

Event-related Potentials (ERP) in Cognitive Neuroscience Research and Applications

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Abstract

This review is aimed at exploring the usefulness of measuring event-related potential (ERP) in cognitive tests and discusses several applications of the ERP technique. Analysis of ERP components is one of the most informative dynamic methods of investigation and monitoring of information processing stages in the human brain. Amplitude and latency of ERP components at specified topographies reflect early sensory perception processes and higher level processing including attention, cortical inhibition, memory update, error monitoring, and other cognitive activities. ERPs provide a method of studying cognitive processes in typical subjects, as well as a sensitive instrument to assess differences in individuals with neuro- and psychopathologies. Despite significant advances in functional neuroimaging, the ERP measure still represents an important tool for brain research in psychiatry, as many psychiatric diseases correlate with certain altered patterns of ERPs. Such ERP alterations can serve as valid biological markers for functional diagnostic or for better understanding of the cognitive functions which are disturbed in psychiatric disorders. Application of ERPs in psychiatric treatment research is an approach aimed at validation of specific ERP measures as sensitive functional outcomes of experimental neuromodulation interventions such as rTMS and neurofeedback. Also discussed are additional aspects of ERP usefulness in psychiatry research and treatment.

Keywords: ERP; qEEG; psychopathology; biomarkers; cognitive neuroscience

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Introduction

In addition to more traditional quantitative electroencephalography (qEEG) techniques, where EEG is assessed during resting conditions with eyes closed and eyes open, there is a recent trend towards a wider usage of event-related potential (ERP) recording methodology for research and clinical applications. This review is not aimed at describing the basic fundamentals of ERP

technology, but rather is intended to discuss a rationale for the usefulness of this methodology in cognitive neuroscience research, functional diagnostic, and also as a valuable neurotherapeutic interventions outcome measure. Event-related brain potentials are described as changes in electrocortical activity recorded from the scalp and are evoked by an external or internal event. This ERP activity is changing very rapidly in time and across cortical topographic fields and is recorded

with high temporal resolution in order of several milliseconds from different scalp locations (Otten & Rugg, 2005). Research based on ERP is an established tool to address various questions in psychology, psychiatry, and neuroscience. Our review is confined to the use of ERP in cognitive neuroscience with a focus on several psychopathologies such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), and schizophrenia (SCZ) to name a few. From the very early period of ERP application there were numerous studies aimed at association of the certain features of ERP waveforms (e.g., ERP components) with specific cognitive processes and further using them as biomarkers of the engagement of these cognitive processes. This approach is based on prior knowledge about the functional significance of specific ERP components and is very useful for inferences about cognitive processes taking place during various experimental manipulations in typical controls and patients with psychiatric conditions. There are several measures used in ERP research, such as scalp topographic distribution, polarity (positive or negative), amplitude, latency, time course, and dipole source localization. These ERP variables may provide important insight about perceptual, cognitive, and motor functions in normal and in psychopathological conditions. Considering the high temporal resolution and low costs of ERP technology, it is logical to assume that ERPs will remain an essential instrument in cognitive neuroscience, neurotherapy, and clinical neurophysiology.

Event-related Potentials (ERP) as a Tool in Cognitive Neuroscience Research

Analysis of ERP components is one of the most informative dynamic methods of investigation of information processing stages in the brain. Amplitude and latency of ERP components at relevant scalp topographic regions-of-interest (ROI) provide information about early sensory perception processes and higher level processing including attention, cortical inhibition, response selection, error monitoring, memory update, and other cognitive activity (Duncan et al., 2009; Polich, 2007). ERP methodology represents a valuable technique for studying normative cognitive processes in typically developing subjects, and at the same time ERP may serve as a sensitive tool to assess differences in children with neurodevelopmental pathologies such as ASD and ADHD, or in adult individuals with various psychiatric conditions (e.g., PTSD, SCZ, substance use disorder [SUD], etc.). Despite

significant advances in functional neuroimaging (e.g., functional magnetic resonance imaging [fMRI] or positron emission tomography [PET]), the ERP still represents an important brain research methodology in psychiatry, as many psychiatric diseases correlate with altered patterns of EEG responses detectable in ERP (Lenz et al., 2008). ERP alterations in psychopathologies can serve as valid and sensitive biomarkers for functional diagnostic purposes. On the other hand, investigation of differences in ERP measures can contribute to better understanding of the cognitive functions disturbed in neurodevelopmental disorders and other psychopathologies.

