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REVIEW ARTICLE

Pearls and pitfalls in brain functional analysis by event-related potentials: a narrative review by the Italian Psychophysiology and Cognitive Neuroscience Society on methodological limits and clinical reliability—part I

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Abstract

Event-related potentials (ERPs) are obtained from the electroencephalogram (EEG) or the magnetoencephalogram (MEG, event-related fields (ERF)), extracting the activity that is time-locked to an event. Despite the potential utility of ERP/ERF in cognitive domain, the clinical standardization of their use is presently undefined for most of procedures. The aim of the present review is to establish limits and reliability of ERP medical application, summarize main methodological issues, and present evidence of clinical application and future improvement. The present section of the review focuses on well-standardized ERP methods, including P300, Contingent Negative Variation (CNV), Mismatch Negativity (MMN), and N400, with a chapter dedicated to laser-evoked potentials (LEPs). One section is dedicated to proactive preparatory brain activity as the Bereitschaftspotential and

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the prefrontal negativity (BP and pN). The P300 and the MMN potentials have a limited but recognized role in the diagnosis of cognitive impairment and consciousness disorders. LEPs have a well-documented usefulness in the diagnosis of neuropathic pain, with low application in clinical assessment of psychophysiological basis of pain. The other ERP components mentioned here, though largely applied in normal and pathological cases and well standardized, are still confined to the research field. CNV, BP, and pN deserve to be largely tested in movement disorders, just to explain possible functional changes in motor preparation circuits subtending different clinical pictures and responses to treatments.

Keywords Event-related potentials · P300 · Mismatch negativity · Contingent negative variation · N400 · Bereitschaftspotential · pN · Laser-evoked potentials · Normative data · Limits · Reliability · Clinical application

Introduction

The event-related potentials (ERP) are obtained from the whole electroencephalogram (EEG), extracting the activity that is time-locked to an event. The definition of "event" includes any physical stimulus or motor response. ERPs include the evoked potentials (EPs) that are responses to stimuli and the motor-related cortical potential (MRCP; or motor-related potential (MRP)). In literature, EPs may refer to early (within 100 ms) brain responses to stimuli requiring passive perception only, while ERPs may refer to late (more than 100 ms) brain responses to stimuli requiring more complex cognitive functions as stimulus processing, e.g. semantic categorization, stimulus selection, decision making, and memory recalling, and behavioral responses. However, giving that the early and late responses usually coexist, together with motor responses, in any task (e.g., the P100 attention effects [1]), including passive perception [2], the term ERP represent any brain potential extracted from the EEG using time-locked related averages, e.g., [3]. ERPs are noninvasively recorded from the scalp and have been used to investigate brain processes for more than half a century [3]. Since 1964, research by Grey Walter and colleagues [4] defined the features of the first cognitive ERP component, called the contingent negative variation (CNV). The year after, Sutton et al. [5] made another advancement with the discovery of the P3 component. Over the next 15 years, ERP component research became increasingly popular, as an inexpensive method to be employed in cognitive neuroscience. The 2000 years celebrated the triumph of neuroimaging techniques, specially fMRI, but the relevance of electrophysiological properties of brain in the interpretation of fMRI maps has been largely recognized [6]. In addition, the magnetoencephalography (MEG) equivalent of ERP, ERF, or event-related field could increase the spatial resolution of brain responses [7]. The averaging technique allows to reduce the signal to noise ratio (SNT) and extract the EEG activity evoked by specific and reproducible tasks. The induced not-time-locked activity, detected by computing the power (or rectified amplitude) of the signal as a function of time in selected frequency bands, could add further details on cognitive processing [8]. The need for easy and cheap procedures to test cognition and emotions could have a role in clinical settings, thanks to the huge amount of attractive results obtained in normal and pathologic brain using functional analysis. The ERPs could be considered biomarkers of early and advanced disease and treatment effects in many neurological and psychiatric conditions. Discussions about replicability and reliability of ERP measures could improve their application [9]. The main indices as the latency of a given component, the mean amplitude across a time window, or the area measurement for a given component at a given sensor location [10] are univariate and apparently sensitive to inter-individual and intra-individual changes, while the topographical distribution of voltages or magnetic/electric fields across the scalp or the temporal sequence of EEG/MEG spectral perturbation are multivariate indices less employable for clinical purposes [11].

Despite the potential utility of ERP/ERF in cognitive domain, the clinical standardization of their use is presently undefined for most procedures. Key reasons are the different recording and analysis methods, the different expertise in clinical neurophysiology or psychology, and the scantiness of studies in large normal and pathological cohorts. Recently, recommendation focused on the factors influencing the reliability of a given ERP, including the recording hardware and sensors, the quantification method, the noise affecting the signal, and the effect size in respect to the expected outcome [9]. The utility of ERP in different psychiatric and neurological disorders has been indicated [12], but they rarely entered in the routine clinical assessment, with few exceptions. Their application is currently focused on disturbance of consciousness [13], cognitive impairment and dementia [14], psychiatric diseases [15, 16], and chronic pain [17].

The aim of the present review is to establish limits and reliability of ERP medical application, summarize main methodological issues, and present evidence of clinical application and future improvement.

The first part of the review focuses on the main standardized ERP methods, including P300, CNV, and MMN, with a chapter dedicated to laser-evoked responses (LEPs) (Table 1). The LEPs are a robust neurophysiological method to test nociceptive pathways, though in the last years their cognitive

Table 1 Advantages, limitations, and clinical applications of the psychophysiological techniques—Part I

Technique	Advantages	Limitations	Clinical applications
P300	Easy to be recorded with stimuli of different modality	Large inter-individual variability	Dementia, disorders of consciousness, psychiatric disorders, ADHD, "Lie detector", brain-computer interface
CNV	High sensitivity for cognitive disorders, marker of prefrontal functions	Scarcely defined normal values	Migraine, movement disorders, psychiatric conditions
MMN	Partially independent of subject's collaboration	Large inter-individual variability	Disorders of Consciousness, cognitive decline, pediatric conditions, schizophrenia, deafness
BP and pN	Identification of motor and cognitive preparation for any voluntary action	Inter-trial interval longer than 1 s, largely depending on the task protocol, pN sensitive to ocular artifacts	Movement and age-related disorders
LEP	Selective assessment of the nociceptive pathway	Reversible cutaneous lesions, cost of the equipment	Neuropathic and non-neuropathic pain conditions, "functional" pain
N400	Assessment of neural bases of language comprehension	Different theories of cognitive significance, morphological variability	Alzheimer's disease, temporal lobe epilepsy, dyslexia, post-stroke recovery

properties and clinical reliability were questioned [18]. One section is dedicated to proactive preparatory brain activity as the Bereitschaftspotential or readiness potentials. In the second part of the review, more recent and/or less standardized techniques, as TMS-EEG, olfactory-related potentials, and event-related fields (ERF) are described. These methods of brain functional analysis are of prospective utility in clinical practice, but the methods of recording and analysis need to be better defined in order to improve reliability [19, 20].

