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The neurophysiology of P 300 – an integrated review

W.-J. HUANG, W.-W. CHEN, X. ZHANG

Department of Neurology, Xuzhou Central Hospital, Xuzhou, Jiangsu, China

Abstract. – Event-related potentials (ERPs) are very small voltages recorded from the scalp which originate in the brain structures in response to specific events or stimuli. They appear as a series of peaks and troughs interspersed in the Electroencephalogram (EEG) waves. The exact neural origins and neuropsychological meaning of the P300 are imprecisely known, even though appreciable progress has been made in the last 25 years. In this review, we will focus on the possible neural generators of this potential. Given the attention and memory operations associated with P300 generation, the first human studies on the neural origins of this ERP focused on the hippocampal formation using depth electrodes implanted to assess sources of epileptic foci in patients. Other lesion studies have found that the integrity of the temporal-parietal lobe junction is involved with either generation or transmission processes subsequent to hippocampal activity and contributes to ERP measures. These findings imply that hippocampal absence does not eliminate the P300, but that the temporal-parietal junction does affect its production. As mentioned till now, the neuroelectric events that underlie P300 generation stem from the interaction between frontal lobe and hippocampal/temporal-parietal function. ERP and fMRI studies using oddball tasks have obtained patterns consistent with this frontal-to-temporal and parietal lobe activation pattern. Further support comes from magnetic resonance imaging (MRI) of gray matter volumes that suggest individual variation in P3a amplitude from distracter stimuli is correlated with frontal lobe area size, whereas P3b amplitude from target stimuli is correlated with parietal area size. Given distinct neuropsychological correlates for P3a and P3b, different neurotransmitters may be engaged for each constituent subcomponent under specific stimulus/task processing requirements. Available data suggest that dopaminergic/frontal processes for P3a and locus-coeruleus-norepinephrine/parietal activity for P3b are reasonable to propose. This dual-transmitter P300 hypothesis is speculative but appears to account for a variety of findings and provides a useful framework for evaluating drug effects.

Key Words:

ERPs, Event-related potentials, P300, Temporal-parietal lobe junction, P3a, P3b, Dopaminergic/frontal processes, Locus-coeruleus-norepinephrine/parietal activity, Hyppocampus.

Introduction

Event-related potentials (ERPs) are very small voltages recorded from the scalp which originate in the brain structures in response to specific events or stimuli[1]. They appear as a series of peaks and troughs interspersed in the Electroencephalogram (EEG) waves. These originate in response to occurrence of a discrete event, which could be (1) presentation of a stimulus or (2) psychological reaction to a stimulus. These electroencephalographic (EEG) fluctuations are, thus, electric potentials time locked to sensory, motor or cognitive events. Recording these voltage fluctuations provides a safe and noninvasive approach to study psychophysiological correlates of mental processes. In terms of electromagnetic origin they are thought to reflect the summed activity of postsynaptic potentials produced when a large number of similarly oriented cortical pyramidal neurons (in the order of thousands or millions) fire in synchrony while processing information[2]. The ERPs have been classified in several different ways. The most common way of classification divides EPR waves into 2 categories: the early waves, or components peaking roughly within the first 100 milliseconds after stimulus, which are termed "sensory" or "exogenous" as they depend largely on the physical parameters of the stimulus. In contrast, ERPs generated in later parts of the recording (beyond 100 ms) reflects the cognitive evaluation of the stimulus and are termed 'cognitive' or 'endogenous' ERPs as they examine sensory information processing by the brain. The waveforms, thus, originating have been described and named according to latency and amplitude.

