Chapter 1

Event-Related Potentials for the Study of Cognition

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http://dx.doi.org/10.5772/intechopen.69308

Abstract

Despite the vast literature on event-related potentials (ERPs), many clinical professionals are still unaware of the huge variety of possible applications they offer. The aim of this chapter is not to show the classical use of ERPs, focused on analyzing the first steps of information processing (sensory pathways). On the contrary, this chapter will be focused on the use of these ERPs in the assessment of cognitive function. In particular, this chapter is mainly focused on the use of ERPs to better understand the neural bases of cognitive impairment from the electrical activity of the brain. Describing all the possible ERP components and their cognitive meaning is a huge endeavor, and this chapter will only be focused on three of them: contingent negative variation (CNV), mismatch negativity (MMN), and P300. To improve the reader's knowledge about these ERPs in cognition, a specific description will be given about the stimulation required to obtain the specific component, the topography, and latency shown. Moreover, a description of the neurophysiological bases of the component, its relationship with psychological processes and neural sources will be also included. Pathological alterations suffered by the component will also be briefly described.

Keywords: cognition, ERPs, latency, neural sources, pathology, topography

1. Introduction

Since the 1960s, a prolific literature has been produced on the field of event-related potentials (ERPs), related to the study of cognitive activity in the brain. In the beginning, these studies were more directed to the study of sensory and motor pathways. However, from studies such as in Refs. [1–3], ERPs were related to cognitive processes such as relevance of the stimulus, uncertainty, or mismatch with a previous stimulus.

Up to the present day, many studies have been published by numerous groups worldwide using this technology. In spite of the crisis that the ERP technique suffered due to the arrival

of neuroimaging, ERPs have survived, and nowadays, still offer an interesting way to explore the cognitive activity with a direct measure of the electrical activity of neurons.

One of the main challenges that ERPs have to overcome is their application in the clinical field through studies that verify the reliability of the technique. Nevertheless, it is necessary to define the possible applications of these potentials to better understand the etiology of cognitive pathology and develop possible therapeutic targeting in this field.

In this chapter, three important ERPs will be detailed: contingent negative variation (CNV), mismatch negativity (MMN), and P300. For each one, several topics will be tackled: (1) a generic description of the component; (2) a brief definition of a procedure that allows evoking the component; (3) evidence of psychological variables that can modulate the component; (4) neurophysiological basis, typical topography, and latency of the component; (5) neural sources identified; (6) alterations that the component suffers in some diseases and its probable meaning.

These three components have been selected because of the order in which they appear in information processing. The first one, CNV, is related to the instants prior to the onset of a stimulus that is expected by the subject. MMN is related to the early phases of the cognitive processing for the stimulus that is evaluated. And finally, P300 represents late phases of the perceptual process and includes many psychological processes of high order.

2. Contingent negative variation (CNV)

2.1. Generic description

In 1964, Walter et al. [2] published a study in which an event-related potential was present prior to the appearance of the stimuli. The psychological meaning of this component was defined as the expectancy caused by a warning stimulus (also called sometimes "cue") that allows the subject to prepare a response in order to react faster and more accurately to the incoming stimuli (known as "imperative stimuli").

2.2. Procedure and characteristics of the component

Diverse paradigms have been used to elicit CNV in diverse sensory modalities: visual [4]; auditory [5]; or the interaction between visual and auditory stimulation [6], and even with proprioceptive information [7]. In the last few years, one of these paradigms has been called "Attentional Network Test (ANT)," which has been highly popular in the study of attentional mechanisms such as expectancy or orienting [8–10]. Depending on the stimulus onset asynchrony (SOAs) used, CNV is present between warning and imperative stimuli in this task [4, 11]. In a basic conception of the ANT paradigm, cues are shown for 150 ms, and then a variable SOA can be defined in a range between 1000 and 2000 ms when the CNV is present. Finally, an imperative stimulus is displayed, and the subject has to respond according to the instructions of the task (see Ref. [4] for a complete description of the parameters of the task; see also **Figure 1** for a schematic of this procedure).