The P300 (P3; late positive component (LPC))

General description The P300, first reported over 50 years ago [21], is probably the most studied component of long-latency (occurring after 100 ms from the stimulus) ERPs. It is elicited whenever a rare but attended and task-relevant (target) stimulus is presented to a subject. The term P300 (also referred to as the P3 or the "late positive component" (LPC)) stems from the wave's positive polarity and its modal peak latency in a young adult, of about 300 ms following the target stimulus (Fig. 1). It has a broad scalp topography maximal in the midline centro-parietal regions, generally similar across different tasks and stimulus modalities [22]. It is a largely supramodal component and can be obtained in different modalities (auditory, somatosensory, visual, olfactory) and even to the absence of an expected stimulus ("emitted" potential) provided this absence is relevant to the task [23] (Fig. 2). The P300 is a prominent component of "endogenous" ERPs (a.k.a. "cognitive potentials") originating from synaptic current flows and associated with patterned activities of cortical neurons related to successive stages in information processing. Unlike the short-latency ERPs, which are obligatory responses determined by the physical parameters of the eliciting stimulus ("exogenous" potentials), "endogenous" ERPs only appear in conjunction with specific perceptual or cognitive operations [24]. The time course of cognitive processes and the amount of neural resources allocated to each of them are expressed, respectively, by the latencies and amplitudes of the corresponding ERP components. In simple discrimination tasks, successive ERP components index different steps in stimulus evaluation process [25]: components P1 and N1 mark stimulus registration; processing negativity (PN) signals that a stimulus is part of a task-relevant sensory channel (stimulus selection); and component N2 marks identification of the stimulus type. The P300 reflects the end of the stimulus evaluation period and is associated with the categorization process of the incoming stimulus as a task-relevant signal (target). Of note, P300 latency specifically measures the stimulus evaluation process ("mental chronometry")[26] and can be dissociated from the reaction time, a measure of the response selection and execution processes [27].

Recording methods and analysis The P300 is usually evoked in the so-called *oddball* paradigm: the subject is presented with a Bernoulli sequence of stimuli in which an infrequent stimulus (target) randomly occurs in a background of standard frequent stimuli. The subject is instructed to respond mentally (count and report the total at the end of the task) or behaviorally (press button) to the target stimuli and refrain from responding to the standard stimuli. The stimuli (in the auditory, visual, or somatosensory modality) are presented every 1–2 s with a fixed or variable interval and probabilities of 0.8–0.9 for standards and 0.2–0.1 for targets. A variant of the

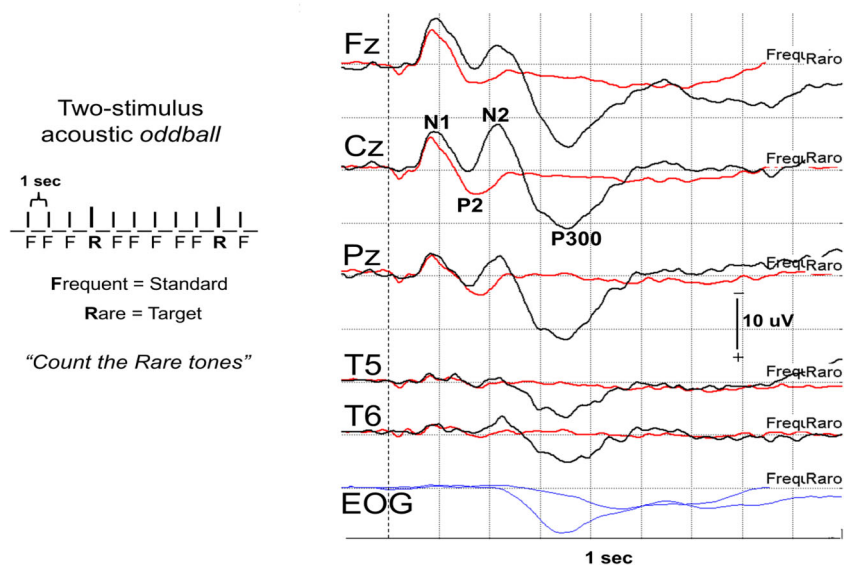

Fig. 1 ERP waveform obtained in a normal 62-year-old male in an auditory oddball paradigm. Reference: averaged earlobes. Average of responses to 160 standard (red lines) and 40 target (black lines) stimuli. Task: to mentally count the rare targets

oddball task is the three-stimulus oddball in which, in addition to the standard and the target stimuli, an infrequent, non-task-relevant (distractor) stimulus is presented which elicits a P3a (whereas the target elicits a P3b). Recently, in the study of conscious access of stimuli, the "Local-Global" paradigm (based on two embedded levels of auditory regularity) has been introduced [28]. It disentangles pre-attentive, unconscious responses such as MMN and P3a evoked by the violation of the local regularity ("local effect") from P3b, considered a signature of conscious processing and elicited by the violation of the global regularity ("global effect"). The

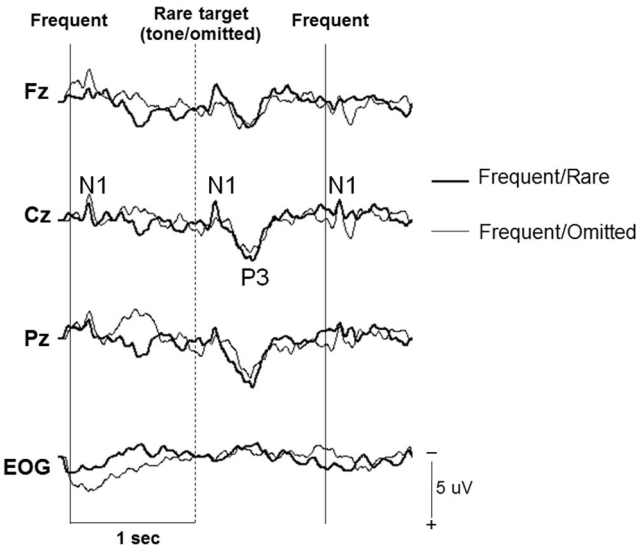

Fig. 2 ERP waveforms elicited in an auditory oddball paradigm (thick lines) or in an omitted target paradigm (thin lines). The omission paradigm was quite similar to the oddball task but the target stimuli were omitted. The task in both paradigms was to silently count the targets. Note that a definite P3 with a similar morphology was recorded in response to target stimuli in both conditions, whereas the peak N1 to targets was observed only in the oddball paradigm

subject's performance in the experimental paradigm should be always reported.