Corresponding Author: Xia Zhang, MD; e-mail: baogaozx@163.com

The P300, first described by Sutton et al[3], is perhaps the most extensively studied ERP component in investigations of cognitive functions. Sutton et al[3] described this waveform as *"the major waveform alteration in the amplitude of the positive-going component which reaches peak amplitude at about 300 ms"*. Subsequently in next few years the essential characteristics of the P 300 were described. Sutton et al[4] showed that the P 300 wave could be elicited by the omission of a stimulus if this omission was informative. The designatory name of P 300 is determined by the fact that its peak latency is about 300 ms when a young adult subject makes a sensory discrimination. Its other designation of P 3 wave comes from the fact that it is the third major positive peak in the later part of any evoked potential[5]. Ritter and Vaughan[6] used the "oddball" paradigm for the first time, wherein a subject detects occasional target signals randomly interspersed among more frequent standard stimuli. Subsequently Vaughan and Ritter[7] focussed on the distribution of this wave and observed that it was predominantly distributed over the parietocentral area of scalp. The details of this waveform along with its neurophysiological and neuropsychological correlates will be described in next sections. Concisely, P 300 wave is a parietocentral positivity that occurs when a subject consciously detects an informative task-relevant stimulus. The P300 has provided much fundamental information on the neural underpinnings of cognition[3,8]. Despite hundred of studies conducted since its discovery, the usefulness of P300 as a practical assessment tool remains limited because its neural generators are still unclear.

The Neural Generators of P 300

The neural generators of P300 remain imprecisely delineated, although appreciable progress has been made in the last 25 years[9-11]. Electrophysiologically, they are thought to reflect the summed activity of postsynaptic potentials produced when a large number of similarly oriented cortical pyramidal neurons (in the order of thousands or millions) fire in synchrony while processing information[2]. It is believed that multiple generators contribute to recording components N2 and P3 belonging to the P-300 Long Latency Auditory Evoked Potential, such as the supratemporal cortex, in the case of component N2, and the reticular formation, lemniscus, inferior colliculus, thalamus, primary cortex, frontal cortex, centro-parietal cortex and hippocampus[12,13], and that it is associated to information processing and not to the activity of the individual's memory[14]. This potential can be altered when there are deficits in the selective attention and alert mechanisms, state of conscience, and psychological conditions that impair attention[12,13].

The exact neural origins and neuropsychological meaning of the P300 are imprecisely known[11]. Given the attention and memory operations associated with P300 generation, the first human studies on the neural origins of this ERP focused on the hippocampal formation using depth electrodes implanted to assess sources of epileptic foci in patients. These recordings suggested that at least some portion of the P300 (P3b) is generated in the hippocampal areas of the medial temporal lobe[15,16]. However, subsequent investigations using scalp recordings on individuals after temporal lobectomy[17,18], experimental excisions in monkeys[19], and patients with severe medial temporal lobe damage[20,21] found that the hippocampal formation does not contribute directly to P300 generation[22]. Indeed, assessment of patients with bilateral hippocampal lesions demonstrated no statistically reliable P300 amplitude or latency differences relative to a matched control group[23]. Discrimination between target and standard stimuli in an oddball paradigm is hypothesized to initiate frontal lobe activity that is sensitive to the attentional demands induced by task performance[24-26]. fMRI and ERP findings have demonstrated frontal lobe activity for the detection of rare or physically alerting stimuli[27,28]. P3a may be generated when such stimuli are processed if sufficient attentional focus is engaged. Patients with frontal lobe lesions demonstrated diminution of P3a amplitude, whereas the same patients demonstrated a parietal maximum for the P3b. Frontal lobe integrity is, therefore, necessary for P3a generation[29,30]. Discrimination between target and standard stimuli in an oddball paradigm is hypothesized to initiate frontal lobe activity that engages the attention focus demanded by task performance[24-26]. Moreover, patients with focal hippocampal lesions evinced reducedP3a amplitude from novel distracters but normal P3b components from targets[31].

P300 amplitude is affected by temporal-parietal junction integrity as its absence greatly reduces component size over the parietal area[32-34]. This connection implies that the P3a and P3b indicate a circuit pathway between frontal and temporal/parietal brain areas[11,35,36].