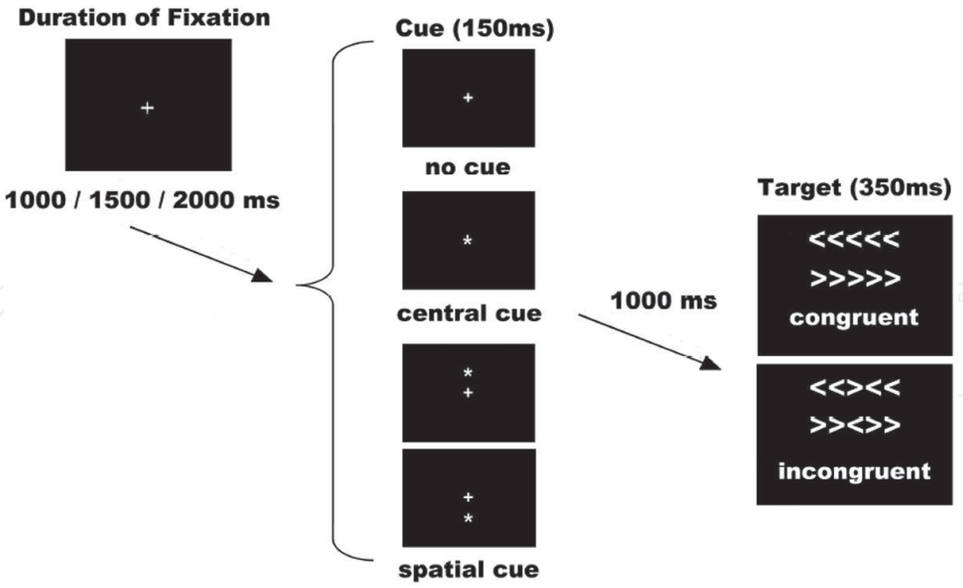

Figure 1. Schematic representation of attention network test. Adapted from Galvao-Carmona [4].

During its history, CNV has been studied extensively in terms of psychological variables that can modulate it. One of the earliest studies was about how uncertainty affects CNV [12]. In the case that the subject is not certainly sure when the imperative stimuli will be displayed, the amplitude grows fast; however, in the case that the subject knows approximately when the imperative stimuli will be presented, the amplitude grows gradually. In the case that there is no need to respond to the stimuli following the warning cue, CNV is not usually elicited [12]. However, some studies have shown that a nonmotoric activity is evoked in the absence of direct overt motor activity [13].

Another interesting fact is that even when the subject is not warned by a cue, there is a slow negative trend in the human brain that represents our general expectancy during an experimental session [4] (see **Figure 2**).

In regard to its relationship with development, Segalowitz and Davies [14] published a study in which it is possible to see the evolution of this component along infancy and adolescence.

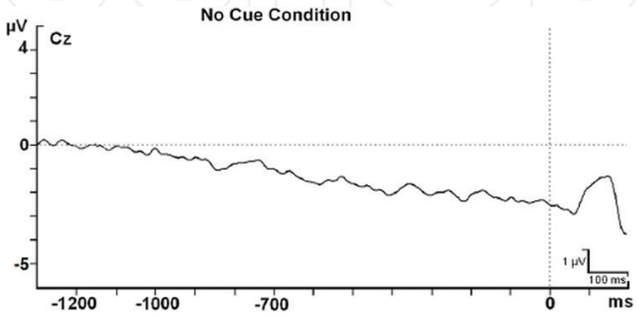

Figure 2. CNV component modulation in the no-cue condition showing a general expectancy during the execution of a warning-target paradigm. Zero value in *x*-axis represents the onset of the imperative stimuli. Adapted from Galvao-Carmona [4].

An increase in the amplitude is correlated with age and represents the maturation of the frontal lobe and, consequently, better behavioral capacities. In the elderly population, CNV has been used to detect different psychological processing of cue-relevant information between this population and younger subjects [15].

The latency of this component depends on the task employed. Sometimes, CNV reaches a peak (or valley) around 400 ms after the onset of the warning stimuli [12]. In other occasions, the component does not reach this maximum negative point and displays a continuous trend to negative values until the imperative stimuli show up [4]. Indeed, one of the critical variables for CNV is the SOA between warning and imperative stimuli [16]. In the case that a SOA of 3 or more seconds is used, two subcomponents can be observed. First, an O-wave, where O represents "Orienting" [17], is present at the beginning of the CNV trace, and then, an E-wave (expectancy and response preparation) [18] appears prior to the onset of the imperative stimulus. If the SOA is reduced, both subcomponents are confounded [19].

With respect to topography, CNV usually shows a maximum value in the vertex, which is symmetrically distributed over the scalp [4]. However, if the subcomponents are clearly distinguished, the O-wave is mainly frontal, and the E-wave is more postcentrally located [19].

The identification of the neural sources for this component remains under debate, perhaps due to the complete set of different processes present in the CNV latencies. Using magnetoencephalography, some authors [20] determined that the neural source for the magnetic counterpart of the CNV was located in the premotor cortex (Brodmann Area 6). In another study, Zappoli described that patients with lobotomy of frontal lobes exhibited decreased amplitude of the CNV [21]. In a study performed in our lab, in which different time intervals of the CNV trace were analyzed, numerous cortical areas were active, and a complex dynamic was present during the process [4]. These cortical areas belong to different lobes, including the frontal, parietal, occipital, and other regions, such as the cingulated lobe and insula, among others (see **Figure 3**).