A minimal recording configuration includes only three midline scalp locations (Fz, Cz, Pz; 10-20 International System) although multiple electrode sites (19; 32, 64, or 128 locations according to the 10-5 International System) [29] are recommended to disentangle overlapping ERP components on the basis of their topographies. Multiple topographic maps of ERPs from different time points provide both temporal and spatial aspects of the waveforms and are useful for comparing experimental effects across subjects. For an accurate recording, ERPs require nonpolarizable Ag/AgCl electrodes with interelectrode impedance below 10 kΩ. Standard online referential recordings use one earlobe or mastoid with offline re-referencing by averaging with the other earlobe/mastoid. It is mandatory to monitor the vertical and horizontal electro-oculogram (EOG) for artifacts originating from saccades and blinks, using electrodes near the eyes (i.e., a diagonal channel). An adequate A/D conversion rate should be twice the highest frequency in the signal to be measured (128 or 256 c/s sampling rate) whereas a band-pass from 0.01 to 100 c/s is optimal, being that ERPs are slow waves. Trials contaminated by non-cerebral artifacts should be removed (either by the investigator or through automatic rejection/compensation procedures) prior to averaging. P300 peak latency is measured at the scalp location where its amplitude is greater relative to a pre-stimulus (usually, 100 or 200 ms) baseline. Baseline-to-peak or area-under-the curve measurements are standard methods for quantifying P300 amplitude. It is recommended to measure the latencies/amplitudes also of the peaks preceding the P300 (i.e., N1, P2, N2).

An advanced quantification includes the factor analysis (such as the principal component analysis, which provides the component structure of ERPs) and the source analysis,

applied to localize the ERP neural generators within the brain [30].

Normative data The P300 characteristics are modulated by a variety of biological variables, including genetic factors [31], with arousal and age being the main determinants. A drop in arousal, which implies a decrease of the amount of attentional resources devoted to the task, has a clear effect on P300, decreasing its amplitude and increasing its latency. The P300 latency changes with age, decreasing with children development up to 14 years and increasing linearly with increased age from 18 to 20 years on (with an estimated slope of 0.9–1.6 ms/year). The modal peak latency spans from 320 ms at the age of 20 years to 420 ms at the age of 80 years. On the opposite, the P300 amplitude declines with increasing age [32]. Individual latency or amplitude data vs age are customarily presented in a scatterplot graph displaying the regression line together with 2.0 or 2.5 standard errors.

Main contribution in cognitive neurosciences and neurological diseases The study of ERPs represents a mainstream of the growing field of neurosciences known as "cognitive psychophysiology" [24] which borrows many conceptual frameworks and experimental paradigms from the domain of neuropsychology. Indeed, the "oddball" task is a variant of the continuous performance task, a test widely employed in neuropsychology for the study of attention [33]. However, ERP studies provide information on brain processes that cannot be obtained with behavioral results. ERPs, being related both with patterns of neuronal activity and with psychological processes, address straight the neural substrates of cognition and allow to identify and differentiate at the millisecond level serial and parallel stages of information processing with a precision not achieved with behavioral techniques. In the clinical arena, as the short-latency stimulus-related ERPs have lost part of their diagnostic role following the growth of advanced neuroimaging, long-latency ERPs still hold their potential for exploring the pathophysiology of cognitive deficits and for diagnosis, providing a useful supplement to neuropsychological assessment.

According to the versatile and popular "context updating" theory [34], the core cognitive operation reflected by the P3 is the updating of some model of the environment activated whenever a conflict arises between new information carried by an incoming stimulus and expectations represented in working memory. The P300 operates therefore as a strategic ERP component (not a simple "Aha!" response) associated with an high-level, attention-driven meta-control operation, linked to central executive functions aiming at a more detailed evaluation of the stimulus [35]. As opposed to "exogenous" short-latency ERPs representing a "bottom-up" flow of sensory input, "endogenous" ERPs (i.e., P300) express a "top-down" modulation of complex neurodynamics. They are mediated through forward and backward neural connections, organized in a hierarchical cortical architecture in which lower level sensory information is continuously confronted with upper level predictions [36]. In such a conceptual framework of sensory processing, P300 and some of the earlier ERP components (i.e., MMN [37]; pP2,[38]; P3a, [39]) appear as deviance detectors acting to monitor the stream of stimuli during cognitive tasks [25]. A fronto-central midline positive component similar to the P300 but in the latency range of 250–300 ms can be observed in response to stimuli that are not task-relevant (deviants). Squires et al.[40] labeled this component P3a to distinguish it from the classical P300, labeled P3b. P3a seems to operate at the stimulus selection stage and is considered representing the cortical component of the orienting response [41]. In sum, the P3a and the P3b are generated by specific cortical systems including frontal and temporo-parietal areas for the processing of cognitive events, subserving the orientation of attention (reflected by P3a) and the contextual integration and subsequent memory storage (expressed by P3b) of salient events [42].

The neural generators of P300 (as emerging from scalp and intracranial recordings, lesional studies, neuroimaging) have multiple cortical and subcortical locations: P300 generators have been found in the superior temporal sulcus, inferior parietal cortex and intraparietal sulcus, lateral and medial prefrontal cortex, the anterior insula, hippocampus, amygdala, thalamus, and premotor and motor cortex [2, 41, 43]. This multiplicity of sources suggest that the P300 is produced by different, partly independent generators organized in an anterior/posterior cortical network with contributions also from subcortical structures.