Stimulus-locked ERP

ERP locked to stimulus reflects the activation of neural structures in primary sensory cortex and in associative cortical areas related to higher order cognitive processes. ERP studies are especially interesting for the purpose of this review as they provide temporal information concerning processes such as attention. Earlier ERP components (such as the P100, N100, and P200) usually relate to attentional selection mechanisms, whereas later components (P300) are more often associated with organization and interpretation of the stimulus. ERP components can be categorized as short-latency (exogenous, e.g., N100) or long-latency (endogenous, e.g., P300) ERPs, which reflect early-stage, modality-specific and late-stage polymodal associative processing, respectively. The early ERP components (e.g., P100, N100) reflect exogenous processes modulated by the physical attributes of the stimulus (i.e., brightness for visual stimuli, loudness of auditory stimuli), rather than by endogenous cognitive processes (Coles & Rugg, 1995). However, it was noted that attention processes may operate even at the early stages of information intake and influence stimulus processing at the later stage (Herrmann & Knight, 2001). In such context, P100 may reflect a facilitation of early sensory processing of attended stimuli, while N100 may reflect the early stage of orienting of attention towards task-relevant target stimuli (Hillyard & Anllo-Vento, 1998; Luck, Heinze, Mangun, & Hillyard, 1990; Näätänen & Michie, 1979).

Posterior visual P100 is generated within the fusiform gyrus (Heinze et al., 1994), whereas N100 is probably generated by distributed dipoles in lateral extrastriate cortex (Gomez-Gonzales, Clark, Fan, Luck, & Hillyard, 1994) with contribution from parieto-occipital and occipito-temporal areas (Yamazaki et al., 2000). Anterior P100 and N100

components occurring within a comparable time window result from frontal generators (Clark, Fan, & Hillyard, 1994). The cognitive functional significance of the midlatency P200 component of ERP has not been completely resolved (Crowley & Colrain, 2004) and existing results are not consistent. Novak, Ritter, and Vaughan (1992) suggested that the P200 represents reflection of activity of an attention modulation process in oddball paradigms. García-Larrea, Lukaszewicz, and Mauguière (1992) proposed that the P200 more probably reflects stimulus evaluation aspects during the classification process and facilitates a first rough stimulus appraisal. It was reported that the extent of required cognitive effort positively correlates with the P200 magnitude (Conley, Michalewski, & Starr, 1999). It could be concluded that P200 reflects attention and discrimination processes as well as task difficulty related variables.

There is a negative endogenous ERP component (N200 or N2b), located over centro-parietal scalp locations and occurring about 180 and 320 ms poststimulus (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Schröger, Karakas, Tervaniemi, & Paavilainen, 1993). This component is associated with categorization, perceptual closure, and attention focusing, ultimately signaling that a perceptual representation has been formed (Potts, Patel, & Azzam, 2004). The posterior visual N2b is enhanced if the presented stimulus contains a perceptual feature or attribute defining the target in the task. An anterior frontal positive component (P2a) in a latency range comparable with the posterior N2b has been reported in working memory and attention tasks. The P2a recorded over inferior prefrontal recording sites appears to be selectively responsive to the evaluation of the task relevance of presented visual stimuli, and source localization places dipoles of this component in the orbito-frontal cortex (Potts, Dien, Harty-Speiser, McDougal, & Tucker, 1998; Potts, Liotti, Tucker, & Posner, 1996). Kenemans, Kok, and Smulders (1993) described this frontal positivity as a component that indexes the hierarchical selection of task-relevant features for further processing. Information about processes related to response conflict detection and processing, as well as inappropriate response inhibition, can be extracted from the fronto-central ERP component N200 (West, 2003; West, Bowry, & McConville, 2004), which is thought to originate from the anterior cingulate cortex (ACC) and prefrontal sources (Donkers & van Boxtel, 2004).

The most studied endogenous ERP is the P300 (300–500 ms poststimulus). The P300 is obtained in an oddball paradigm, wherein two stimuli are presented in a random order, one of them frequent (standard) and another one rare (target; Polich, 2003; Pritchard, 1981). A modification of the task has been used where a third, also infrequent novel distracter is presented along with the standard and rare target stimuli. It was reported that these novels elicit a fronto-central P300, so-called P3a, whereas the rare targets elicit a centro-parietally distributed P300, so-called P3b (Katayama & Polich, 1998; Polich, 2003). The P3a is recorded at the anterior frontal locations and reflects frontal activity (Friedman, Simpson, & Hamberger, 1993; Knight, 1984). The P3a to novel distracter stimuli is generated by contribution of brain structures, including the hippocampus (Knight, 1996) and medial and inferior frontal (Baudena, Halgen, Heit, & Clarke, 1995; Elting et al., 2008), dorsal PFC and anterior cingulate cortex (Dien, Spencer, & Donchin, 2003). In a three-stimulus oddball task the P3a is interpreted as “orienting” to novel distracters, and the P3b as an index of ability to sustain attention to target. Source localization techniques have claimed that multiple brain areas are involved in the generation of the visual P3b: the hippocampus and parahippocampal areas, the insula, the temporal lobe, occipital cortex, and the thalamus (Goto, Brigell, & Parmeggiani, 1996; Herrmann & Knight, 2001; Mecklinger et al., 1998; Rogers, Basile, Papanicolaou, & Eisenberg, 1993). Most studies agree that the P3b has multiple dipole sources (Halgren, Marinkovic, & Chauvel, 1998; Knight, 1997; Townsend et al., 2001).