2.3. Psychological meaning and pathology

Once the component was described, many studies have been performed to find alterations in the component and the possible meaning in diverse pathologies. In Huntington disease (HD), de Tommaso et al. [22] examined a sample of mild, demented, and nonmedicated HD patients. The main result was that CNV amplitude was reduced in these patients compared to healthy control subjects, and this reduction was significantly correlated to the bradykinesia score. A strong activation in the posterior part of the cingulated cortex in HD is likely responsible for the amplitude reduction, and some authors suggested that it is probably caused by a basal ganglia dysfunction.

With regard to Alzheimer's disease, Zappoli et al. [23] found no significant CNV activity in these patients, who also showed slower reaction times and other EEG alterations. However, another group [24] observed that the CNV amplitude was not different between groups, also showing low test-retest reliability, which makes it difficult to be applied in the clinical field.

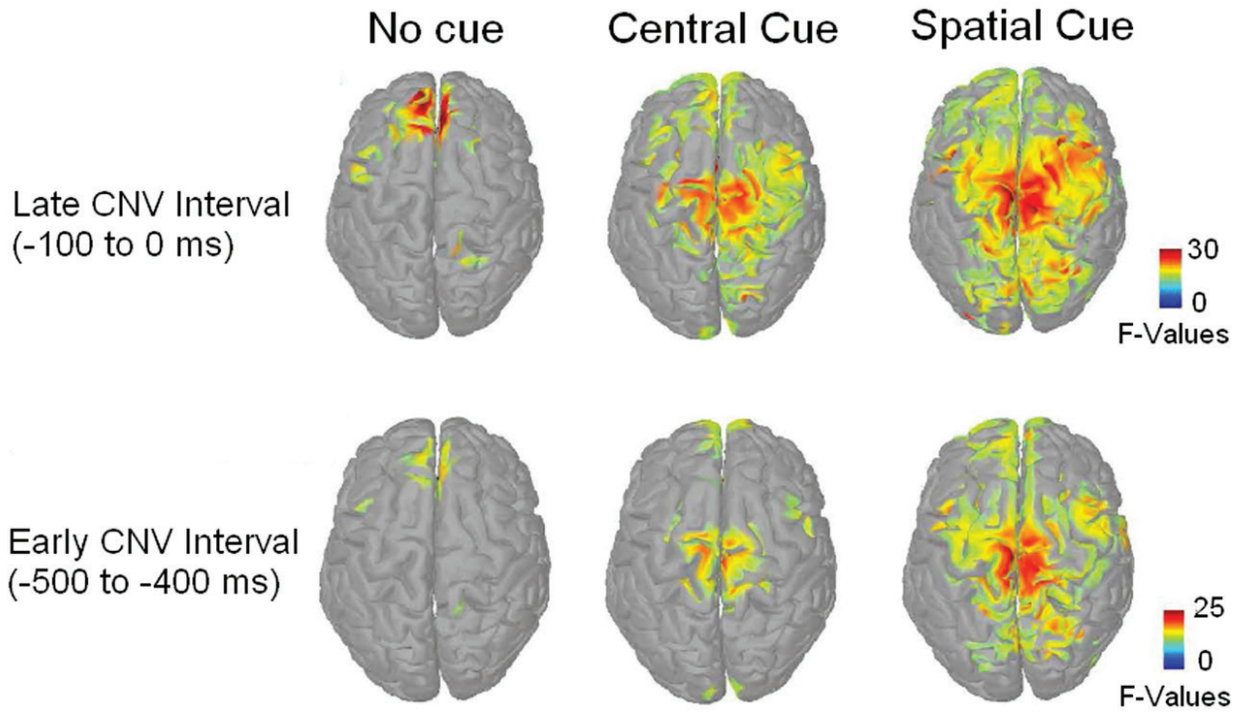

Figure 3. Cortical activation maps presented in *Z*-scores according to the baseline and showing significant activity (FDR-adjusted $p < 0.01$). Sources of the CNV effect were estimated in 2 CNV intervals of interest, −500 to −400 and −100 to 0 ms before the target stimulus. Adapted from Galvao-Carmona [4].

In other pathologies, CNV has been used to determine if any anatomical structure could be related to a specific cognitive impairment. For instance, Kuoppamäki et al. [25] observed that Parkinson patients with bilateral lesions in the globus pallidus present a deficit in motor tasks and alterations in the early phases of CNV.

From our laboratory, a study in a sample of multiple sclerosis patients, reduced amplitude of CNV was associated with impairment in the alerting and orienting attentional mechanisms. These results were also in accordance with neuropsychological scores from attentional tests [26] (see **Figure 4**).