Clinical applications Being a valuable tool for assessing cognitive functions, the P300 has been used as an assay to investigate clinical populations. An extensive literature is available describing changes in the P300 parameters (latency and amplitude) and topography in a wide range of neurological, psychiatric, and developmental disorders [44]. The initial suggestion for the clinical utility of P300 came from the finding of significantly prolonged peak latency in patients with dementia compared to normal aged subjects as well as patients with neurological disorders but not demented [45]. At that time, it was a major breakthrough demonstrating that the increased P300 latency indexed a slowing of cognitive functions specific to the dementing illnesses.[1] A number of subsequent studies confirmed the increased latency and decreased amplitude of P300 in patients with Alzheimer's disease (AD) compared to elderly controls, already in the early stages of the disease [46]. Moreover, similar alterations have been observed in patients with mild cognitive impairment [47, 48] and in individuals with familial AD gene mutations [49], suggesting a peculiar sensitivity of ERPs to AD neuropathology prior to its clinical expression. Also, P300 abnormalities have been reported in

the normal adult offspring of patients with AD, demonstrating the possible role of P3 as a pre-clinical marker of the disease [50]. P300 measures may distinguish between cortical and subcortical dementias [51–53]and between dementia and depression-associated dementia [54]. Overall, the P300 emerges as a reliable test for investigating cognitive function in clinical applications, mainly in the early stages of the dementing diseases when the clinical evaluation can be challenging [55]. Sensitivity has been estimated at 70% (comparable to other standard biomedical tests) whereas specificity is low [55, 56].

The P300 has been proposed as a "brain fingerprinting" tool in forensic medicine as a variant of the customary autonomic nervous system testing (such as electrodermal conductance), on the assumption that crime-relevant stimuli will elicit an enhanced P300 only in knowledgeable (guilty) participants [57]. The use of ERPs for the detection of concealed information in criminal cases, however, demands qualified and accredited professionals [58]. The P300 is also successfully employed in Brain-Computer Interfaces used for communication and control in patients with severe paralysis (i.e., motor neuron disease, neuromuscular disorders, cervical spine injuries, stroke, locked-in syndrome) [59].

Lately, the auditory P300 has been useful to probe covert conscious processing in non-communicating brain-injured patients with prolonged disorders of consciousness (pDoC, i.e., vegetative state/unresponsive wakefullness syndrome, minimally conscious state) [60–63]. Inspired by the consensus that P300 is a marker of conscious access of task-relevant stimuli, over 60 studies have been conducted in pDoC patients with long-latency ERPs (for a critical review see [13]). A positive prognostic value of P300 has been demonstrated in coma patients [64].

Evidence of altered P300 amplitude and latency in patients with schizophrenia compared to controls was consistently reported, with the strongest effects obtained from the auditory modality and in paranoid subtype [65].

Similar findings have been observed in patients with depression, with increased P300 latency related to major depressive episodes and decreased amplitude more associated to psychotic features [66]. However, inconsistence and heterogeneity in clinical characteristics of patients and in pharmacological treatment may limit the interpretation.

Regarding pediatric patients, P300 alterations have been reported in children with attention-deficit/hyperactivity disorder, with decrease in P3b amplitude with respect to typical development children likely reflecting deficits in attention orienting and resource allocation [67]. P3b amplitude abnormalities emerged also in children with autism spectrum disorder, suggesting the presence of deficit in the domain of attention and working memory [68].

Advantages and limits The main limit to the use of P300 in basic research as well as in clinical studies is the inter-subject latency/amplitude variability, due to a number of biological determinants, which demand consideration from the researchers. Non-cerebral artifacts are another source of concern, mostly for clinical populations (Table 1).

Perspectives A promising research strategy, involving P300, to provide new insights into the neural systems engaged in specific cognitive activities, is the investigation of the spatio-temporal dynamics of brain activities obtained by integration of multiple imaging techniques, combining the high temporal resolution of ERPs and the excellent spatial sampling provided by functional MRI [69].

The contingent negative variation (CNV)

General description The contingent negative variation (CNV) or "expectancy wave," first described by Walter et al. [4], is a slow cortical shift that emerges between two paired stimuli, the first (S1) being a warning stimulus, the second (S2) being an imperative stimulus that requires the subject to perform a motor task. When the interval between S1 and S2 is sufficiently long (> 1.5 s) [70], two components may be identified: the early and the late CNV, associated respectively to the orienting attentional shift and the preparation of motor response. It has been applied to neurological and psychiatric conditions, to explore the attentional mechanisms and the cognitive processing preceding the motor response, though its use is limited to research paradigms.

Methods of recording and analysis A typical CNV paradigm consists of a sequence of couples of stimuli (trial) in which an S1 warning stimulus is followed by a S2 imperative stimulus. At S2 arrival, the subject is invited to press a button as quickly as possible. The presence of an operant response on S2 (usually a motor task but also a mental task [71]) is necessary to elicit the expectancy wave [4]. The inter-trial interval randomly could vary between 3 and 10 s [4]. CNV can be evoked by combining visual and auditory stimuli or using stimuli consisting of a single sensory modality [4, 72]. For most healthy adult subjects, maximum CNV amplitude occurs after about 30 trials [73].

In order to obtain a better reproduction of this response, electrical signals with very long-time constants (at least >6 s) are required [74]. Usually, the analysis epoch for each CNV is 5 s with a 500 ms pre-stimulus baseline before S1. The CNV amplitude is measured as total area (negative shift between S1 and S2) and as two temporal windows of interest: the early orienting window (early CNV) (between 500 and 700 ms following S1) and the late window (late CNV) (200 ms preceding S2) compared with the pre-stimulus baseline [70, 75]. The

minimum equipment to record a reliable CNV consists of three recording electrodes on Fz, Cz, and Pz derivations, referred to the linked mastoids. The band-pass filter is 0.1–0.3 to 30–100 Hz. The electro-oculogram is mandatory.

Normative data The CNV is mainly evoked in midline scalp locations, and the main CNV amplitude is rarely larger than 20 μV at Cz [74]. A moderate-to-high reliability has been reported for all CNV components, especially the early CNV [76]. A relationship between CNV amplitude and reaction time following S2 is present: the larger CNV amplitude, the shorter the response time [72, 77] (Fig. 3).

Developmental research demonstrated that children tend to have smaller, less negative CNV components compared to adults [78, 79]. Additional data indicate that the CNV amplitudes gradually become more negative throughout development into young adulthood [80]. Moreover, a progressive amplitude reduction for CNV waves was found in the older subjects [81]. Taken together, these data indicate that the developmental trajectory of the CNV and its components strictly reflects on one side the frontal lobes maturation throughout childhood and adolescence and, on the other side, the early brain involution processes related to minimal and sub-clinical decrement of orienting, attentiveness, and response preparation capabilities.

