this state. Different patients used different strategies with a common denominator of concentrating on a particular external object. The number of training sessions for each patient depended on several factors such as age, type of ADHD, learning curves, and parent reports, and varied from 15 to 22 (mean 17). The termination criteria were: (1) stabilization of training performance during the last three to five sessions, and (2) stabilization of patient's behavior according to parents' reports. Sessions were administrated two to five times per week for 5–8 weeks. The dynamics of the biofeedback

parameter (training curve) was obtained for each patient and for each session.

It should be noted that not all patients were able to reliably elevate the relative beta activity even after 10–20 sessions. The quality of patient's performance, i.e., the ability of a patient to increase the neurofeedback parameter during training periods, was assessed. We considered the training session to be successful if a patient was able to increase the biofeedback parameter during training periods in more than 25% of sessions in comparison to resting periods. Patients were referred to as "good performers" if they were successful in more than 60% of sessions. Seventy-one patients (82.5%) were assigned to the "good" performance group. Those patients who had less than 60% successful training sessions were referred to as "bad performers". Fifteen patients (17.5%) were assigned to the "bad" performance group. This group was considered as a control group in the following data analysis.

To test functioning of the executive system, ERPs in the auditory two-stimulus GO/NO-GO task were recorded before and after all sessions of neurofeedback. ERPs to NO-GO cues superimposed on each other in "before" and "after" recordings are presented in Figure 3.8a. One can see enhancement of the positive component at the frontal leads after 20 sessions of the relative beta training.

The grand average ERPs differences and their maps computed by subtraction of the ERPs made before any interventions from those made after 20 sessions of the relative beta neurofeedback are presented in Figure 3.8b,c. A statistically significant increase of ERPs in response to NO-GO cues was found in the group of good performers, but not in the group of bad performers (not shown in Figure 3.8). It should be noted that the relative beta training did not change early (with latencies of 80–180 ms) components of ERPs, but induced significant enhancement of later positive components. Thus, our data indicate that this type of relative beta training does not effect auditory information processing in the human brain, while significantly changing the functioning of the executive system reflected in later ERP components.

Theoretically, our protocol differs from conventional protocols, because elevation of the biofeedback parameter in our study could be achieved by increasing beta power, and/or by decreasing theta as well as alpha power. However, as the results of our study indicate, the application of this relative beta protocol turns out to be as effective as conventional protocols. Indeed, 80% of our patients were able to significantly increase their neurofeedback

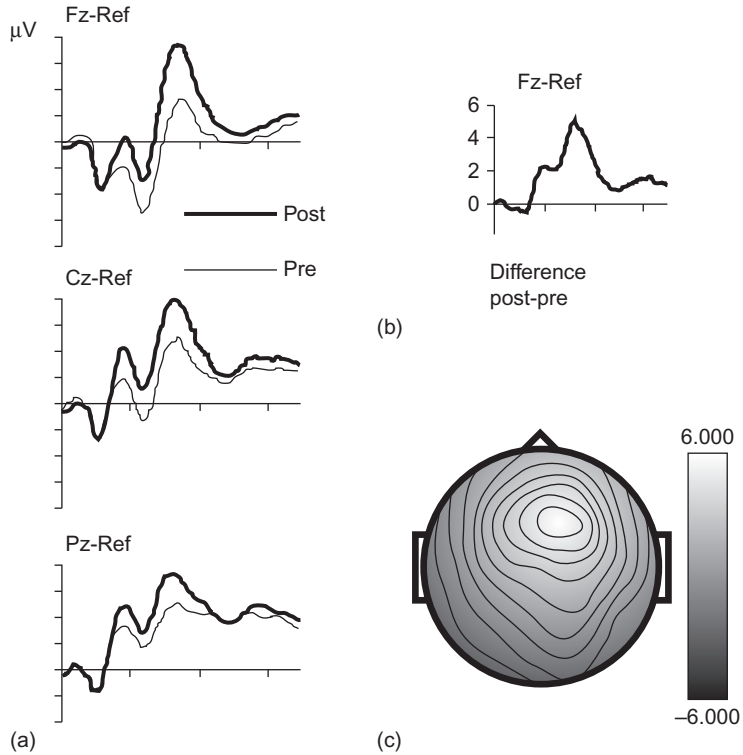

Figure 3.8 ERPs in the two-stimulus auditory GO/NO-GO task recorded before and after 20 sessions of relative beta training. (a) Grand average ERPs in response to NO-GO stimuli in the two-stimulus auditory GO/NO-GO test for the group of good performers before and after 20 sessions of the relative beta training. Thin line: ERPs taken before training; thick line: ERPs taken after 20 sessions of training. (b) ERPs differences induced by 20 sessions of neurofeedback in the group of good performers. (c) Map of the ERP changes induced by 20 sessions of neurofeedback. *(Adapted from Kropotov et al., 2005.)*

parameters in more than 60% of sessions. Moreover, according to parents' assessment by the SNAP-IV, neurofeedback significantly improved behavior as reflected in changes of inattention and impulsivity.