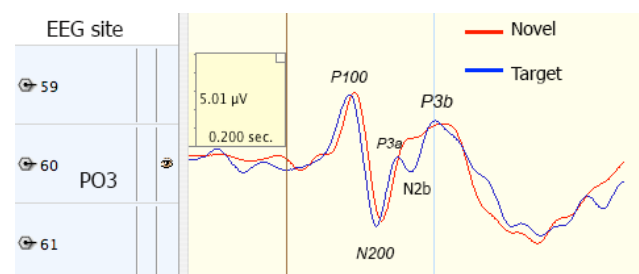


Figure 1. Screenshot of a stimulus-locked posterior ERP in a visual three-category oddball task with novel distracters. At the parieto-occipital PO3 site there are clearly visible P100, N200, N2b, P3a, and P3b components to target stimuli.

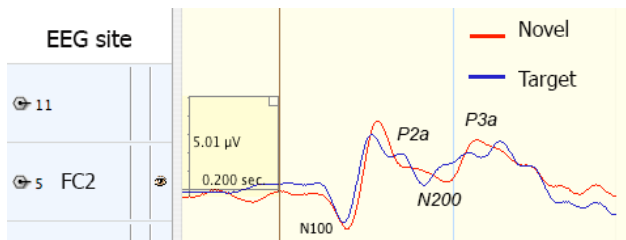


Figure 2. Screenshot of an anterior ERP in a visual three-category oddball task with novel distracters. At the fronto-central FC2 site there are clearly visible N100, P2a, and N200 components to target stimuli and P3a component to novel distracter stimuli.

Response-locked Error-related Potentials

Application of ERP methodology is not limited only to the evaluation of responses to sensory stimuli in various cognitive tasks; they also can be used to assess motor-response-related processes. Some type of ERPs can be used to understand response-related neural processes. One important executive function known to be compromised in psychopathologies is the ability to select a contextually appropriate response among several competing ones, and simultaneously inhibit contextually inappropriate responses to avoid committing an error. Another executive deficit observed during performance on speeded reaction time tasks in neuro- and psychopathologies (e.g., ASD, SCZ, SU disorders) is manifested in an abnormality related to response error monitoring, error recognition, and subsequent posterror response correction.

Error sensitivity can be readily examined by measuring response-locked ERP components associated with brain responses to errors. Two specific components relevant in this context are the error-related negativity (ERN, more rarely referred to as Ne) and the error-related positivity (Pe). The ERN is a response-locked negative ERP deflection, emerging between 40 and 150 ms after the onset of the incorrect behavioral response—a commission error (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). Usually this negative wave is followed by a positive wave referred to as the Pe potential. Although there is discussion about the exact meaning of the Pe (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005), most studies indicate that the Pe is related to the conscious recognition of the error (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001) or the attribution of motivational significance to the committed error (Falkenstein et al., 2000). This suggests that the ERN reflects an

initial automatic brain response as a result of an error, and the Pe possibly indicates the conscious reflection and comprehension of the error (Overbeek et al., 2005). The magnitude of the ERN is associated with behavioral evidence of self-monitoring (i.e., self-correction and posterror slowing responses) and therefore is interpreted as a biomarker of error processing (van Veen & Carter, 2002). Dipole modeling has localized ERN sources to the caudal ACC, while Pe has been localized to the more rostral ACC division (Bush, Luu, & Posner, 2000; Gehring & Knight, 2000; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; van Veen & Carter, 2002; West, 2003). ERN and Pe are generally accepted as valid neural indices of response-monitoring processes in psychophysiological research and clinical neurophysiology.

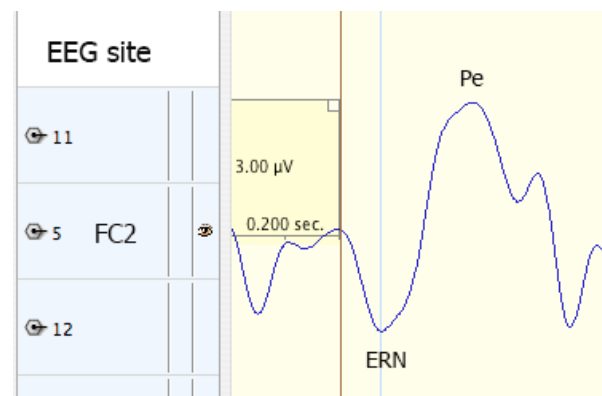


Figure 3. Screenshot of commission error-response locked ERP in a flanker task. There is a negative deflection around 100 ms posterror (i.e., error-related negativity—ERN) followed by an error-related positivity (Pe).

