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# WHAT CAN EVENT RELATED POTENTIALS CONTRIBUTE TO NEUROPSYCHOLOGY?

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## SUMMARY

*While psychometrics measures brain functions in terms of behavioral parameters, a recently emerged branch of neuroscience called neurometrics relies on measuring the electrophysiological parameters of brain functioning. There are two approaches in neurometrics. The first relies on the spectral characteristics of spontaneous electroencephalograms (EEG) and measures deviations from normality in EEG recorded in the resting state. The second approach relies on event related potentials that measure the electrical responses of the brain to stimuli and actions in behavioral tasks. The present study reviews recent research on the application of event related potentials (ERPs) for the discrimination of different types of brain dysfunction. Attention deficit-hyperactivity disorder (ADHD) is used as an example. It is shown that the diagnostic power of ERPs is enhanced by the recent emergence of new methods of analysis, such as Independent Component Analysis (ICA) and Low Resolution Electromagnetic Tomography (LORETA).*

**Key words:** *neurometrics, electroencephalography (EEG), Attention Deficit-Hyperactivity Disorder (ADHD)*

## **NEUROMETRICS: EEG SPECTRA**

In order to analyze perceptual, cognitive, memory, and affective functions of the brain, neuropsychologists rely on psychometrics, which measures these functions in terms of behavioral parameters, including omission and commission errors, reaction time, etc. A recently emerged branch of neuroscience, 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 the name in the 1970s, neurometrics is „a method of quantitative EEG that provides a precise, reproducible estimate of the deviation of an individual record from the 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).

Entrepreneurs began to take notice of the potential of neurometrics in the late 1980s. Two commercial systems were sequentially registered. The first, called the Neurometric Analysis System, was registered in 1988. It was based on normative data from the University of New York, and was published by John et al. (1977). The second system, the Neuroguide Analysis System, was registered in 2004, and was based on normative data from the University of Maryland, published by Thatcher et al. (1998). Each of these systems represents 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 normality.

The parameters that are measured in these two databases are spectral characteristics of spontaneous EEG recorded in an eyes-closed condition for the Neurometric Analysis System, and in both eyes-closed and eyes-open conditions for the Neuroguide Analysis System. The spectral characteristics of spontaneous EEG include absolute and relative EEG power in different frequency bands and different electrodes, 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. For example, the 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 presumably 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 several neuronal mechanisms.

The above mentioned databases have been very helpful in defining neuronal correlates of some brain dysfunctions, such as ADHD (Chabot, Serfon-

tein, 1996; Bresnahan et al., 1999; Clarke et al., 2001), traumatic brain injury (Thatcher et al., 1999), and dementia (Prichep et al., 1994). The limitation of these databases is that they explore only the statistical parameters of spontaneous EEG recorded in the resting state of human subjects, and do not take into account brain reactions in different task conditions.

## **NEUROMETRICS: EVENT RELATED POTENTIALS**

Another important aspect of brain functioning is the response of the brain to stimuli and actions induced by those stimuli. The electrical brain response is measured by event related potentials (ERPs), which are potentials generated by cortical neurons, recorded from the human head and associated with information flow in various cortical areas. The information flow is evoked by some event (for example, a repetitive stimulus presented sequentially during a sensory discrimination task or repetitive flexing of a finger during a simple motor task). ERPs are usually obtained by an averaging technique, which extracts a temporal pattern common for the event that is repeated many times during the behavioral task.

It should be noted here that the field of event related potentials evolved later than EEG spectral analysis. One of the first ERP waves, named P300, was discovered over 40 years ago. Later on, other ERPs waves were discovered, such as P300 novelty, mismatch negativity, N400, error related negativity (for a review see Kropotov, 2009). During 40 years of intensive research in many laboratories all over the world, a vast amount of empirical knowledge has been collected regarding the functional meaning of the extracted waves. At the same time, many studies have shown the power of these characteristics of brain response for discriminating patients with different brain disorders.