In the psychopathological field, one of the main disorders studied with CNV has been schizophrenia. Some authors have described a reduction of the amplitude related to the frontal lobe dysfunction, and it was manifested in the frontal-central derivations and at the early CNV phase [27]. At the same time, some studies have been focused on the relationship between CNV and some items of questionnaires used in the assessment of negative or positive symptoms [28]. Another interesting field is related to the study of the neural mechanisms underlying cephalea and migraine. In their study, Siniatchkin et al. [29] selected three groups: migraine, chronic daily headache, and healthy control subjects. CNV values were lower for the migraine group, especially at the beginning of the CNV. Chronic daily headache patients showed a reduced negativity of the late component of CNV. An interesting result was the absence of habituation to CNV in both types of patients and the potential application of CNV in diagnostic and therapeutic strategies for these pathologies.

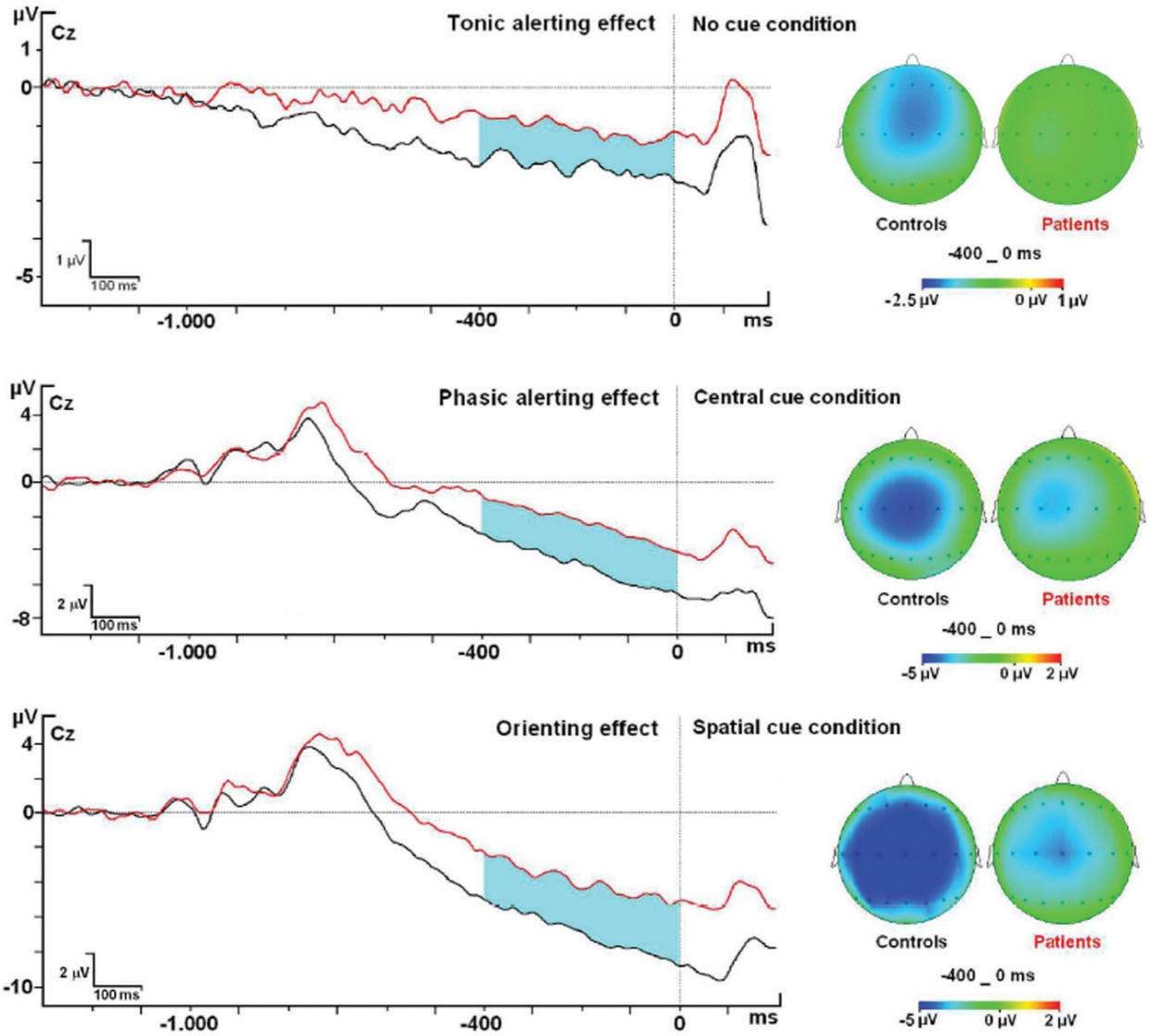

Figure 4. Contingent negative variation modulations at Cz electrode and topographic maps for healthy control subjects and patients in the attention network test. Adapted from Vazquez-Marrufo [26].