Performance on behavioral tasks is monitored by a brain system that is responsive to errors (Falkenstein et al., 2000; Gehring & Knight, 2000; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Luu, Flaisch, & Tucker, 2000; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003). Evidence from fMRI, qEEG, and ERP studies outlines that error monitoring is a function of the medial frontal cortex (MFC), including the supplementary eye fields, rostral cingulate motor area, and dorsal anterior cingulate cortex (ACC; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). One of the important research questions is whether the error-related frontal activity is associated with a premorbid trait reflecting an initial deficiency of behavioral control and regulation, and whether this deficit can be

generated as a result of neuropathological states associated with behavioral control deficits typical for psychiatric conditions. Several clinical research studies have demonstrated excessive error processing in patients with obsessive–compulsive disorders (OCD; Johannes et al., 2001), anxiety disorders (Markela-Lerenc et al., 2004) and Tourette syndrome (Gehring, Himle, & Nisenson, 2000). Yet, reduced error processing manifestations were reported in borderline personality disorder (de Bruijn et al., 2006) and schizophrenia (Mathalon et al., 2002). In psychiatric studies, a decreased ERN is typically related to increased severity of psychomotor poverty symptoms (Bates, Liddle, Kiehl, & Ngan, 2004). Furthermore, error processing has also been found to be reduced in nonclinical traits such as high impulsivity (Ruchow, Spitzer, Grön, Grothe, & Kiefer, 2005).

Neuroanatomically and functionally, the anterior cingulate cortex (ACC) provides an interface between frontal action selection processes, limbic emotion or motivation processes, and motor output regulation (Coles, Scheffers, & Holroyd, 2001; Holroyd & Coles, 2002; Taylor, Stern, & Gehring, 2007). The integral role of the ACC in self-monitoring and guiding attention in goal-directed actions suggests that it may be an important focus for ADHD research. In ASD, disturbances in attention regulation and behavioral rigidity may result in social orienting deficits and a chronic disruption of social information processing and social learning that together may contribute to the social-cognitive and emotional deficits observed in autistic children (Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Klin, Jones, Schultz, & Volkmar, 2003; Mundy, 1995; Mundy & Neal, 2001). In our studies on error monitoring in autism (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b) we showed that the ERN and the Pe component of the response-locked ERP were substantially decreased in children with autism as compared to typically developing (TD) controls and even as compared to children with ADHD. In particular, the amplitude of ERN was less negative and latency of both ERN and Pe were prolonged in the ASD group as compared to the TD children. The ERN is an EEG measure associated with the commission of errors, thought to be independent of conscious perception (Franken, van Strien, Franzek, & van de Wetering, 2007), while the Pe is thought to reflect the motivational or emotional significance of the error or, in another words, the conscious evaluation of the error (Overbeek et al., 2005). The findings that both ERN and Pe are altered in autism may suggest that ASD

patients are not only less sensitive to committed errors but that they are also less aware of their errors, probably attributing less significance to them. Inadequate and inflexible responsiveness to errors may underlie one of the typical characteristics of autism spectrum disorders, namely, the persistence of stereotyped repetitive behaviors. The sum of the group differences across these behavioral and stimulus- and response-averaged ERP indices of the ASD patients' performance is that it reflects global deficits in attentional processes, more specifically deficits in effective differentiation of target and distracter stimuli. This latter interpretation is supported by the significant differences between the ASD patients and typically developing controls in terms of both the stimulus-locked and response-locked ERP amplitudes and latencies, and the correlation between subjects' behavioral performance measures and specific ERP components magnitude.

Structural and functional deficiencies of the ACC may contribute to the atypical development of joint attention and social cognition in autism (Mundy, 2003). Such interpretation of the results of the ERN/Pe deficits found in several studies (Bogte, Flamma, van der Meere, & van Engeland, 2007; Henderson et al., 2006; Sokhadze, Baruth, El-Baz, et al., 2010) is consistent with many aspects of theory and research that suggests that ACC-mediated response monitoring may contribute to social-emotional and social-cognitive development in autism (Mundy, 2003). However, while emphasizing the possible role of ACC-related self-monitoring deficits in autism, Mundy (2003) also noted that according to Devinsky and Luciano (1993) these ACC impairment-related behavioral deficits emerge only when they are combined with disturbances in other related functional neural networks, e.g., dorsolateral prefrontal cortex (DLPFC).

