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The P300 wave of Event-Related-Potential.

Sheshav Somani *, and Jyostna Shukla.

Department of Physiology, S.M.S. Medical College, Jaipur- 302004. Rajasthan. India.

Review Article

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*For Correspondence

Department of Physiology, S.M.S. Medical College, Jaipur- 302004. Rajasthan, India.

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ABSTRACT

The brain is capable of elaborating and executing different stages of information processing. However, exactly how these stages are processed in the brain is still unknown. Discovery of the P300 event-related potential (ERP) stimulated the use of brain recording methods to assess human cognition. The P300 wave is considered to reflect an information processing cascade associated with attention and memory mechanisms. The P300 wave is a positive wave deflection in the human event related potential. The P300 wave is commonly elicited in an Oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. The P300 wave only occurs if the subject is actively involved in detecting the target stimuli. Its amplitude varies with the improbability of the target. Its latency varies with the difficulty to discriminate the target with standard stimuli. In patients with decreased cognitive ability, amplitude is smaller and latency is longer than age matched control subjects. The P300 is comprised of P3a that results from an early attention related process stemming from a working memory representational change, and P3b occurs when the attention-driven stimulus signal is transmitted to temporal and parietal structures. The exact neural origin of P300 wave is not known and its role in cognition is not clearly understood. The P300 wave may have multiple intracerebral generators including hippocampus and various association areas of neocortex. As the relationship between neurotransmitter function and the concomitant neuro electric signals recorded at the scalp are clarified, articulating how these variables interact will fulfil the cognitive promise that the P300 inspired when it was discovered over 40 years ago.

INTRODUCTION

The Event-Related Potential (ERP) is a time-locked measure of electrical activity of the cerebral surface representing a distinct phase of cortical processing [1]. ERPs provides online information about neurophysiological processes related to a range of cognitive tasks [2]. ERPs exhibit excellent time resolution, they reflect the processing of information millisecond by millisecond [3]. A convergence of approaches is beginning to limn the basic circuitry and transmitter systems related to P300 generation, with theoretical inroads being made into how this brainwave is associated with the experience of mental events [4].

The P300 wave is a centro parietal positivity that occurs when a subject detects an informative task relevant stimulus. The P300 name derives from the fact that its peak latency is about 300ms when a young adult subject makes a simple sensory discrimination [5].

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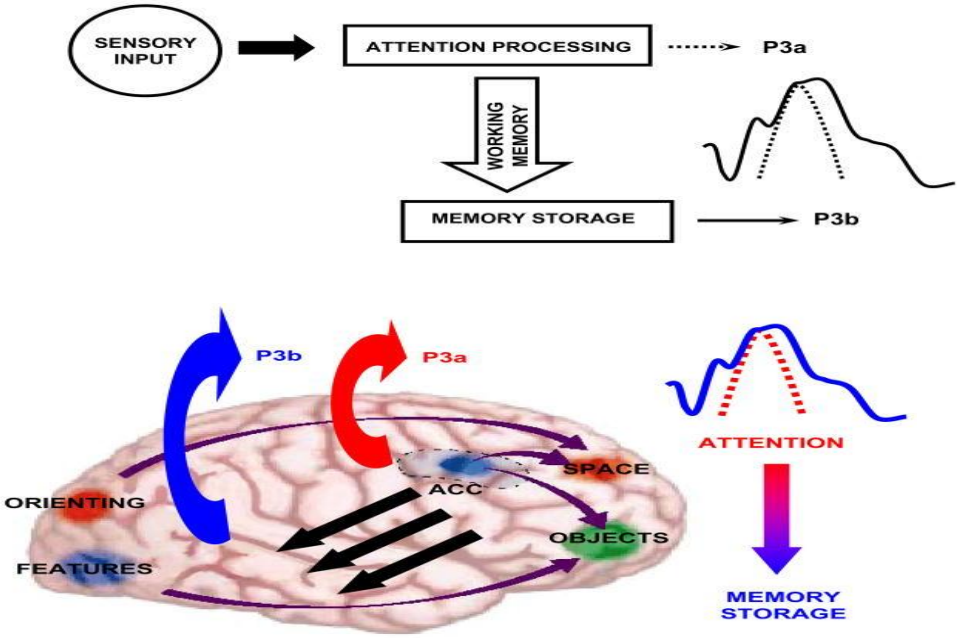
It has also been called the P3 Wave because it is the third major Positive peak in the late sensory evoked potential and Late positive component(LPC) [6].