3. Mismatch negativity (MMN)

3.1. Generic description

Described for the first time by Näätänen et al. [3], mismatch negativity appears when a change in a stream of stimulation is detected. This generic fact has been employed in different approaches for studying the bases of cognition in healthy and pathological subjects.

3.2. Procedure and characteristics of the component

A typical way to obtain this component consists of using an auditory oddball task, in which two types of stimuli are listened to binaurally through headphones: standard stimuli (1000 Hz tones and a probability of 0.80) and deviant stimuli (2000 Hz tones and a probability of 0.20).

The interstimulus interval can be around 1 s, and the intensity of auditory stimuli can be set at 70 dB. The duration of the stimuli is 50-ms plateau and a 10-ms rise-fall time. Two blocks with 200 trials (including 80 deviant stimuli) are enough to obtain the MMN [30]. See **Figure 5** for a schematic representation of the experimental procedure.

The component can be elicited during active tasks (counting deviant stimuli) [30] or during passive tasks [3]. Indeed, this last option can be extremely useful in some pathological conditions, such as coma [31]. MMN shows up as the result of subtraction between the standard and deviant associated waves. This component is evoked not only by a change in the frequency but also in pitch duration, intensity of stimuli…, and so forth. [32]. Other properties such as short SOAs [33] or the saliency of the deviant stimuli [34] produce greater MMN amplitudes.

Although MMN is usually based on auditory procedures, it can also be obtained with visual stimulation [35, 36] or even other sensory modalities [37]. The component is present even in newborns [38], and, during childhood, MMN presents differences in latency and topography with respect to adults, which suggests a development of the component throughout youth [39]. In healthy aging, elderly subjects showed a reduction in the amplitude [40], as well as a delay in the latency [41].

With regard to the specific parameters of the component, the latency is between 150 and 250 ms after the onset of the stimuli, and its distribution is fronto-central in the scalp (although the topography depends on the location of the reference) [42]. In auditory paradigms, neural generators are located in the primary and nonprimary auditory cortex, although they can also include frontal lobe areas, the thalamus, and the hippocampus, as evidenced by intracranial studies with animals [42].

3.3. Psychological meaning and pathology

The main application of MMN has probably been as an exponent of accuracy in the discrimination of small changes in stimuli in untrained [43] or trained subjects [44]. Since the presence of standard stimuli is necessary for obtaining MMN in deviant stimuli, this component has

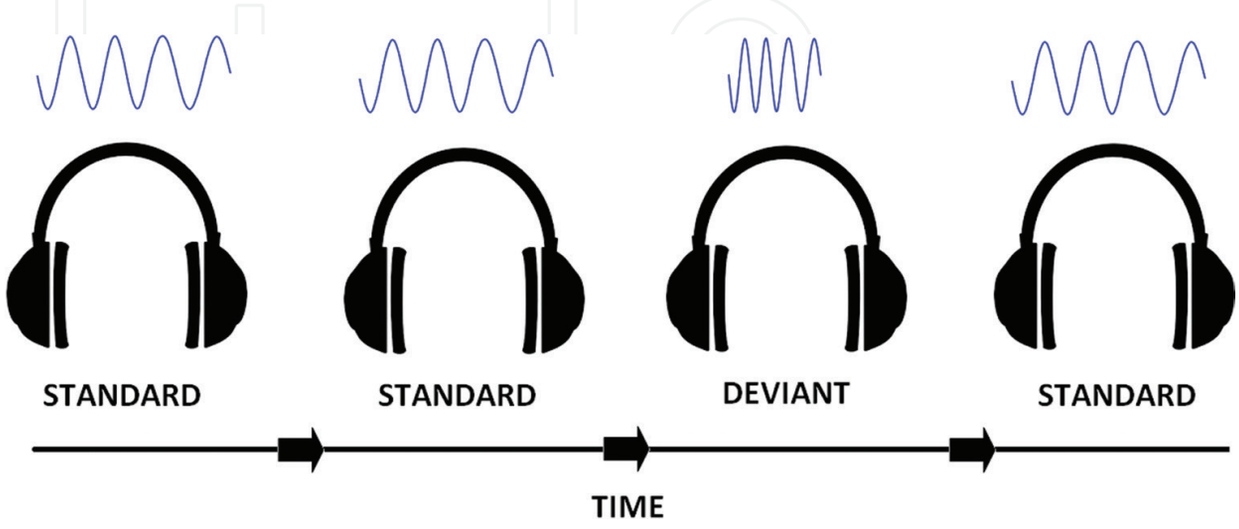

Figure 5. Schematic representation of the experimental procedure to evoke a MMN response.

also been proposed as an index of the violation of the memory trace built during the experiment by the standard stimuli [45].