P3b appears to occur when subsequent attentional resource activations promote memory operations in temporal-parietal areas[31,37,38,39]. Indeed, elegant cellular recording studies in primates indicate that information induced by changes in frontal activation during a matching-to-sample task is shunted to infero-temporal structures that index task context updating for future stimulus presentations[40]. Thus, it is reasonable to suppose that P3a and P3b generation stems from frontal and temporal/parietal activations[41,42]. This view is congenial with the neurocognitive assumptions that incoming stimuli invoke top-down attentions witching, and that bottom-up memory-driven operationsguide response organization and production[43-45]. ERP and fMRI studies suggest that a frontal attention mechanism governs neural responsivity to novelty[46-49], thereby, implying top-down control[50-53]. Attentional resources used to maintain memory items in parietal regions may result from response organization produced by bottom-up processing[54-56]. In sum, stimulus characteristics and task demands are determinants of distracter evaluation and contribute to the different topographic and timing outcomes observed at the scalp[57-60].

Other lesion studies have found that the integrity of the temporal-parietal lobe junction is involved with either generation or transmission processes subsequent to hippocampal activity and contributes to ERP measures[32-34,61]. These findings imply that hippocampal absence does not eliminate the P300, but that the temporal-parietal junction does affect its production. As outlined above, the P3a is produced when the attention focus required for the primary discrimination task is interrupted by an infrequent non target stimulus event, which does not have to be perceptually novel. ERP studies on humans with frontal lobe lesions have found that patients produced a clear diminution of the P3a from the distracter stimulus, with a parietal maximum for the P3b from the target stimulus[29]. Frontal lobe engagement is, therefore, necessary for P3a generation and mechanisms of attention control[30,35,62]. In addition, the hippocampal formation is also involved in "novelty" information processing, as patients with focal hippocampal lesions demonstrate reduced P3a amplitude from distracters but normal P3b components from targets relative to controls[31]. P3a amplitude from novel auditory distracter stimuli was virtually eliminated over frontal electrode sites for lesion patients compared to controls, whereas P3b amplitude from the target stimulus was generally similar between the groups at the parietal site.

ERP and fMRI findings have demonstrated frontal lobe activity for the detection of rare or alerting stimuli[27,28,63]. P3a appears related to the neural changes in the anterior cingulate when incoming stimuli replace the contents of working memory, and communication of this representational change is transmitted to infero-temporal lobe representation maintenance mechanisms[40]. P3b results from memory storage operations that are initiated in the hippocampal formation with the updated output transmitted to parietal cortex[31,39]. Thus, P3a is produced when a demanding stimulus commands frontal lobe attention; P3b is produced when attention resources are allocated for memory updating in association cortex.

As mentioned till now, the neuroelectric events that underlie P300 generation stem from the interaction between frontal lobe and hippocampal/temporal-parietal function[31,42]. ERP and fMRI studies using oddball tasks have obtained patterns consistent with this frontal-to-temporal and parietal lobe activation pattern[63-67]. Further support comes from magnetic resonance imaging (MRI) of gray matter volumes that suggest individual variation in P3a amplitude from distracter stimuli is correlated with frontal lobe area size, whereas P3b amplitude from target stimuli is correlated with parietal area size[68]. Such results may underlie individual P3a and P3b variability[50,69-71]. Initial neural activation during auditory oddball discrimination may originate from right frontal cortex[72], as P300 amplitude is larger over the right compared to left frontal/central areas[73-75]. After frontal processing of the incoming stimulus, activity appears to propagate between the cerebral hemispheres across the corpus callosum[76,77]. This hypothesis is supported by evidence that larger callosal fiber tracts are associated with larger P300 amplitudes and shorter latencies for left- compared to right-handed individuals[73,77,78], since these groups differ in their corpus callosum size[79,80].

Principal component analysis has been used for analysis of P 300. PCA has isolated the Supplementary Motor Cortex (SMC) or cingulate gyrus as the possible generators for the Novelty P3[81]. Another method of analysis, the Quadruple-dipole modelling of somatosensory-evoked P3b has localized its origin specifically to the hippocampal and parietal cortical regions[82]. The role of temporal-parietal junction has also been implicated by physical lesion studies which show that

with damage to tissue in this region, a loss of the P3b waveform is observed[35,83]. Invasive cerebral electrode recordings have also localized the temporal-parietal junction as the generator for the classical P300[84]. The analysis of auditory-evoked potentials by brain electric source analysis and multiple-dipole modelling indicates more specific regions of the hippocampus and temporal lobe as the putative generators of P 300[85].