Classically, the P300 response is divided into 2 sub components: P3a and P3b. The P3a component is mainly distributed in frontal regions and its usual latency ranges from 220 to 280milliseconds. P3a amplitude exhibits rapid habituation which depends on novelty of stimuli. P3a reflects automatic cognitive processing and the orientation response. This Novelty P300 is sometimes called the P3a [2].

In contrast, the P3b component presents a centro parietal topography and a longer latency usually comprised between 280 – 600milliseconds. For eliciting the P3b component, the subjects here must produce an active discrimination either by pressing a button or silent counting. The P3b is linked to the closure of cognitive processing before starting the motor response and is maximally distributed over parietal sites [7]. The functional significance of the P3a is not as well understood as that of the P3b. Indeed, the former component could reflect involuntary switching of attention (or attentional reallocation) to distraction from the primary task [8]. Another interpretation is that the P3a could reflect the inhibition of response processes that normally follow the detection of target stimuli [9]. The P3b is thought to reflect immediate memory mechanisms triggered when the mental model or schema of the stimulus environment is refreshed and updated [10]. In studies on ERPs, measurement of the P300 is generally centered on the P3b and elicited via an auditory or visual oddball paradigm (based on the detection of infrequent stimuli among a train of regular stimuli) [11].



Genesis of P300 (P3a & P3b)

Oddball Paradigm

In a very simple but widely used experimental task – the so called oddball paradigm – the participant is presented with two stimuli differing in some sensory characteristic (pitch of a tone, outlines of a geometrical shape, etc.). One of the stimuli (rare, target, significant) is presented relatively less frequently than the other (frequent, non-target, insignificant). A participant should make some response – either covert (such as silent counting) or overt (such as pressing a button) – to a rare target stimulus. The other stimulus does not require a response.

In this case, non-target deviant stimuli that disrupt the ongoing oddball task generate both a large fronto - central P3a or Novelty P3 [12] and a later parietal P3b [13,14,15].

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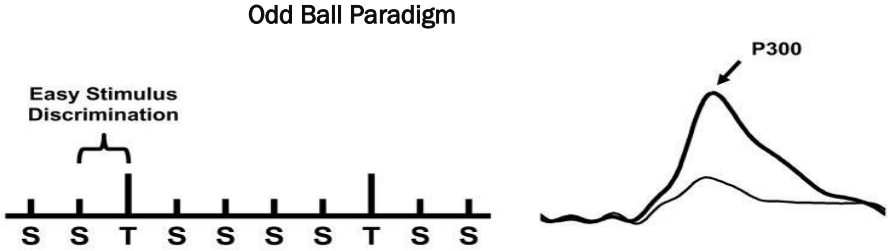
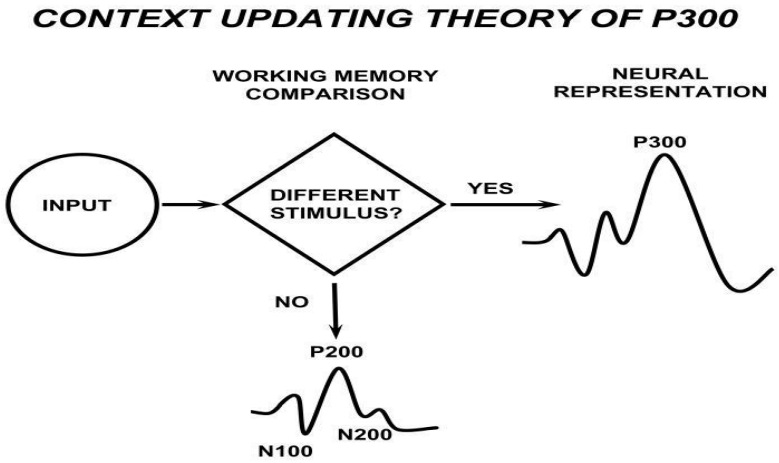


S - Standard or Frequent stimulus
T – Target or Infrequent stimulus

P300 Amplitude

Amplitude (μV) usually is defined as the difference between the mean pre stimulus baseline voltage and the largest positive-going peak of the ERP waveform within a time window determined by stimulus modality, task conditions, subject age, etc [4].

P300 scalp distribution is characterized as the amplitude change over the midline electrodes (Fz, Cz, Pz) that increases from the frontal to parietal electrode sites for target stimuli [16].