Main contribution in cognitive neurosciences and neurological diseases The CNV is the electrophysiological signature of a task-specific preparatory state that facilitates the stimulus perception and the required response. It reflects the activation of multiple brain areas, which compose a specific sensorimotor neural set attentionally controlled by frontoparietal networks [82, 83]. This "expectancy wave" is associated with selective behavioral functions, such as attention, preparation, estimation, and voluntary motor control [72, 84, 85]. When the interval between S1 and S2 is sufficiently long (> 1.5 s) [70], two components may be identified: the early and the late CNV, associated respectively to the orienting attentional shift and the preparation of motor response. Specifically, it has been demonstrated that the late CNV, when evoked by a double-choice reaction time task, involves attentional processes also related to stimulus anticipation beyond motor readiness alone [86].

Several studies have demonstrated that frontal regions are important in the genesis of the CNV, especially the dorsolateral prefrontal cortex [87–89]. Additional neural influences have been suggested, such as the supplementary motor cortex,

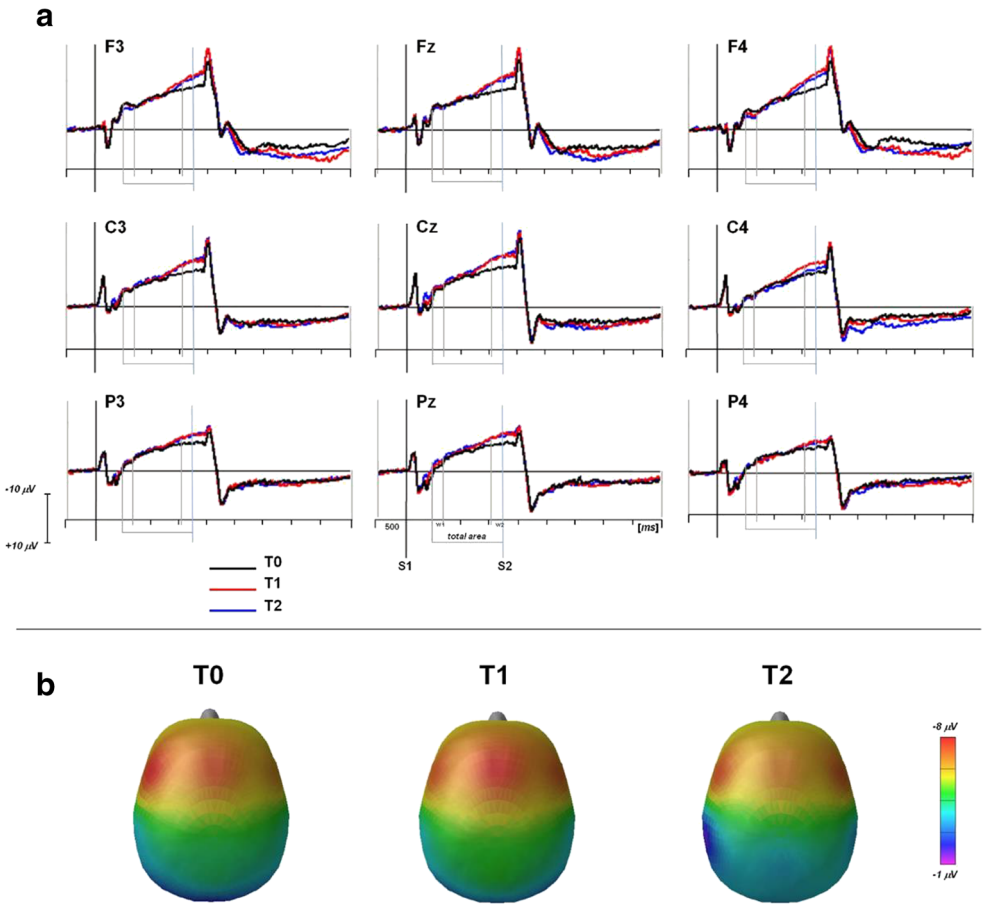

Fig. 3 **a** Grand averaged CNV waveforms, with early CNV, late CNV, and total areas highlighted, superimposed at three consecutive time points (T0—black lines, T1—red lines after 30 min and T2—blue lines after 30 min from T1). W1, early CNV; W2, late CNV; S1, warning stimulus (flash); S2, imperative stimulus (tone; standard: 1000 Hz, target: 2000 Hz). **b** Scalp potential maps at 600 ms (mean value of W1-CNV) for T0, T1, and T2 (modified from [77])

primary motor cortex, anterior cingulated cortex, basal ganglia, thalamus, orbitofrontal cortex, and even parietal areas [90–95].

Clinical applications The peculiar characteristics of the CNV contributed to better define the psychophysiological features in several neurological diseases. CNV studies in migraine shed light on the abnormal central information processing associated to this disorder. The early CNV was repeatedly found increased in amplitude in migraineurs, and a deficit of habituation, specifically again in the early CNV, was also found [96]. These alterations are proven to worsen intercritically, especially during the days preceding the attack, and to normalize during the attack [97–100]. Moreover, the use of β-blockers, calcium antagonists, and anti-epileptic drugs, which are prophylactic agents effective in reducing the frequency of attacks, is associated to the normalization of the early CNV amplitude and its habituation [101–104]. This data supports the hypothesis that the hyperresponsivity in stimulus processing, and the consequent enhanced neuronal energy demand [105, 106] could contribute to the pathophysiology of migraine; moreover, the normalization of the CNV in migraine could reflect the improvement of its clinical course.

The CNV has been extensively studied also in movement disorders, especially Parkinson's disease (PD), in which the dopamine deficit leads to a dysfunction in basal ganglia-thalamo-cortical loops. The total CNV amplitude, especially the late CNV amplitude, is reduced in PD patients [107–115], and this reduction can be restored by dopaminergic medication [116] and subthalamic nucleus deep brain stimulation [115], thus giving evidence that the basal ganglia deficit has consequences on the activity of prefrontal cortex functioning [117]. Moreover, they suggested that CNV is modulated by dopamine. Many studies confirmed these observations [118–120], pointing to CNV as a useful tool for measuring variations induced by treatments that target the dopamine system. Moreover, a reduced CNV amplitude was also found in Huntington disease, suggesting an abnormal activation of the attentional processing related to the functioning of the associative cortices in this disease [121]. Lastly, CNV amplitude resulted to be decreased also in dystonic syndromes such as writer's cramp and cervical dystonia, with movement-specific abnormalities. The CNV was of reduced amplitude, in fact, only when the act to perform after the imperative stimulus was related to the affected body part (hand movement or head rotation, respectively) [122–124]. This finding points to the fact that in dystonia, also traditionally considered a basal ganglia disorder, a deficit in cortical anticipatory activity linked to the preparation of specific motor act is present.