With regard to its application in several pathologies, attenuated amplitudes in patients with schizophrenia have been reported in Ref. [46]. This reduction has been interpreted as a poor social/occupational and executive functioning in these patients [47].

With respect to bipolar disorder, several studies have shown contradictory results for this component (for a review, see Ref. [45]. The main conclusion is that there is no clear evidence of auditory discrimination ability in these patients after all.

In multiple sclerosis, some studies have reported alterations in this component, showing deficits in the auditory discrimination system [48]. Moreover, some authors have shown that the amplitude reduction in MMN could be linked to disorganization of spectral modulations (beta and gamma bands) in patients with low EDSS. These results suggest a complex set of alterations even in the early phases of this disease [30] (see **Figure 6**).

In stroke patients, an amplitude reduction in MMN has been found for changes in tone duration and frequency after a left-hemisphere stroke [49]. Another approach in the stroke field has been the use of this component as an assessment of function recovery in patients [50].

With regard to development, some studies have been focused on the use of MMN to determine deficits in dyslexic children. In particular, a reduction in the amplitude of this component found by Shafer et al. [51] could represent a poor auditory discrimination or language learning disability for phonetic cues in these patients. In autism spectrum disorder, some studies have shown an increase in the amplitude of this component with nonspeech stimuli and the opposite effect with speech stimuli [52, 53].

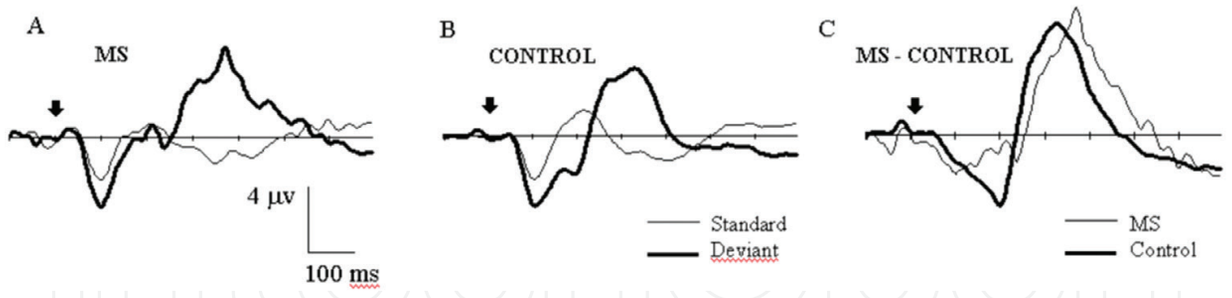

Figure 6. (A and B). Event-related brain potentials (ERPs) elicited at Cz in the deviant and standard conditions for MS patients and the control group, respectively. (C). Difference wave (MMN) (deviant—standard) for both groups. In all cases, arrows indicate the incoming of the tone. Adapted from Vazquez-Marrufo [30].

4. P300

4.1. Generic description

Chapman and Bragdon [1] described a positive wave around 300 ms after the onset of numerical and nonnumerical visual stimuli, and the subject was required to solve a problem with

those numbers. These authors suggest that this positive wave was originated because the numbers were relevant to the task. A vast number of studies have found multiple possible meanings for this component, and a general consensus accepts that P3 represents the summation of different areas in the brain with diverse psychological processes intertwined. Indeed, P3 has two clear distinguishable subcomponents with different psychological meanings. In a simplified conception, P3b is evoked by relevant stimuli (target) and not usually evoked by standard stimuli in several paradigms (i.e., oddball task). On the other hand, P3a is evoked by the presence of novel stimuli along a sequence of target and standard stimuli.

4.2. Procedure and characteristics of the component

In this section, a brief description of a visual oddball paradigm is presented in comparison to the auditory type described in the MMN section (see Ref. [54] for complete specifications). In this "visual oddball task," the subject is asked to discriminate uncommon visual stimuli (target) from a sequence of frequent stimuli (standard). In this study, the target stimulus (probability: 25%) was a rectangle with a checkerboard pattern comprising red and white squares. The standard stimulus (probability: 75%) was equivalent in size and pattern but with black and white squares. Both stimuli were presented in the center of the screen and the size of both stimuli was 7.98 and 9.42 (visual angle) on the x and y axes, respectively. The duration of the stimuli was 500 ms, and the interstimulus interval was 1 s, which is the time when the subject could respond. The task for the participants was to press a button whenever a target stimulus appeared and ignore the standard stimuli. It is also possible to elicit P3 if the task is not a motor response, e.g., the subject just counts the targets silently [55]. Only one block with 200 trials (50 target stimuli) is enough to evoke the P3 component (see **Figure 7**).