Context Updating Theory

The P300 indexes brain activities underlying revision of the mental representation induced by incoming stimuli [17]. After initial sensory input, an attention-driven comparison evaluates the representation of the previous event in working memory. If no stimulus attribute change is detected, the current mental model or "schema" of the stimulus context is maintained, and only sensory potentials are evoked. When a new stimulus is detected, the "updating" of the neural stimulus representation in working memory occurs and P300 is produced [4].

The context-updating hypothesis is the major theoretical account of P300, although other positions have emerged [18, 19]. However, as the P300 can reflect habituation and dishabituation, this ERP component clearly indexes fundamental attention and memory-related operations [20,21].

Resource Allocation and P300

The P300 context-updating ion hypothesis was derived in large measure from manipulating target stimulus probability in the oddball task. Discriminating a target from a standard stimulus produces a robust P300 that increases in amplitude as the global and local sequence probability for the target stimulus decreases [22,23]. These findings implied that P300 originates at least in part from working memory comparisons, and that conscious awareness may be related to stimulus sequence effects [24,25]. P300 amplitude reflects the neural activity related to memory when the stimulus context is updated [26].

P300 amplitude therefore reflects the strength of memory formed during encoding and storage processes that varies across serial position in recognition tasks [4].

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Target to Target Interval

TTI determines how quickly resources can be redirected to process target stimuli [27].

P300 event related potential (ERP) measures are affected by target stimulus probability, the number of non targets preceding the target in the stimulus sequence structure, and inter stimulus interval (ISI). Each of these factors contribute to the target to target interval (TTI), which also has been found to affect P300. Amplitude increased as TTI increased for both auditory and visual stimulus conditions, where as latency tended to decrease with increased TTI [28].

P300 Latency

Latency (ms) is typically defined as the time from stimulus onset to the point of maximum positive amplitude within this same time window [4].

P300 latency is thought to index classification speed, which is proportional to the time required to detect and process a target item [29, 30]. P300 peak latency changes over the scalp and is shorter over frontal areas and longer over parietal areas [31,32]. Semantic-based compatibility tasks produce a larger P300 latency/response time difference compared to spatial compatibility tasks. Furthermore, P300 latency has been used as a metric for timing mental events producing other ERP components [33,34]. P300 may originate from the neural events that link stimulus perception and event response [35].

Individual differences for P300 latency are correlated with mental speed, such that shorter latencies are related to superior cognitive performance [36]. The neuropsychological tests that produce the strongest correlation between P300 latency and cognitive capability assess how rapidly subjects can allocate attentional resources [37,38]. P300 latency decreases as children develop[39,40] and increases with normal aging.[41,42] Component latency also becomes longer as dementia level increases[43,44], although how brain insult or disease prolongs ERP timing is unclear [45,46].

P300 wave Physiological Variations

1. *Gender* – Women and men have no statistically significant differences in the ERP Parameters [47].
2. *Age* – With increasing age, P300 wave amplitude declines and latency increases linearly due to slowing down of information processing and a decline of short term memory [45].
3. *Circadian rhythms* – Despite some variation, no statistically reliable results were found for either P300 amplitude or latency, but some variations are due to variation in arousal level [48].
4. *Food intake* – P300 amplitude is reduced when food has not been consumed recently and increased when food is ingested. P300 latency is relatively unaffected by recency of food intake. It may be related to general changes in arousal level with food consumption [49].
5. *Seasonal variation* – It depends on the amount of daylight that varies with the seasonal change. Seasons with more light might be conducive to increased activity and overall arousal [50].
6. *Menstrual Cycle* – P300 amplitude is found to be larger during ovulation than at other times [51]. The affective or arousal quality of stimulus items can interact with hormonal changes and contribute to P300 Variability when the eliciting stimulus is emotionally neutral.
7. *Exercise* – Exercise can contribute to intellectual performance and imply that energetical activities affect the CNS and, therefore cognitive function. Frequent physical exercise may also have facilitatory effects on mental performance [52].
8. *Sleep Deprivation* – P300 amplitude tends to decrease and latency increase as sleep begins and with sleep disorders that produce fatigue demonstrating similar results [53]. Hence, changes in arousal level stemming from sleep and its disruption affect P300 amplitude and latency.
9. *Drugs*: Caffeine affects P300 amplitude and to a lesser extent peak latency depending on the level of mental fatigue. These findings suggest that caffeine effects on P300 wave are influenced by arousal level [54].