ERPs AS INDEX OF tDCS EFFECT

tDCS – transcranial direct current stimulation – is a technique of neuromodulation that applies direct current (i.e., a flow of electric charge that does not change direction and value) to the brain by means of electrodes placed on the head. Only 10% of the electric current passes through the

cortex. However, this current seems to be enough to induce substantial changes in excitability of cortical neurons. Experiments indicate that anodal stimulation (at least as applied to electrodes located above the motor cortex) increases excitability of neurons while the cathodal stimulation has an opposite effect (Nitsche & Paulus, 2000).

The first report of ERP changes during tDCS in humans was made by a group from the University of Goettingen, Germany (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004). They found that cathodal polarization induced a mild facilitatory after-effect on P100 whereas anodal polarization induced no after-effect. Later, a group from University of Rome "La Sapienza" (Italy) found that tDCS at 1 mA induced changes in ERPs that persist after polarization ends. tDCS was applied through surface electrodes placed over the occipital scalp (polarizing) and over the anterior or posterior neck-base (Accornero, Li Voti, La Riccia, & Gregori, 2007). tDCS was applied at two durations, 3 and 10 min and both polarities. Visual evoked potentials were obtained with black-and-white pattern-reversal checkerboards (two cycles per degree), at two levels of contrast. To avoid habituation owing to a constant checkerboard-reversal rate, patterns were reversed at a frequency of 2 Hz ±20%.

In this study anodal polarization reduced VEP-P100 amplitude whereas cathodal polarization significantly increased amplitude; but both polarities left latency statistically unchanged (Figure 3.9). These changes persisted for some minutes after polarization ended depending on the duration of tDCS and on the contrast level of visual stimuli, with lower contrast exhibiting higher effect.

In a pilot study with ERPs obtained in a GO/NO-GO task we attempted to find effects of anodal polarization on cognitive ERPs components. The anodal stimulation was 0.2−0.4 mA with 20 min duration. ERPs in the two-stimulus GO/NO-GO task described above were recorded before and after tDCS. In order to obtain reliable ERPs in each subject, 200 trials were presented in each condition. Seven healthy subjects (students from St Petersburg State University) participated in this pilot study. Some results are shown in Figure 3.10. As one can see, anodal stimulation at the area located between Pz, P3, and Cz induced changes in the N2 component, likely produced by altering excitability of neurons in the cingulate cortex.

We can conclude that in contrast to spontaneous EEG reflecting neuronal mechanisms of cortical self-regulation, ERPs are associated with stages of information flow within the cortex. ICA provides a powerful