Multiple studies have defined variables that can modulate this component. An interesting finding is about P3 being evoked by the absence of a stimulus if it is relevant to the subject [56]. Another important issue about this component is that it has been observed with different

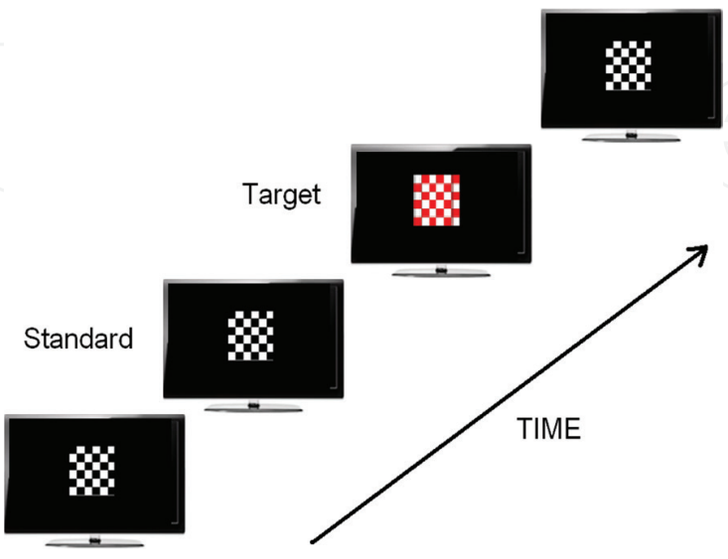

Figure 7. Schematic representation of a visual oddball to elicit P3.

sensory modalities (auditory, visual, somatosensory, olfactory, or taste stimulation) [57]. P3 amplitude is mainly independent of sensory modality; however, it is possible to find some differences in shape and latency when auditory and visual stimulation are compared [58]. When using auditory stimulation, different features of the stimulation, such as the tone frequency or the use of a mask of white noise, can affect P3 latency [59].

An important consensus regarding the meaning of P3 is that it reflects the timing of cognitive processes. However, on the other hand, it is not correlated with reaction time [60]. Considering the multiple psychological processes comprised in the component, there does not seem to exist a strong correlation between P3 and behavioral response.

With regard to age, children showed an increase in latency and a decrease in amplitude in the 1st years of life compared to adults (up to 3 years) [61]. Considering the entire lifespan, Goodin et al. [62] showed the natural evolution of latency decrease and amplitude increase in young subjects and that of latency increase and amplitude decrease in elderly subjects. A considerable number of publications have been focused on studying this component in other species. This component or similar waves have been described in rats [63], cats [64], monkeys [65], or mice [66], among other studies.

P3 latency peaks around 350 ms and, in particular, P3a and P3b are around 240 ms and 350 ms, respectively [67]. However, it is possible to find a P3 peak in a range that goes from 300 to 500 ms depending on many variables (type of task, difficulty…, and so forth). [55]. With regard to topography, the maximum amplitude of the P3 wave is seen at the parieto-occipital area for P3b and as fronto-central derivations for P3a [57]. With aging, the topography can change with a more frontal distribution; however, the scalp distribution is defined similarly by task requirements when it is compared with young subjects [68]. Concerning neural sources for this component, multiple studies have described controversial results about them. In particular, diverse cortical lobes (frontal, parietal, and temporal) or the hippocampus are defined as relevant for the generation of the P3 component (see Ref. [69] for a review).

4.3. Psychological meaning and pathology

Nowadays, there are many suggestions about the psychological meaning of this component: (1) inhibition that ends the activation related to stimulus processing [70]; (2) expectation and relevancy of the stimulus [71]; (3) selective attention [72]; (4) updating of working memory [73]; (5) activation generated by the sequence of frequent stimuli [74]; (6) speed of cognitive processing and allocation of brain energy resources [75]; (7) difficulty of the task [76]; (8) emotion and motivation [77, 78]. As was pointed out previously, it can be asserted that P3 comprises multiple processes and its modulation can be determined by different variables in different ways, sometimes increasing/decreasing either the latency or amplitude and sometimes opposing some variables to others.