Perspectives of Application of ERP as Outcomes in Treatment Research

There are several important practical applications of ERP testing in neurodevelopmental disorders. The first one is the application of ERP tests for functional evaluation as this method has substantial diagnostic potential. The question of using ERP parameters as a diagnostic tool was discussed by Kemner, van der Gaag, Verbaten, and van Engeland (1999), who used multivariate analysis and found that several parameters (mainly P300) showed differences among patients with autism, ADHD, multiple complex developmental disorder (MCDD), and dyslexia. When ERP parameters were used as

variables in discriminate analysis, it was possible to classify several child psychiatric groups and a normal control group well above chance level, with classification occurring in 46% of the cases. When only clinical groups were compared (ASD, ADHD, MCDD, dyslexia), the classification correctness reached 60% (Kemner et al., 1999). However, autism is only one of numerous psychiatric and neurological disorders in which parietal P300 (P3b) is abnormal. Attenuated P3b was found in schizophrenia (Ford, 1999), bipolar disorder, ADHD, and alcoholism to name a few (review in Picton, 1992; Polich & Herbst, 2000; Pritchard, 1986) and cannot be considered as a specific marker for ASD. Expanding the topographical areas of ERP measurements (e.g., frontal, parietal, etc.) and adding earlier potentials (e.g., N100) and error-related potentials (i.e., ERN and Pe) may increase the diagnostic potential for clinical and functional evaluations of ASD.

Our error-related potential findings (Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Sokhadze, El-Baz, Tasman, et al., 2014; Sokhadze, Tasman, Sokhadze, El-Baz, & Casanova, 2016) revealed that autism is associated with reduced error processing and impaired behavioral correction after an error is committed. Because adequate error processing is necessary for optimal behavioral performance, it is plausible that these deficits contribute to the maintenance of the preservative behaviors typical for autism. Impairments in an ability to correctly and timely evaluate committed errors and to learn from errors may lead to behavior that is rigid and repetitive rather than adaptively guided by action outcomes. Deficits in adjustments of erratic behavior during interaction with peers may as well affect social interaction of children with autism and in those with ADHD. Elucidating the neurobiological basis and clinical significance of response monitoring and correction deficits in ASD and ADHD represents a promising direction for further qEEG, and specifically ERP-based, research. The ERP variables along with behavioral performance measures can be used as functional outcome measures to assess the effectiveness of behavioral interventions (e.g., Applied Behavioral Analysis [ABA] in ASD), cognitive-behavioral therapies (CBT; e.g., exposure therapy in PTSD) or neurotherapies (e.g., repetitive transcranial magnetic stimulation [rTMS] in ASD, or neurofeedback in children with ADHD or neurofeedback in adult patients with SUD) and thus may have important practical implications. The application of ERP indices in standardized

visual or auditory oddball tasks as an outcome measure in diagnostic and posttreatment evaluations seems to be a feasible approach considering the growing interest in qEEG assessments of individuals with neurological and psychiatric disorders.

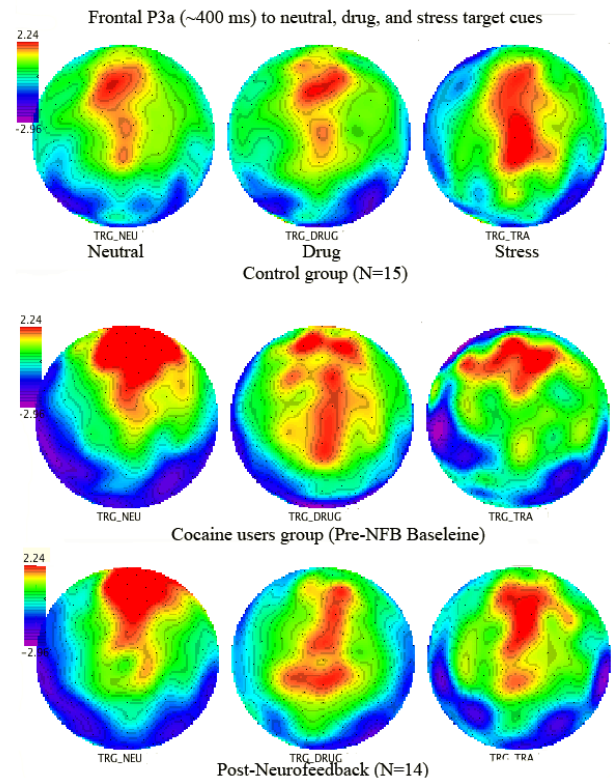


Figure 4. Topographic maps during drug- and traumatic-stress-related cue reactivity task in typical controls and patients with cocaine substance use disorder (CUD). There are depicted responses around 400 ms to neutral, drug-, and stress-related target cues in control and SUD group before and after Theta/SMR neurofeedback training course. Drug users as compared to controls showed at baseline test higher response in a form of enhanced P3a (red color) to drug cues at the fronto-central regions that were reduced post-neurofeedback training. It should be also noted that typical controls showed normative enhanced P3a to stress cues, while the SUD group had lower reactivity to stress cues at the baseline.