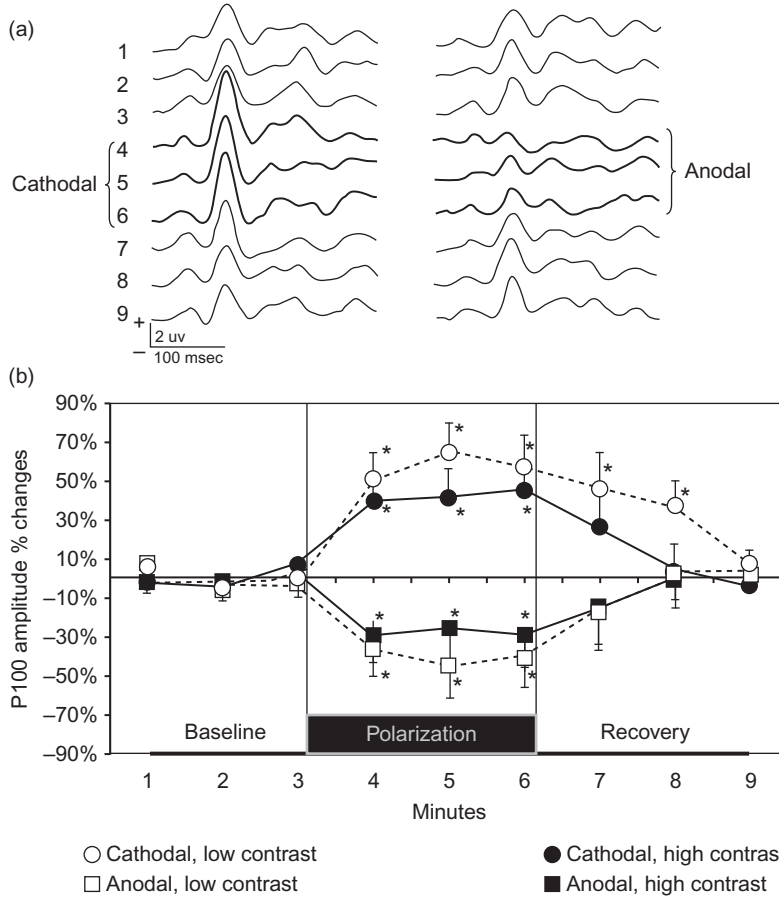

Figure 3.9 Effect of tDCS on visual evoked potential (VEP). (a) VEP modulation in a representative subject: each trace is an average of 60 visual stimuli sampled sequentially a minute. tDCS was applied for 3 minutes. (b) Grand average VEP P100 amplitude modulation induced by tDCS. *(Adapted from Accornero et al., 2007.)*

tool for decomposing ERPs into functionally meaningful components. The independent components of the two-stimulus GO/NO-GO are generated in distinct cortical areas and show different time dynamics. These components index different psychological operations in sensory systems (such as detecting salience of the visual stimulus) and the executive system of the brain (such as action suppression and conflict monitoring). Two of those components (salience and action suppression components) significantly differ between ADHD and healthy populations. They can be considered as endophenotypes (biological markers) of ADHD. The

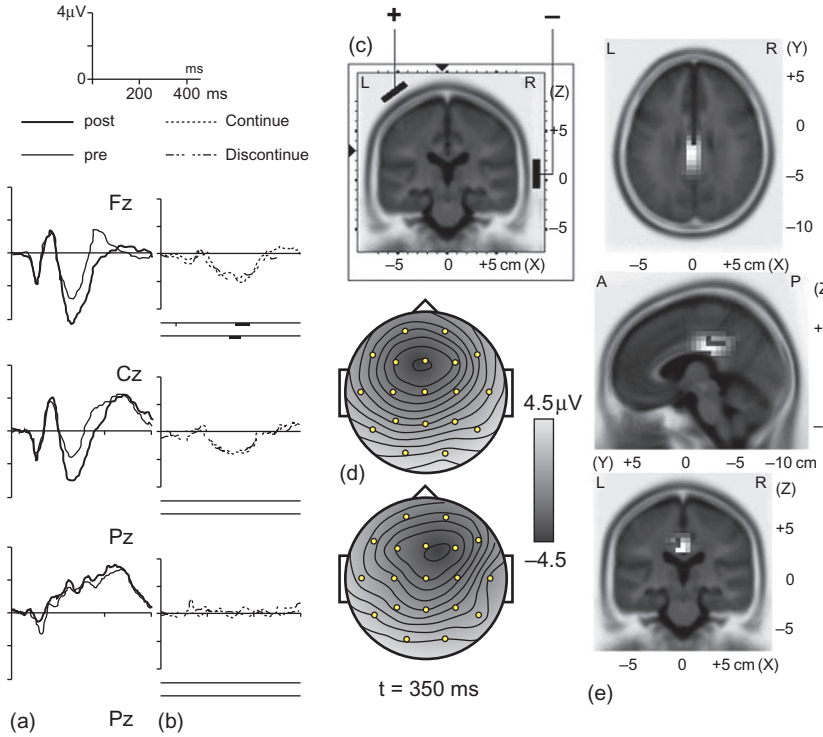

Figure 3.10 ERP to the first stimulus in the two-stimulus GO/NO-GO paradigm. ERPs were recorded before (thin line) and after (thick line) 20 minutes of tDCS. Electrodes were placed between Pz, P3, and Cz for anode and on the right mastoid for cathode. (a) ERPs in common reference montage to the first stimulus (Continue condition) before (pre, thin line) and after (post, thick line). (b) ERP differences (post−pre) for both Continue and Discontinue conditions. (c) Schematic presentation of electrode placement. (d) Maps of ERP differences (post−pre) taken at 350 ms after the first stimulus for Continue and Discontinue conditions. (e) sLORETA image of generators of the tDCS effect.

independent components of ERPs can be used as a diagnostic tool for defining functional impairment in a particular patient's brain as well as for defining effects of tDCS and neurofeedback in healthy subjects and patients.

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