   Tobacco can affect both latency and amplitude measures. It is suggested tentatively that nicotine contributes to electro cortical activity most likely by affecting arousal level, and that these changes influence P300 amplitude and latency depending on the dosage level and the task performed.[55,56]

Neuropsychology of P3a and P3b

Several ERPs appear related to the P3a, which are elicited by distracter stimuli inserted into the target/standard sequence. When perceptually novel distracters (dog barks, color forms, etc.) occur in a

series of more typical stimuli (tones, letters of the alphabet, etc.), a frontal/central P300 can be elicited with a relatively short peak latency that rapidly habituates [57, 58]. This potential has been called the "novelty P300" and is interpreted as reflecting frontal and hippocampal activity [59].

As novelty P300 amplitude decreases with repeated stimulus presentations, it may be more directly related to the orienting response than the P3b [60, 61]. If non-novel repeated stimuli (tones, letters, etc.) are used as distracters that do not require a response in a three-stimulus oddball, a "no-go" P300 is elicited [62,63]. The P300 from this type of distracter has a maximum amplitude over the central/parietal areas [64,65]. The scalp distribution for the no-go P300 is more central than the target P300, which has linked the no-go to response inhibition mechanisms [66]. Replication of the original visual novelty P300 tasks compared novel non-repeating abstract color stimuli and non-novel repetitive 33 blue-square distracters [8]. The easy task yielded a central maximum distribution for the novel stimuli and a central/parietal maximum P300 potential for the non-novel stimuli i.e., the same topography as the no-go P300. The hard task produced central maximum topographies for both the novel and non-novel distracters. P3a has a central maximum, whereas P3b has a parietal maximum. Peak latency for both potentials was shorter over the frontal and longer over the parietal electrode sites. P3a and P3b have distinct topographic amplitude distributions.

Novelty processing is modulated by contextual and familiarity effects. Non-repeating stimulus events define novel items, whereas repeating stimulus events engage top-down processing so that novelty P300 and P3a may differ with respect to how attentional processes are engaged for distracter stimuli.[67] Stimulus evaluation engages focal attention (P3a) to facilitate context representational maintenance (P3b), which is associated with memory operations [4, 60].

Neural origins of P3a and P3b

P300 neural generators are imprecisely delineated, although appreciable progress has been made in the last 25 years [68]. Patients with frontal lobe lesions demonstrated diminution of P3a amplitude, whereas the same patients demonstrated a parietal maximum for the P3b. Frontal lobe and hippocampal integrity are therefore necessary for P3a generation [69]. Some portion of the P300 (P3b) is generated in the medial temporal lobe. P3b amplitude is positively correlated with hippocampal size relative to the temporal lobe size. Integrity of the temporal-parietal lobe junction is involved with either transmission or generation processes subsequent to hippocampal activity and contributes to component recordings at the scalp [70]. These findings suggest that P3a and P3b are produced by a neural circuit pathway between frontal and temporal/parietal brain areas.[8] 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 [71].

P3a may be generated when such stimuli are processed if sufficient attentional focus is engaged. P3b appears to occur when subsequent attentional resource activations promote memory operations in temporal-parietal areas [72]. 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 stimulus presentations.[73] It is therefore reasonable to suppose that P3a and P3b generation stem from frontal and temporal/parietal activations respectively [74].

A frontal attention mechanism governs neural responsively to novelty, thereby engaging top-down control [75]. 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.

Neuro Pharmacology of P300

Dual Transmitter Hypothesis

The exact neurotransmitter systems underlying P300 generation are unclear, although various mechanisms have been implicated [76]. Available data suggest that since P3a is related to frontal focal attention and working memory, it is likely mediated by dopaminergic activity. Since P3b is related to temporal-parietal processes, it is associated with with norepinephrine activity [77]. The locus-coeruleus-norepinephrine (LC-NE) system underlies parietal P300 (P3b) generation for a target detection task. The suggestion that LC-NE contributes to P300 generation is consonant with attention resource allocation and arousal-related effects in humans [78]. The topographic LCNE activation of temporal-parietal areas also is in agreement with overall P300 characteristics [19].