Recently, the practical application of ERPs have been accelerated by introducing new mathematical techniques for ERP analysis. One of these techniques is artifact correction by means of spatial filtration. The essential point here is that one of the factors that had been limiting the application of ERPs was the contamination of EEG traces by eye blink artifacts. Indeed, during any task (especially with the presentation of visual stimuli) subjects usually blink. When people blink their eyeballs (which represent strong electrical dipoles) move reflexively upward and induce a large potential at the frontal electrodes, which interferes with the EEG signal. For many years the most effective method of dealing with artifacts was simply the discarding of trials with eyes blinks. This led to a decrease in the number of trials used for ERP computation, and eventually to a decrease of the signal-to-noise ratio of the ERP signal. In 1996 a new method for artifact correction was suggested (Makeig et al., 1996). The method is based on Independent Component Analysis (ICA), which, when applied to EEG, is a new technique that decomposes EEG data into features with minimal mutual information. The basic

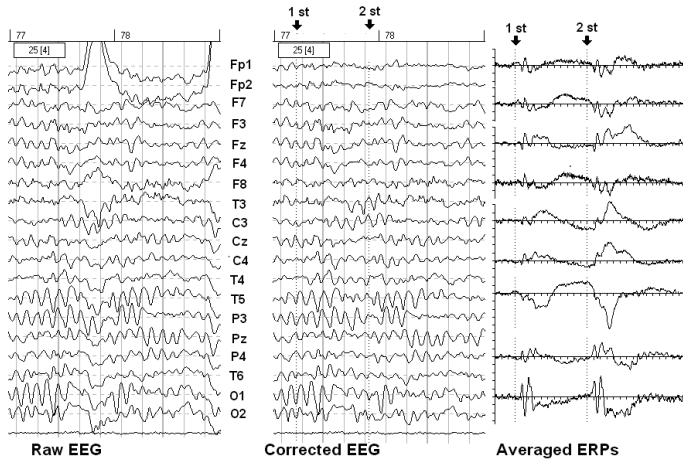


Fig. 1. Stage of computing event related potentials (ERPs). Left – 19-channel raw EEG recorded in a healthy subject while he performs a two stimulus task. Y-axis – potential value, X-axis – time (number at the top are in seconds). Each trail consists of presentation of two stimuli st1 and st2. The names of electrodes (against each trace) include the first letter associated with the area where the electrode is placed, and the number indicating the side and placement within this area. Fp1, Fp2 – prefrontal, F3, F4, – frontal, Fz – frontal midline, C3, C4 – central, Cz – central vertex, P3, P4 – parietal, Pz – parietal midline, F7, F8 – anterior temporal, T3, T4 – mid temporal, T5, T6 – posterior temporal. Odd numbers indicate left hemisphere. Even numbers indicates right hemisphere. Note large deviations of potential at the frontal electrodes induced by an eye blink. Middle – the same EEG fragment after artifact correction by zeroing the independent component corresponding to the eye blink. Left: event related potentials computed by averaging EEG fragments over all trials in the task. One can see that positive and negative fluctuations before the first stimulus presentation in all trials cancelled each other thus giving almost zero potential.

idea of the application of ICA for artifact correction is the decomposition of the EEG signal into two components: one that corresponds to neuronal electric activity, the other that corresponds to artifacts. Each component consists of a waveform, describing the time course of the modeled activity, and a topography vector, describing how the waveform contributes to each recorded signal. Simply zeroing the artifact component in the ICA decomposition was shown to be a powerful tool for artifact correction in general and for eye blink correction in particular (Fig. 1).

## **APPLICATION OF ICA FOR SEPARATING FUNCTIONALLY MEANINGFUL ERP COMPONENTS**

In ERP analysis ICA is used not only for artifact correction. There are at least three different methods of applying ICA for decomposing ERPs into functionally meaningful components. These methods deal with different input and output datasets, and allow us to address different questions:

- 1) The input data for the first method represent non-averaged single-trial ERP epochs in a single subject. The location of ICA components is defined separately for each subject. Cluster analysis is further applied to observe what is common for the grouped subjects (Debener et al., 2005);
- 2) The input data for the second method is a collection of averaged ERPs recorded in response to many stimulus types and many task conditions (Makeig et al., 1999);
- 3) The input data for the third method represent a collection of averaged ERPs recorded in a few conditions but in many subjects (Olbrich et al., 2002).