P 300 in Neurological Conditions

Although P300 has been traditionally viewed as originating from superficial cortical structures, but it has also has shed light upon diseases linked etiologically to deep brain structures, including the basal ganglia. Especially efforts have been laid in evaluating its role in Parkinson's disease. For instance, it has been found that anterior P3a is attenuated in amplitude in patients with Parkinson's disease[86], with concomitant P300b anomalies[87]. Furthermore, differences in NOGO-P3 (and NOGO-N2) waveforms indicate dysfunctional frontal-lobar inhibitory processing[88], and may be useful as objective measures of Parkinsonian progression or functional limitation. Marked reduction or even absence of P3 distributions in visual search tasks has been observed in patients with the neurodegenerative disorders involving basal ganglia. These include choreiform movement disorder Huntingtons Disease, which classically demonstrates caudate nuclear atrophy, but also may manifest cortical symptoms (89). In addition to deeper structures, other neurological conditions involving cortex also show impairments in P 300. Alzheimer's disease, which typically affects the temporal and associative cortex regions, shows prolonged P300 latency and attenuated amplitude[90]. Based on these findings, it has been proposed that P300 activity may serve as a useful marker of attention and as a screen for combination-drug therapy in investigations of anti-Alzheimer drugs[91]. Traumatic or other insult to the prefrontal cortex is reflected in diminished amplitude of the novelty P3 response to a novel stimulus[29]. This amplitude change further correlates with reduced attentional shift towards novel stimuli[46].

P300 latency may also be applied clinically as a diagnostic tool and a prognostic marker for recovery after cortical insult although a consensus has not been reached in this context. A small study of patients with ischemic stroke has shown that changes in P300 latency correlated with subclincal damage to the right parietal lobe. In another study, magnitude of alteration in P300 in the subacute phase of stroke correlated with functional recovery after several months time[92]. Theoretically, P300 is likely comprised at the cellular level by a series of neuronal subnetworks which develop at differing rates.

The Neurotransmitters Involved in P 300

The neurotransmitters systems underlying P300 generation are as yet unclear, although various mechanisms have been implicated[93,94]. Given distinct neuropsychological correlates for P3a and P3b, different neurotransmitters may be engaged for each constituent subcomponent under specific stimulus/task processing requirements. Available data suggest that dopaminergic/frontal processes for P3a and locus-coeruleus-norepinephrine/parietal activity for P3b are reasonable to propose. This dual-transmitter P300 hypothesis is speculative but appears to account for a variety of findings and provides a useful framework for evaluating drug effects. These considerations and a strategy for evaluating acute and chronic drug-use effects are reviewed next. Several lines of evidence imply catecholaminergic mediation for frontal P300 generation: (1) Parkinson patients who have decreased levels of dopamine demonstrate deficient P300 measures[95,96]. (2) The dopamine antagonist sulpiride increases P300 in low-amplitude subjects and decreases it in high-amplitude subjects[97]. (3) Pharmacological studies have found dopaminergic mediation of P300 amplitude and latency[98,99]. (4) Children at elevated risk for alcoholism evince dopamine-related genetic differences associated with P300 amplitude deficits[100], which may be related to dopamine level differences underlying an "endophenotype of alcoholism"[101]. Although systematic amplitude topography comparisons of these effects have not been performed, the findings taken together suggest a frontal/central focus for the contribution of P3a to overall P300. In addition, a review of the wide-ranging P300 neuropharmacology literature suggests that the locus-coeruleus-norepinephrine (LC-NE) system underlies parietal P300 generation in a simple target detection task[55]. Since the neuropharmacological evidence stems primarily from ERPs elicited in rat, cat, and monkey populations, differences in paradigm and task performance need to be considered in evaluating these outcomes. However, the suggestion that locus-coeruleus-norepinephrine (LC-NE) contributes to P300 generation is consistent with attention resource

allocation and arousal-related effects in humans[102,103]. The topographic LC-NE activation of temporal-parietal areas also implies P3b contribution to overall P300.