In the clinical field, P3 has been used extensively in many diseases. Our group has referred in some studies to alterations of the amplitude (decrease) and latency (increase) of P3 in multiple sclerosis [79, 80] (see **Figure 8**). Comi et al. [81] has shown that a longer latency in P3 may be related to demyelination. An increased latency is also observed in diverse types of dementia

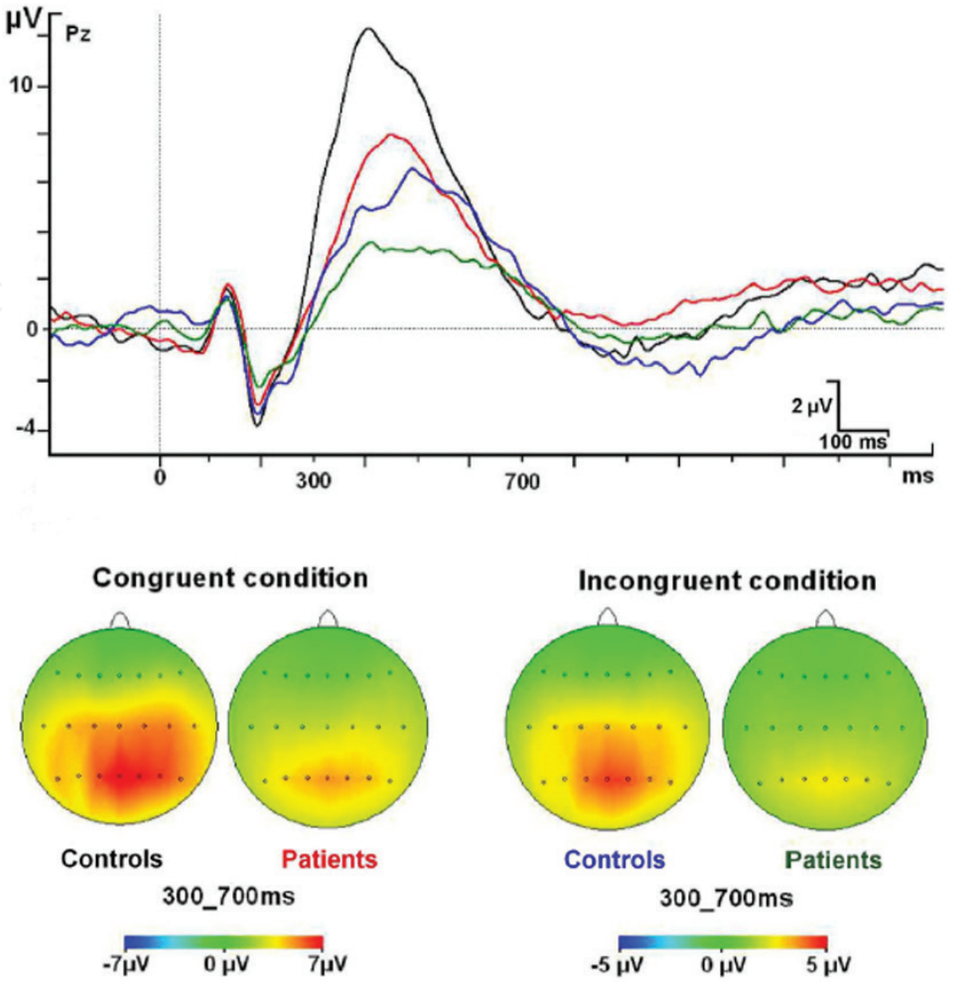

Figure 8. P3 component modulations at Pz electrode and topographic maps for ANT test. Note the reduction in the amplitude for multiple sclerosis patients in both conditions (congruent and incongruent). Adapted from Vazquez-Marrufo [80].

(Alzheimer, multiinfarction dementia, and lacunar dementia); on the other hand, in pseudodementia, the altered parameter is amplitude, which is flattened [82].

In Parkinson's disease, an amplitude decrease has also been observed by O'Donnel et al. [83]. However, other authors suggest that this reduction is more related to the dementia associated with the disease, rather than Parkinson itself [84].

P3 has also been useful as an indicator of the presence of a traumatic lesion (e.g., prefrontal cortex). It has been related to P3a and behavioral responses indicating a reduced attentional shift toward novel stimuli [85]. It is also possible to assess the evolution in the subacute phase of a stroke from changes in the P3 component [86].

In the psychopathology field, schizophrenia has received a remarkable attention with P3 studies. One general finding is decreased amplitude, which seems to be correlated to the presence of negative symptoms [87, 88]. Another potential application of P3 consists of assessing the neurodegenerative process in this pathology. Martin-Loeches showed a negative correlation between P3 amplitude and prefrontal CSF volume in these patients [89].

5. Conclusion

As a general conclusion, the ERP literature presented in this chapter shows an amazing field to explore, which relates the electric activity of the brain to the cognitive processes. It seems that a vast number of applications could be developed in the next few years, in our understanding of how information is processed in the brain, identifying anatomical structures where these processes occur, and their hierarchical organization.

However, one of the main challenges for this field is to study reliability tests that guarantee the health professionals that the assessment is reproducible and valid to be applied in the clinical field.

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