The CNV has also proven to be helpful in order to shed light on cortical mechanisms during information processing in psychiatric patients, especially in schizophrenia. Beside the reduction of the CNV amplitude, schizophrenic patients may display an enhanced negative potential after S2, which has been called post-imperative negative variation (PINV) [125–127]. On the contrary, in healthy subjects, CNV negativity typically returns to baseline after S2. In schizophrenic patients, the presence of a PINV has been interpreted as an "abnormal CNV duration" [128]. These patients, in fact, display a difficulty to correctly prepare for incoming stimulus and response evaluation [129] reflecting a problem of movement control [127] during the resolution of the task request at S2. This psychophysiological pattern is compatible with the prefrontal cortical dysfunction in schizophrenia.

Advantages and limits The CNV has been widely used both in healthy subjects and in many pathological conditions. It has been demonstrated to be useful in delineating and understanding impacts of diseases on cognition, and to some extent in evaluating the efficacy of treatments; nonetheless, its role as a diagnostic or prognostic tool is still debatable. Age and sex-related normal ranges were poorly defined, as well as its potential role in defining specific aspects of cognitive dysfunction or drugs effects (Table 1).

Perspective As for all ERPs, the CNV has the advantage of allowing an excellent temporal resolution of selective cognitive processes. A characteristic of this ERP is that, during a double-choice reaction time task, which is the most appropriate to evoke the CNV, many psychophysiological functions are engaged consecutively, such as anticipation and discrimination of the upcoming stimulus and motor preparation. Thus, it reflects a preserved sensorimotor integration of all these processes, which could be isolated analyzing the different windows of interests especially for longer interstimulus intervals. Consequently, the disruption of this phenomenon is a trustworthy index of an alteration of associative functions, which would be specifically explored in neurological and psychiatric diseases.

Mismatch negativity (MMN)

General description Originally described by Näätänen et al. [130], the auditory mismatch negativity (MMN) is a component of the event-related potential (ERP) to an odd stimulus in a sequence of acoustic stimuli. It provides a valid objective measure of the accuracy of the echoic information processing of an intact human brain or of a dysfunctional one [131]. The MMN is automatically generated whenever there is a mismatch between the neuronal model of the physical features of the standard stimulus and the deviant one appearing at around 100–250 ms from the onset of the stimulus variation [132].

In addition to the bilateral sources of the MMN located in the vicinity of the primary auditory cortex, predominantly activated in the hemisphere contralateral to the ear of stimulation, there is also a frontal generator involving mainly the right hemisphere [93, 133, 134]. There seems to be a small delay in the frontal activation compared to the activation of the auditory cortex [135], which supports the hypothesis that the detection change signal generated by the auditory cortex may induce the frontal addressing mechanism of attention [136]. Moreover, a visual MMN (vMMN) was obtained for detecting a phonological mismatch in reading [137]. This section mainly concerns the best-known auditory MMN and includes some hints on the visual MMN.

Methods of recording and analysis The MMN is more evident when the subjects ignore the stimuli [138] and can be administered, for example, while the participant reads or watches videos or even sleeps (for infants). The auditory MMN can occur in response to deviance in pitch, intensity, or duration [139]. The fact that the MMN elicitation depends on unconscious processes is proven by the smallest difference in frequency required between sinusoidal pure acoustic tones such as 1000 Hz for the standards and only 1020 Hz, 1050 Hz, or 1100 Hz for the deviants in the most often used paradigms in clinical settings [140]. The researchers have also adopted more complex paradigms in experimental scenarios such as those developed in order to study the functional specialization of the human auditory cortex in processing phonetic and musical sounds [141]. The minimum of recording electrodes is located in Fpz, Fz, and Cz, referred to the nasion.

Regarding the analysis, a suggested methodological condition is to adopt an acquisition time of 600 ms including 200 ms before the stimulus and 400 ms after; signals can be band-pass filtered at 0.1–0.3 to 30–100 Hz and sampled at twice the high-pass filter; responses must be averaged separately for each stimulus type in each subject, and a 0-μV baseline must be determined as the mean amplitude of the pre-stimulus period [142]. Then, in order to quantify the MMN, covered by brain electrical activity, the evoked response to the standard tone can be subtracted from the corresponding deviant stimulus response [142]; it is usually evident on the frontal sites and on the mastoids due to the inversion of the dipole [143, 144] (Fig. 4). Recording several scalp derivations and mapping data certainly allows a clearer identification of the evoked potential concerned [143].

Normative data According to the literature, the MMN is identified as the maximum negative deflection occurring from 100 to 250 ms following the elicitation of the deviant stimulus [132, 145, 146]. The latency and the amplitude are the most important parameters to identify the possible auditory processing disorders [145]. Normative data at Fz for the auditory MMN in healthy young adults are 180.5 ± 33.84 ms for the latency and 3.2 ± 1.60 μV for the amplitude [147].

Main contribution in cognitive neurosciences and neurological diseases The auditory MMN is an index of pre-attentive processing [148] and a memory-based change-detection brain response to any discriminable change in a stream of acoustic stimulation, including abstract-type changes or a rule derived from the recent stimulation [149–151]. The capability of MMN to index violations of abstractions from sequential patterns indicates a link between automatic processes and high-level cognitive functions in the auditory cortex. This leads to the concept of a primitive sensory intelligence, with substantial complex auditory analysis occurring outside the focus of the mere perception [145]. By varying the interstimulus interval (ISI) between tones, for instance from 1 to 3 ms, MMN parameters become neural markers of human echoic memory in different age groups [147, 152, 153].

Kimura et al. [154] proposed that previous visual MMN findings can be regarded as the evidence of the existence of unintentional prediction about the next state of a visual object in the immediate future, on the basis of its temporal context, and that such predictive processes may provide a tool for adaptation to the visual environment at both the neural and behavioral levels.

Clinical applications There is a wide clinical applicability of the auditory MMN, which represents a relatively easy to use and not expensive method. For its property to be elicited regardless of the attention, MMN can be used both during sleep [155] and states of coma, in the latter becoming a measure of the prediction of its outcome and of the pharmacological effects [156, 157]. Clinicians can find the need to use passive paradigms also in order to assess cognition of patients with normal vigilance but unable to cooperate; this is the case of infants [158], of patients with oppositional character in association to difficulties in understanding a task such as young individuals with autism with mental retardation [142] or adults with dementia [159], and of subjects with incapacity to perform standard neuropsychological tests because of speech or motility problems, such as amyotrophic lateral sclerosis sufferers [160, 161].