ERP Components as Biomarkers

To be useful as a biological marker, the changes in ERP biomarkers during cognitive tests have to be both sensitive and specific. Traditional neurophysiological studies compare a group of healthy controls with a group of patients and report significant differences in selected ERP measures.

This is a useful approach for diagnostic purposes, but it also needs to be linked with theoretical models that may advance understanding of brain function and neuropathology specific psychopathologies, for example, when comparing ASD and ADHD. To achieve this goal, it is necessary to use cognitive functioning tests and demonstrate that specific function abnormality is reflected in and correlates with specific ERP changes (Başar & Güntekin, 2008). A potential approach to achieve this goal is to identify the cognitive deficit typical for a patient group and use already known, or potentially useful, ERP correlates of this impaired function (e.g., the degree of attention deficit with ASD and ADHD). During performance on a cognitive task, patients with the pathologies of interest (ASD, ADHD) are proposed to yield ERP markers assessing the attention-related deficits as compared to the matched control group. The approach of studies for our group (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011) was based on using both stimulus-locked ERPs (e.g., frontal N100, P2a, P3a, parietal N200, P3b, etc.) and response-locked ERPs (ERN/Pe) during cognitive tests aimed to identify specifics of their alterations in ASD and in ADHD groups, as well as their differences from the neurotypical typical (NT) children, and consider them as useful biomarkers of above conditions.

Event-related Potentials in ASD and ADHD

ASD

ERP studies of visual processing commonly employ an oddball discrimination task of selective attention in which the participant responds to an infrequent target stimulus among more frequent nontarget stimuli (Vohs et al., 2008). Most investigations into visual processing in ASD have focused on higher level, long-latency ERPs, like the P300 (Courchesne, Courchesne, Hicks, & Lincoln, 1985; Courchesne, Lincoln, Kilman, & Galambos, 1985; Courchesne, Lincoln, Yeung-Courchesne, Elmasian, & Grillon, 1989; Hoeksma, Kemner, Kenemans, & van Engeland, 2006; Kemner et al., 1999; Townsend et al., 2001; Verbaten et al., 1991). The centro-parietal P3b amplitude has been found to be similar (Courchesne, Courchesne, et al., 1985; Courchesne, Lincoln, et al., 1985; Courchesne et al., 1989; Hoeksma et al., 2006), reduced (Townsend et al., 2001; Verbaten et al., 1991) and augmented (Kemner et al., 1999) in ASD to target stimuli compared to controls. There have been fewer studies on early-stage (i.e., 50–200 ms) visual processing in ASD (Jeste & Nelson, 2009). In our prior ERP study (Baruth, Casanova, Sears, & Sokhadze, 2010; Sokhadze, Baruth, et al., 2009) on

novelty processing in ASD, we reported that the ASD group showed significantly higher amplitudes and longer latencies of early frontal ERPs and delayed latency of P3a to novel distractor stimuli. Our results suggest low selectivity in pre-processing and late-stage overprocessing in integrative regions in the prefrontal cortices. Shorter latency and higher amplitude of the early frontal negativity in the autism group with minimal differentiation of response magnitude to either target or nontarget stimuli is an interesting finding that was replicated in several of our reports (Sokhadze, Baruth, Tasman, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, Casanova, & Baruth, 2013) where different visual oddball tasks were used. The visual N100 is considered as an index of stimulus discrimination (Hopf, Vogel, Woodman, Heinze, & Luck, 2002). The visual N100 generally is augmented during preattentive stimulus processing (Hillyard, Hink, Schwent, & Picton, 1973) and is larger towards task-relevant target stimuli (Luck et al., 1990). The ASD group shows clearly augmented and delayed frontal P3a that might result in an impaired early differentiation of target and nontarget items (e.g., on N100 stage) and more effortful compensatory strategies involved for successful target identification, as well as following correct motor response selection. In addition, frontal P200 (P2a) was found to be equally more positive to all stimuli in the ASD group with a lack of stimulus discrimination; as P2a were indiscernible between target and distracter stimuli in the ASD group, wherein in the control group P2a was more positive to targets. The P200 over frontal ROI has been associated with the hierarchical selection of task-relevant features (Kenemans et al., 1993). In ASD globally augmented cortical responses, especially to irrelevant stimuli at early stages of visual processing, probably are complicating stimulus discrimination processes at the stage of the P200. In general, the ASD group showed prolonged latencies to standard and rare nontarget illusory Kanizsa figures in a visual oddball task. These results suggest that individuals with ASD probably overprocess information needed for the successful differentiation of target and distracter stimuli. One of the possible explanations might be sought in the local hyperconnectivity hypothesis of autism. The topic of neural and functional connectivity abnormalities was always considered as an extremely important one in current ASD neuropathology theories (Belmonte et al., 2004; Courchesne & Pierce, 2005; Just, Cherkassky, Keller, & Minshew, 2004; Minshew & Williams, 2007; Welchew et al., 2005). Some authors consider ASD as disorder of neural connectivity (Coben, Chabot, & Hirshberg, 2013).