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Clinical Relevance

1. *Alzheimer's disease* – P300 amplitude is found to be typically smaller and latency longer for Alzheimer's disease patients compared to unaffected controls [79,80]. P300 measures for Alzheimer's disease are relatively stable regardless of task or modality and can discriminate between Alzheimer's disease and controls at the group level [46].
2. *Alcoholism* – P300 amplitude is reduced and P300 latency is prolonged.[81] The explanation usually given is that alcoholic patients exhibit arousal, attentional and memory disturbances. P300 amplitude reduction could be related to family history of alcoholism. P300 amplitude is reduced in subjects at high risk for alcoholism compared to subjects at low risk [82].
3. *Schizophrenia* – Earlier studies have shown lower P300 amplitude compared to controls because the task requires a cognitive effort that is impaired [83]. Recent studies has shown that in schizophrenic patients P300 amplitude is particularly lowered in the left temporal regions, and this finding is not influenced by medication of the patients [84]. This finding is probably due to reduction in the volume of gray matter in the left anterior Hippocampus – amygdala and the left superior temporal gyrus with enlargement of left sylvian fissure [85].
4. *Depression* – Earlier studies have found reduced P300 amplitude in depression. Information processing alterations found in depressions could be localised on preparations, selection and motor processes prolonged reaction time rather than on later stages of information processing as evidenced by normal P300 latency. A significant co relation was found between P300 amplitude and the suicidal risk scale [86].
5. *Post Traumatic Stress Disorder* – Many studies have found lower P300 amplitude in patients as compared to controls who were exposed to a traumatic event without developing the disorder [87].
6. *Panic Disorder* – A clinical feature of panic disorder is the loss in the capacity to integrate incoming information with a cognitive context. P300 amplitude is unpredictable in panic disorder [88]. P300 latency is found to be prolonged [89].

Brain fingerprinting

Brain fingerprinting is a controversial forensic science technique that uses electroencephalography to determine whether specific information is stored in a subject's brain. It does this by measuring electrical brainwave responses to words, phrases, or pictures that are presented on a computer screen.

History

Farwell's brain fingerprinting originally used the well known P300 brain response to detect the brain's recognition of the known information. Later, Farwell discovered the P300-MERMER "Memory and Encoding Related Multifaceted Electroencephalographic Response", which includes the P300 and additional features and is reported to provide a higher level of accuracy and statistical confidence than the P300 alone. Farwell and colleagues report less than 1% error rate in laboratory research and real-life field applications [90].

Technique

The application of this in brain fingerprinting is to detect the P300 as a response to stimuli related to the crime or other investigated situation, e.g., a murder weapon, victim's face, or knowledge of the internal workings of a terrorist cell.[91] Because it is based on EEG signals, the system does not require the subject to issue verbal responses to questions or stimuli. The person to be tested wears a electrode cap with EEG recording electrodes that measure the EEG from several locations on the scalp. The subject views stimuli consisting of words, phrases, or pictures presented on a computer screen. Stimuli are of three types:

- "Irrelevant" stimuli that is irrelevant to the investigated situation and to the test subject.
- "Target" stimuli that are relevant to the investigated situation and are known to the subject, and
- "Probe" stimuli that are relevant to the investigated situation and that the subject denies knowing.

Probes contain information that is known only to the perpetrator and investigators and not to the general public or to an innocent suspect who was not at the scene of the crime. Before the test, the scientist identifies the targets to the subject, and makes sure that he/she knows these relevant stimuli. The scientist also makes sure that the subject does not know the probes for any reason unrelated to the crime, and that the subject denies knowing the probes. The subject is told why the probes are significant

(e.g., "You will see several items, one of which is the murder weapon"), but is not told which items are the probes and which are irrelevant [91].

Since brain fingerprinting uses cognitive brain responses, brain fingerprinting does not depend on the emotions of the subject, nor is it affected by emotional responses. Brain fingerprinting is fundamentally different from the polygraph (lie-detector), which measures emotion based physiological signals such as heart rate, sweating, and blood pressure. Also, unlike polygraph testing, it does not attempt to determine whether or not the subject is lying or telling the truth. Rather, it measures the subject's brain response to relevant words, phrases, or pictures to detect whether or not the relevant information is stored in the subject's brain [92].

By comparing the responses to the different types of stimuli, the brain fingerprinting system mathematically computes a determination of "information present" (the subject knows the crime-relevant information contained in the probe stimuli) or "information absent" (the subject does not know the information) and a statistical confidence for the determination. This determination is mathematically computed, and does not involve the subjective judgment of the scientist.

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