Given that P3a is related to focal attention mechanisms mediated by dopaminergic activity and that P3b requires temporal-parietal integrity where dense NE inputs are found, a dual transmitter hypothesis underlying P300 generation appears plausible. One approach to these issues in humans is to assay ERP effects before and after acute drug intake and compare individuals who have been selected based on their chronic drug-use frequency. If P3a and P3b topographic distributions vary as a function of acute and/or chronic drug use, development of a metric for assessing individual reactions to drug effects can be pursued. Baseline, placebo, and drug challenge measures are obtained to compare low-use and high-use subject groups. If ERPs do not vary across experimental drug conditions (left panel), it is reasonable to infer that the underlying neurotransmitter systems are similar between the use groups. If ERP measures do vary across experimental drug conditions (right panel), it is reasonable to infer that the underlying neurotransmitter systems are different between the use groups. This approach permits the evaluation of acute and chronic drug use changes on the neurotransmitter systems that contribute to individual differences in ERP scalp recordings. Topographic changes in P3a and P3b from different drugs can, then, be developed to characterize how the central nervous system (CNS) is affected by short- and long-term changes to neurotransmitter systems.

The Dual Transmitter Hypothesis

The neurotransmitter systems underlying P300 generation are yet unclear, with various mechanisms implicated[93,94]. However, available data suggest that P3a is related to frontal focal attention and working memory mediated by dopaminergic activity, and that P3b is related to temporal-parietal activity where dense norepinephrine inputs are found[55,104- 107] The P3a and P3b amplitude data were obtained using a three-stimulus paradigm to compare unaffected controls, patients with restless leg syndrome, and patients with Parkinson's disease. Restless leg syndrome is thought to originate from dopaminergic deficits, with greater such deficits found for Parkinson's disease patients[108]. As indicated by the topographic mappings, P3a amplitude from the distracter stimulus is robust for the controls, decreased for the restless leg syndrome patients, and virtually eliminated for the Parkinson's patients. P3b from the target stimulus for the controls and restless leg patients is comparable, but greatly reduced for the Parkinson's patients. These data suggest that at least the P3a and some portion of the P3b are affected by dopaminergic activity[107].

Several lines of evidence imply catecholaminergic mediation of frontal P300 (P3a) generation: (1) Parkinson patients who have decreased levels of dopamine demonstrate deficient P300 measures[95,96]. (2) The dopamine antagonist sulpiride increases P300 in low-amplitude subjects and decreases it in high-amplitude subjects[97]. (3) Pharmacological studies have found dopaminergic mediation of P300 amplitude and latency[98,99]. (4) Children at elevated risk for alcoholism demonstrate dopamine-related genetic differences associated with P300 amplitude deficits[100], which may be associated with an ''endophenotype of alcoholism'' that likely originates from externalizing disorders[101,109]. A comprehensive review of the wide-ranging P300 neuropharmacology literature suggests that the locus coeruleus- norepinephrine (LC-NE) system underlies parietal P300 (P3b) generation for a target detection task[55]. Since the neuropharmacological evidence stems primarily from ERPs elicited in rat, cat, and monkey populations, differences in paradigm and task performance need to be considered in evaluating these outcomes. However, the suggestion that LC-NE contributes to P300 generation is consonant with attention resource allocation and arousal-related effects in humans[110,103,111]. The topographic LC-NE activation of temporal-parietal areas also is in agreement with overall P300 characteristics[112].

The Genetic Underpinnings of P 300

The genetic underpinnings for P300 are consonant with findings for ERPs and personality attributes such as introversion/extraversion, sensation seeking, and impulsivity[113,114]. Although the relationship among ERP measures and personality is murky, a correlation between individual differences for personality-related arousal levels and P300 is generally observed: low arousal individuals have smaller P300 amplitudes compared to high-arousal individuals who have larger P300 components[115,117]. This relationship is modulated by biological factors[102], differences among paradigms[118], and psychopathology[119-121]. These effects could be related to individual differences for attentional resource capabilities that may stem from variability for neurotransmitter function[100,107].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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