An example of the application of ICA for a collection of ERPs recorded in a modification of the GO/NO GO paradigm is presented below. The study involved 312 healthy subjects ranging in age from 18 to 45, approximately half of whom were female (N=172). The subjects were recruited from among the students of St. Petersburg State University (recorded by I.S. Nikishena), the staff of the Institute of the Human Brain of the Russian Academy of Sciences (recorded by E.A. Yakovenko), students of the Norwegian University of Science and Technology, Trondheim (recorded by S. Hollup), and healthy subjects from Chur, Switzerland, recruited by Dr. Andreas Mueller (recorded by E.P. Tereshchenko, I. Terent'ev and G. Candrian). The investigation was carried out in accordance with the Helsinki Declaration, and all subjects gave their informed consent.

A modification of the visual two-stimulus GO/NO GO paradigm was used (Fig. 2). 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 along with an artificial "novel" sound, referred to as "H+Sound".

All visual stimuli were selected to have a 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, while the novel sounds appeared unexpectedly (the probability of appearance was 12.5%).

The trials consisted of presentations of paired stimuli with inter-stimulus intervals of 1 s. The duration of stimuli was 100 ms. Four categories of trials were used (see Fig. 2): A-A, A-P, P-P, and P-(H+Sound). The trials were grouped into four blocks with one hundred trials each. In each block a unique set of five A, five P, and five H stimuli were selected. Participants practiced the task before the recording started.

The subjects sat upright in an easy chair looking at a computer screen. The task was to press a button with the right hand in response to all A-A pairs as fast as possible, and to withhold button pressing in response to other pairs: A-P, P-P, P-(H+Sound) (Fig. 2). According to the task design, two preparatory sets were distinguished: a "Continue set," in which A is presented as

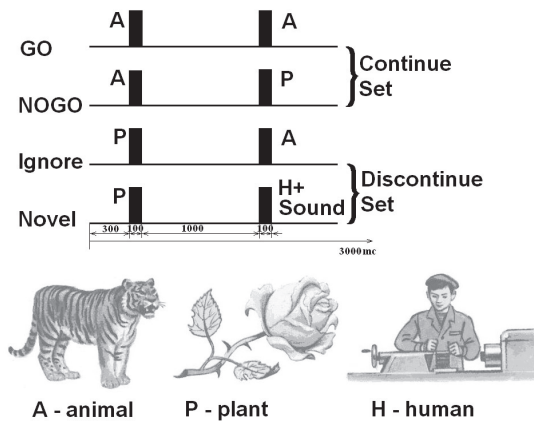


Fig. 2. Schematic representation of the two stimulus GO/NOGO task. From top to bottom: time dynamics of stimuli in four categories of trials. Abbreviations: A, P, H stimuli are “Animals”, “Plants” and “Humans”. GO trials are when A-A stimuli require the subject to press a button. NOGO trials are A-P stimuli, which require suppression of a prepared action. GO and NOGO 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 first stimulus and the subject is presumed to prepare to respond; and a “Discontinue set,” in which P is presented as the first stimulus, and the subject does not need to prepare to respond. In the “Continue set” A-A pairs will be referred to as “GO trials,” A-P pairs as “NO GO trials.” Averages for response latency and response 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. All subjects performed the task quite precisely, with average omissions in GO (A-A) trials of 1.7%, and a mean number of false alarms in NO GO (A-P) trials of 0.7%. The mean latency of responses was 398 ms, with a standard deviation of 146 ms.

EEG was recorded from 19 scalp sites. 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.