Our studies (Baruth, Casanova, El-Baz, et al., 2010; Baruth, Casanova, Sears, et al., 2010; Baruth et al., 2011; Casanova et al., 2012; Sokhadze, Baruth, El-Baz, et al., 2010; Sokhadze et al., 2012a; Sokhadze et al., 2012b; Sokhadze, Baruth, et al., 2009; Sokhadze, El-Baz, et al., 2009; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al. 2014) suggest that nontarget ERP responses in oddball paradigms should be routinely studied along with target responses in order to improve the diagnostic capabilities of cognitive ERPs. Notably, nontarget responses may help to decide whether abnormal responses to target (P3a, P3b) are related or not to a deficit in the mobilization of attentional resources (García-Larrea et al., 1992).

ADHD

Studies of P300 in ADHD have suggested that children with this diagnosis have attenuated P300 to both auditory and visual stimuli (Barry, Johnstone, & Clarke, 2003; Klorman et al., 1983; Klorman, Salzman, Pass, Borgstedt, & Dainer, 1979). A decreased P3b has been reported in conjunction with an augmentation at frontal sites (Banaschewski et al., 2003; Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004; Dimoska, Johnstone, Barry, & Clarke, 2003; Duncan et al., 2009; Johnstone & Barry, 1996; Johnston, Madden, Bramham, & Russell, 2011; Jonkman et al., 1997; Jonkman, Kenemans, Kemner, Verbaten, & van Engeland, 2004; Smith, Johnstone, & Barry, 2004). In ADHD populations, ERP studies which concentrated on visual selective attention found a smaller early frontal negativity in ADHD as compared to controls, suggesting deficiencies in early attention processes (Jonkman et al., 2004; Satterfield, Schnell, & Nicholas, 1994; van der Stelt, van der Molen, Gunning, & Kok, 2001), while no abnormalities were found for the N200. Studies using other attention paradigms (e.g., continuous performance, oddball and choice reaction time tasks) have provided evidence for smaller P3b in visual oddball tasks (Barry et al., 2003). In sum, several studies found reduced frontal amplitudes (e.g., N100, N200) in ADHD, which can be taken as suggesting a deficit in selective attention manifested in ERP alterations.

ERP as Trauma-related Cue Reactivity in PTSD

Whereas the P300 in general is thought to represent “context updating/closure” (Donchin & Coles, 1988), in three-stimuli oddball task the P3a is interpreted as “orienting,” and the P3b as an index of an ability to maintain sustained attention to target (Alho,

Lavikainen, Reinikainen, Sams, & Näätänen, 1990; Potts et al., 2004). The anterior P3a indexes the contextual salience of the rare stimuli, whereas posterior P3b is indexing task-relevance of the stimuli (Gaeta, Friedman, & Hunt, 2003). The three-stimulus category oddball paradigm provides possibilities for delineating the cognitive processes engaged in this task when motivational salience of novel distracter stimuli is manipulated. Among the most widely used manipulations are the selection of pictorial, auditory, or audio-visual modality cues related to trauma in patients with PTSD (e.g., gun shot in combat-related PTSD). These stimuli are used as rare novel distracters and the main ERP component of interest is usually fronto-central P300 (P3a). Higher novelty P3a amplitudes have been observed in responses to phobia-related images among persons with spider phobias and dental phobias (Kolassa, Musial, Mohr, Trippe, & Miltner, 2005; Schienle, Köchel, & Leutgeb, 2011). Meta-analysis of PTSD studies using ERP (Karl, Malta, & Maercker, 2006) noted higher P3a amplitudes to trauma-related pictorial cues in PTSD trauma-exposed subjects than in trauma-exposed subjects without PTSD.