The MMN is ideal to address if working memory impairment is due to premature trace decay using paradigms with a different ISI between tones; in this perspective, there are interesting reports in aging and in numerous neuropsychiatric diseases such as Alzheimer's disease, Parkinson's disease [162], and schizophrenia [163, 164]. Moreover, MMN deficits index deficient *N*-methyl-d-aspartate (NMDA) receptor function affecting memory-trace formation and hence cognition, in different clinical conditions; in particular, it represents a key mechanism that can

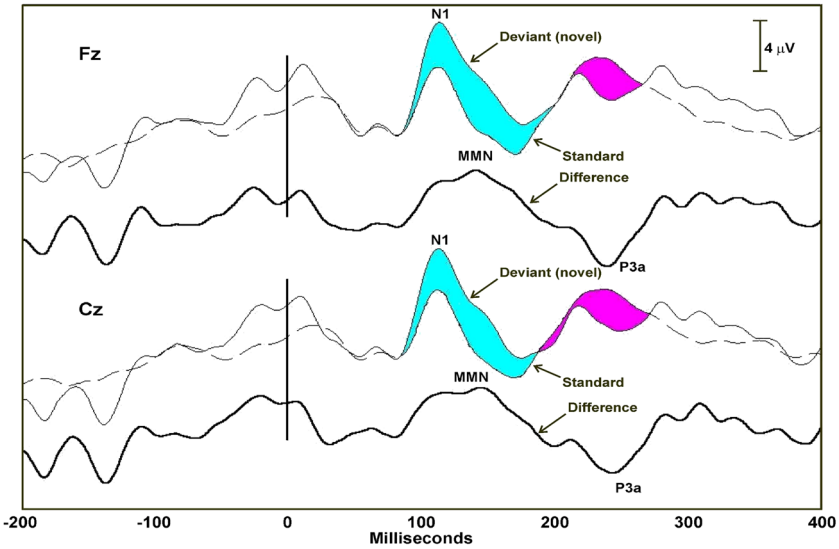

Fig. 4 Example of responses obtained from one subject after the delivery of standard and deviant (novel) stimuli (vertical lines), from two midline scalp locations. The difference between the two waveforms in the time windows of interest are indicated in turquoise (MMN) and raspberry (P3a). Also, the difference waveform is show below each pair of responses

help explain major clinical and pathophysiological aspects of schizophrenia and other psychotic disorders [165, 166].

The MMN represents an objective index of neurodegeneration, and the broad spectrum of pathologies characterized by reduced amplitude and/or prolonged latency of this ERP component in both baseline and complex measurements has led to assert that MMN deficiency appears to indicate cognitive decline irrespective of the specific symptomatology and etiology of the different disorders [167]. Hence, cognitive decline can now be objectively measured with the MMN [131]. Similar to some other ERP components, MMN has an indication also in depicting subtle, sub-clinical, probably reversible alterations in pre-attentive processing that cannot always be captured with traditional neuropsychological tests due to different sensitivity [168]; this is the case, for instance, of narcolepsy [169, 170]. Finally, as the MMN can be detected even in animals such as the mouse, it might provide a useful biomarker for assessing the effects of the drugs developed to fight the cognitive and functional impairments of patients, such as those with schizophrenia [171].

Because of the relative early stage of research on visual MMN in patients, its potential for clinical application is not yet fully appreciated. However, reports of impairment of the visual MMN are already available in different clinical conditions, such as dementia, mild cognitive impairment, schizophrenia, schizoaffective disorders, mood disorders, spinocerebellar ataxia, autism, mental retardation, dyslexia, panic disorder, deafness, and hypertension, and in physiological aging [172].

Advantages and limits In the present, the MMN methodology is not definitely regarded as a tool of everyday clinical work with which reliable measurements can be obtained at the level of individual patients [173–175], despite the encouraging inputs by Näätänen et al. [167] in a review approaching this aspect to a great extent (Table 1).

Perspectives Nowadays, the magnetoencephalographic (MEG) equivalent of the MMN can be applied in both basic research and clinical studies with a gain in spatial resolution [176]. Within the arrangement of normative data that might prove to be sensitive for the detection of subtle and preclinical changes due to abnormal brain aging, a research agenda might be planned involving large numbers of healthy subjects, with age divided by decades, in whom not only the MMN is recorded but also neuroimaging techniques can be paralleled [147].

In a needed translation from basic research to clinical and developmental perspectives, further studies combining electrophysiological and behavioral data in clinical populations are needed to validate the MMN as a clinical tool for the assessment of sensory memory duration, also at the individual level [177].

The Bereinshaftpotential and the prefrontal negativity (BP and pN)

General description In everyday life, voluntary actions are constantly monitored by internal and external factors; complex interactions between motor and cognitive brain areas are needed to achieve the intended action in a proper fashion. Notably, a recent challenge for neuroscience research has become the understanding of how preparatory brain activities can be linked to performance of the following motor behavior. In this context, ERPs represent a suitable tool to unveil the temporal dynamics of brain activities underpinning action preparation. Indeed, two main preparatory action-related ERP components exists: the well-known Bereitschaftspotential (BP

[178]) and the recently discovered prefrontal negativity (pN [179]). The BP reflects the progressive cortical excitability of supplementary and cingulate motor areas in self-paced [180] and externally triggered motor tasks [19, 181], which was interpreted as an index of motor readiness [182]. The pN, whose source has been localized in the pars opercularis of the inferior frontal gyrus [2, 38, 183], has been associated with proactive top-down cognitive control (especially inhibition) of an upcoming response for both externally triggered [38] and self-paced [184] tasks. There is increasing evidence that the BP and the pN modulations might predict motor and cognitive action performance, respectively [185–188]. Differently from the contingent negative variation (see the above paragraph), the BP and the pN are not contingent to cue presentation (e.g., [19]).

The BP is a slow negative wave rising 1–3 s before movement onset at medial central and frontal scalp sites, showing a wide radial distribution. The BP amplitude, timing, and topographical distribution differ between externally triggered and self-paced tasks. In externally triggered response tasks, the BP is usually measured as mean amplitude in the last 500 ms preceding stimulus presentation at medial central leads (Cz and CPz), whereas in self-paced tasks it is more anterior, earlier, and larger, peaking at medial frontal scalp sites (FCz, Cz) up to 500 ms before the movement, when the negativity becomes steeper and lateralized, turning into the negative slope (NS').