A visual inspection of grand average ERPs to the second stimuli in GO, NO GO, Novel and Ignore trials (Fig. 3) shows that GO, NO GO and Novel stimuli in comparison to Ignore trials evoke late positive fluctuations with different peak latencies, amplitudes and distributions. Topographic mappings of

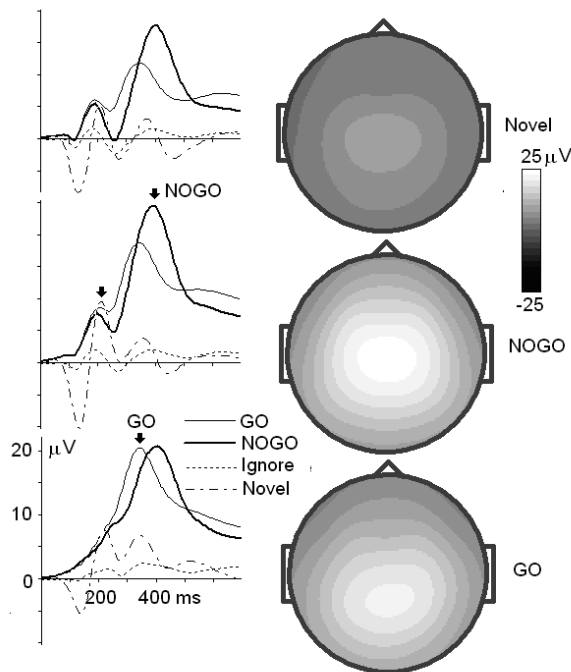


Fig. 3. Grand average ERPs in response to the second stimulus in pairs for GO, NOGO, Novel and Ignore conditions. Montage – linked ears reference. Position of electrodes is according to the 10-20 system. Maps of scalp potentials at peak latencies of late positive waves in response to GO, NOGO and Novel cues are presented at the right. On graphics – X-axis – time in ms, Y-axis – potential in  $\mu\text{V}$

the potentials at peak latencies of positive wave forms corresponding to P3 GO, P3 NO GO and novelty P3 are presented on the right side of Fig. 3.

The goal of Independent Component Analysis (ICA) is to utilize the differences in scalp distribution between the different generators of ERP activity to separate the corresponding activation time courses (Makeig et al., 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 all ERP scalp locations x time series matrix. The 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) the spatial distribution of component generators remains fixed across time;
- 3) the generators of spatially separated components vary independently from each other across subjects (Makeig et al., 1996; Onton, Makeig, 2006).

Briefly, the method implemented in our study was 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). 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  $19 \times T$  matrices and  $U$  is  $19 \times 19$  matrix.  $S(t)$  are maximally independent. In our study, 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 the mixing matrix) and the  $i$ -th column of the mixing matrix represents the topography of an  $i$ -independent component;  $S_i$  represents the time course of the  $i$ -independent component. The ICA method (Makeig et al., 1996) was implemented in the analysis software by a senior researcher in our laboratory, V.A. Ponomarev.

The time courses of six independent components extracted for Continue and Discontinue conditions are presented in Fig. 4. These components constitute around 90% of the ERP signal. The S-LORETA imaging approach was used for locating the generators of the ICA components on the basis of their topography. The free software is provided by the Key Institute for Brain-Mind Research in Zurich, Switzerland (<http://www.uzh.ch/keyinst/loreta.htm>). For the theoretical issues of this method see (Pascual-Marqui, 2002). S-LORETA images of the components depicted in Fig. 4 are divided into two groups: sensory (visual related) components (upper row) and executive (bottom row).

The sensory related components are similar for Continue and Discontinue conditions. One of the components is localized in the occipital lobe and is