Most of the studies on PTSD report abnormalities in the P300, which provide presumptive evidence for impaired cognitive processing in this disorder (Attias, Bleich, Furman, & Zinger, 1996; Blomhoff, Reinvang, & Malt, 1998; Charles et al., 1995; Felmingham, Bryant, Kendall, & Gordon, 2002; Karl et al., 2006; Kimble, Kaloupek, Kaufman, & Deldin, 2000; Stanford, Vasterling, Mathias, Constans, & Houston, 2001). Studies finding attenuated P300 attribute their results to concentration impairment (McFarlane, Weber, & Clark, 1993) or attention deficits (Charles et al., 1995; Metzger, Orr, Lasko, McNally, & Pitman, 1997; Metzger, Orr, Lasko, & Pitman, 1997). Increased P300 amplitude was explained as due to altered selective attention (Attias et al., 1996) or heightened orientation to threatening stimuli (Kimble et al., 2000). Several studies emphasize that P3a enhancement in PTSD is expressed when distracters are either trauma-related or novel stimuli in oddball tasks (Bleich, Attias, & Furman, 1996; Drake, Pakalnis, Phillips, Padamadan, & Hietter, 1991; Felmingham et al., 2002; Weinstein, 1995). Increased P300 (P3b) amplitude in PTSD is thought to reflect attentional bias towards threat stimuli and reduced P300 (P3b) amplitude is thought to reflect a consequent reduction in attentional resources to nonthreatening stimuli.

Some ERP-based Psychophysiological Approaches to Schizophrenia Research

One of the most trivial applications of ERP methods in psychopathology diagnostics is directed to the search of specific ERP features typical for the psychopathology of interest. The goal of such searches is to identify sufficiently sensitive and specific ERP markers for the particular mental disorder (schizophrenia, PTSD, etc.). Following modern concepts in psychophysiology, however, it should be considered that it is not a search for a single marker (e.g., centro-parietal P3b amplitude), but rather for multivariate discriminators of the patterns of ERP measures, even though such approaches are not yet frequently used in research and clinical applications. Psychophysiological studies based on ERP have an important role in the study of symptomatically heterogeneous, clinically diverse, and differentially medically treated psychopathologies. It is important to note that in psychophysiological oriented research it would be recommended, when possible, to analyze behavioral response during performance on tasks and concurrently analyze parameters of ERPs at preselected topographies, in order to identify the stage of information processing when cognitive dysfunction seems to be more obviously manifested. It seems feasible to illustrate some efficient applications of ERP methods, and in particular cognitive neuroscience techniques, for the understanding of the neurobiological basis and specifics of certain psychopathologies (e.g., schizophrenia) where auditory ERPs have been widely examined. Identification of those ERP altered in schizophrenia adds information about specifics of cognitive dysfunctions in this disorder. ERPs are a powerful tool to investigate the time course of brain wave activity during cognitive processing in schizophrenia because ERP components can serve as markers for cognitive processing stages. The ERP P300 analysis has already been routinely used in schizophrenia research in an oddball paradigm in auditory sensory modality. One of the main reasons for its broad application in psychopathology research is the fact that, in schizophrenia, attenuation of P300 amplitude and prolonged latency have been described by many researchers (Ford, 1999; Ford et al., 2001; Gallinat et al., 2002; Turetsky, Colbath, & Gur, 1998a, 1998b). P300 is often, but not always, observed to be more reduced over the left than right temporal lobes in patients with schizophrenia, as it was outlined by Ford et al. (2001). It can be definitely stated according to Turetsky et al. (1998a, 1998b) that reduced amplitude of the P300 ERP is a

robust and consistent finding in schizophrenic patients. The relationship between the frontal P300 and hallucinations is consistent with both the cognitive orienting function of this component and the role of the anterior cingulate in this ERP activity. Correlated left temporal and frontal dysfunction is consistent with fronto-temporal disturbance in some schizophrenics (Turetsky et al., 1998b). However, ERP abnormalities are not manifested only in P300 responses (P3a, P3b). The majority of studies reported findings that schizophrenics patients had reduced P300, N200, and N100 amplitudes and increased P300 latencies. The ERP abnormalities shown in most studies appear to be enduring trait of the disorder.

Conclusion

ERPs are reflecting stages of information processing. The analysis of ERPs could provide for important outcome measures, a potential cortical “signature” of response patterns associated with core behavioral and cognitive abnormalities that characterize various psychopathologies. Furthermore, when analyzed along with behavioral (reaction time, accuracy, etc.), response-locked potentials (e.g., ERN), event-related potential data-based biomarkers will offer insights into the psychophysiology of psychopathologies. The relative low cost of ERP methods means that the proposed biomarker will be accessible to many individuals and to those studies requiring large samples. EEG modalities are noninvasive and can be tolerated by many individuals who would otherwise not be able to participate in alternative studies (e.g., fMRI).

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