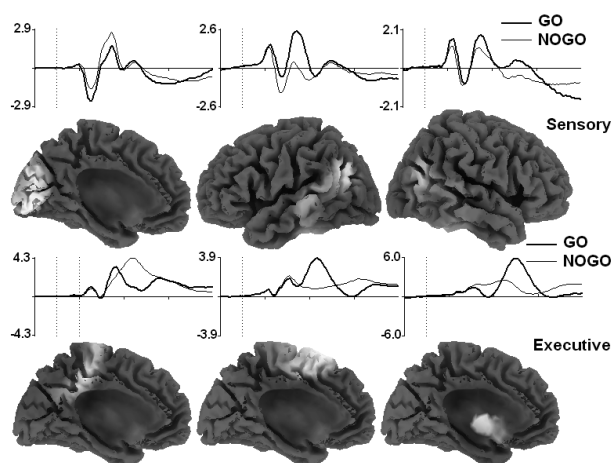


Fig. 4. Independent components of event related potentials in the two stimulus GO/NOGO task. Independent component analysis was applied to a collection of event related potentials computed separately for each subject ( $N=297$ ) and for Continue (GO and NOGO) task condition. Time course graphs: Y-axis is the component amplitude in standard units. S-LORETA images are computed on the basis of component topographies



associated with the visual N1 wave (see, for example, Hillyard, Anllo-Vento, 1998). The other two visual components are localized over the temporal-parietal junction at the left and right hemispheres. These two ICs appear to correspond to the bilateral occipito-temporally distributed N170 waves described in numerous studies on the ERP correlates of object processing (Itier, Taylor, 2004). Although the exact neuronal generators of this wave are still debated, it may reflect structural visual encoding (Rossion et al., 2003).

The executive components are generated in the parietal, premotor and anterior cingulate cortical areas. The parietal component dominates during a 300-400 ms time window in the GO condition, in contrast to the NOGO condition. The peak latency (around 340 ms) and topography of this component fit the corresponding parameters of a conventional P3b wave, which is elicited in oddball paradigms in response to rare targets (for a review see Polich, 2007). Several functional meanings of the P3b components have been suggested (for recent reviews see Polich, 2007). The most influential of these relates the component to the updating of working memory (Donchin, 1981), though this was loosely defined at the psychological level, and was not associated with a neurophysiological circuit or cellular mechanism(s), which led to criticism (Verleger, 1988).

The late positive wave to NOGO cues includes two ICs. The first component has a central distribution with a peak latency of 340 ms. According to S-LORETA imaging this component is generated over the premotor cortex (Brodmann area 6). The involvement of this part of the cortex in motor inhibition has been demonstrated by the fact that direct stimulation of the pre-supplementary motor cortex in epileptic patients inhibits ongoing, habitual motor actions (Ikeda et al., 1993). A recent meta-analysis of fMRI studies in GO/NO GO tasks demonstrates that Brodmann area 8 is one of the most commonly activated areas of the cortex (Simmonds et al., 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 the present study with inhibition of a prepared motor action in response to NO GO cues.

The second NO GO-related IC identified in the present 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, in contrast 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, referred to as the N2 NO GO (Pfefferbaum et al., 1985; Bekker et al., 2005). Since this N2 NO GO peaks before a virtual response, it has been associated with response inhibition (Jodo, Kayama, 1992) and conflict monitoring (Nieuwenhuis et al., 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 et al., 1998), the medial posterior cortex (Nieuwenhuis et al., 2003), and the right lateral orbitofrontal areas (Bokura et al., 2001). S-LORETA imaging in the present study supports source localization of the component in the anterior cingulate cortex. Taking into account the involvement of the anterior cingulate cortex in a hypothetical conflict monitoring operation (van Veen, Carter, 2002; Schall et al., 2002; Botvinick, 2007), we associate the P400 frontal-central IC selected in the present study with conflict monitoring.

## **DIAGNOSTIC POWER OF INDEPENDENT COMPONENTS**

Here we present some results of our own multi-centre study, carried out within the framework 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). The study included recordings of 150 ADHD children (24 girls), ranging in age from 7 to 12 years, and 168 ADHD adults, ranging in age from 18 to 50 years. Fig. 5 shows the results from the children's group for comparison between two age matched groups of healthy subjects (taken from the Human Brain Index reference normative database) and ADHD children recorded under the same task conditions. The results of the adult group will be published in 2010 in the forthcoming book, *Neurodiagnostics in ADHD*.

Seven independent components, constituting around 90% of the signal, were separated from the collection of ERPs recorded in response to GO and NO GO stimuli. Four of them are presented in Fig. 5. As can be seen, only one component significantly (with a 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 inhibitory control in children with attention deficit.

This result fits well with numerous fMRI studies on ADHD children performing GO/NO GO and Stop tasks. These studies showed a decrease of metabolic activity in the prefrontal cortex (also known as hypofrontality) in the ADHD population, in comparison to healthy controls (Rubia et al., 1999; Zang et al., 2005).

Impairment in response inhibition has been conceptualized as a core of ADHD by many authors, including Russel Barkley (1997), the leading figure in the field of ADHD. However, attempts to test this hypothesis in ERP studies have been controversial. In these studies the N2 NO GO wave was considered as an index of inhibition. The N2 is obtained when the ERP to a NO GO (or Stop cue) is contrasted to the ERP to a GO cue. An international team from the University of Goettingen in Germany and the University of Zurich in

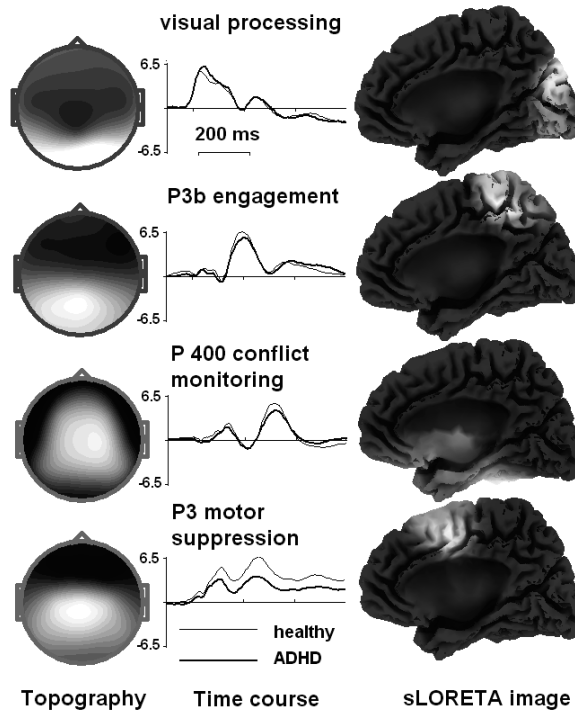


Fig. 5. Independent components of ERPs in response to NOGO cues in ADHD and healthy children. Components are computed for array of 300 individual ERPs for GO and NOGO task conditions in response GO and NOGO cues in the two stimulus GO/NOGO task. Four out seven independent components with largest variances are presented. Left – topography of the component. Middle – time dynamics to NOGO cues in ADHD (thick line) and healthy control children (thin line) of age for 7 to 12 years old. Right – LORETA images of the corresponding components

Switzerland (Banaschewski et al., 2004) recently reported a failure to find any deviations from normality in an ADHD group in the N2 component of ERPs in a variant of the GO/NO GO paradigm – the CPT-A-X task. In contrast, in a study at the University of Texas (Pliszka et al., 2000) ERPs in another variant of the GO/NO GO paradigm – the Stop signal task – showed a remarkable decrease of the N2 component in the ADHD group in comparison to healthy subjects. In response to all Stop signals, control participants produced a large negative wave at 200 msec (N200) over the right inferior frontal cortex, which was markedly reduced in ADHD children. The N200 amplitude was significantly correlated across subjects with the response–inhibition performance.

The inconsistencies of the N2 deficit in the ADHD population are probably due to the heterogeneity of the psychological operations involved in GO/NO GO tasks. Recently, ICA was applied to a collection of individual ERPs in response to GO and NO GO cues in two-stimulus visual GO/NO GO tasks.

The selected six independent components with different topographies and time courses constituted 87% of the artifact-free signal variance. Three of them were loaded into the frontally distributed N2 wave. According to S-LORETA, these three independent components were generated in the supplementary motor cortex (motor suppression component), left angular gyrus (sensory comparison component) and anterior cingulate cortex (conflict monitoring component). Consequently, the N2 effect in ADHD depends very much on the task, and on how these operations are involved in task performance.

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