The pN is another slow rising proactive negativity emerging in its early phase over lateral prefrontal sites (AF7/8, AF3/4) with bilateral radial topography or on more medial frontopolar scalp sites (Fp1, Fpz, Fp2) with medial radial distribution in the later phase [186]. The pN initiates 800 ms before stimulus onset and peaks concomitantly to it [19] (Fig. 5).

Methods of recording and analysis The BP can be recorded with any voluntary movement, while the pN emerges in complex motor tasks only [19]. In self-paced tasks, these components must be obtained triggering the EEG with movement onset by means of electromyographic recording over the effector or, more simply, using key press triggering [189–191]. In externally triggered response tasks, the BP and the pN can be similarly obtained triggering the EEG on both events and responses [19, 192]. These findings paved the way to study proactive cognitive brain processing in any cognitive task, from simple response tasks (SRT) to oddball, sustained attention, Go/No-go or spatial attention tasks [2, 19, 191, 193] with sufficient interstimulus interval (minimum 1 s) to allow adequate brain preparation for the following trial.

Both the BP and the pN components are low-frequency waves and require a very low high-pass filter (lower than 0.1 Hz) in order to detect them. A minimum of 200 trials per participant is required to appreciate these components after the averaging procedure; however, 400 trials are suggested for clean ERPs. The pre-stimulus or the pre-movement interval should be between 1 and 2 s, and the baseline correction should be based at least on the first 200 ms of the interval.

Normative data In self-paced motor tasks, the BP peaks concomitantly to the movement, with amplitudes ranging from 6 to 10 μV at FCz (e.g., [180]). In externally triggered motor tasks, the BP peaks at stimulus onset, with amplitudes ranging from 2 to 4 μV at CPz; in these latter tasks, the BP does not peak at response onset, owing to the concomitant stimulus-related positivity (e.g., [19]). The BP is affected by many factors, including movement complexity and its consequences [179, 187, 189–191]. In externally triggered tasks, its amplitude has been consistently associated with response speed: the larger the BP, the shorter the response time (RT) [184, 186, 188]. Further, whilst the BP showed reduced amplitudes (~ 1 μV) in pre-adolescent children compared to adults [187], this component seems to be not affected by aging [191].

Th pN is detectable on prefrontal or anterior frontal leads with amplitudes typically ranging from 1 to 4 μV, depending on the task to be performed. In a large-sample normative study, the pN amplitude has been correlated with response accuracy and consistency [186]. The pN is robustly affected by age: in children, it is almost absent, and response accuracy and consistency are low [187], whereas in adults its amplitude gradually increases with age, especially after the 35th year, reaching about 7 μV at 85 years. This pN hyperactivity is mitigated by an active lifestyle [191]. In SRTs, the pN is usually absent in young people but becomes evident after the 50th year [191]. Nonetheless, both pN and BP are enhanced in young-adult multiple sclerosis patients [194].

Main contribution in cognitive neurosciences and neurological diseases The BP component has been largely explored in both healthy and patients' populations. In self-paced motor tasks, it has been proposed that reduced pre-movement activation reflects a more efficient cortical function in line with the "neural efficiency" hypothesis [195, 196]. Conversely, in externally triggered response tasks, increased motor readiness has been associated to improved behavioral performance [185, 197, 198]. Indeed, the association between enhanced BP amplitudes and faster RTs supports the proposal that the BP amplitude increase might reflect the tonic activity of a "speed system," superintended by the supplementary motor area [188, 199]. Regarding the BP timing, it has been found that, compared with healthy controls, Parkinson's disease patients showed delayed BP latency during a simple spontaneous thumb-pacing experiment, interpreted as impaired planning, preparation, and initiation of volitional acts [200].

The pN component has been associated to proactive top-down control and proactive inhibition, according to its bilateral or right-lateralized distributions [38, 184, 201]. The pN amplitude has been associated with enhanced sustained

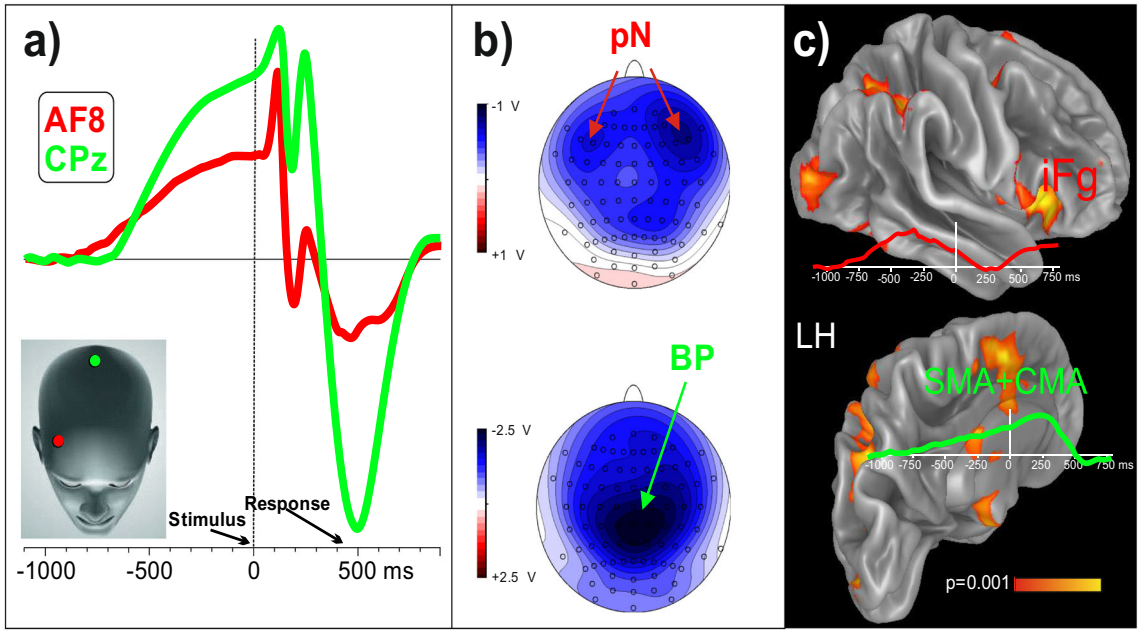

Fig. 5 Temporal evolution, scalp distribution and brain localization of the prefrontal Negativity (pN) and the Bereitschaftspotential (BP) in a discriminative response task (DRT)

attention on the task [188]. Further, increased right-lateralized pN activity has been found in self-decided inhibition during self-paced motor tasks [184] and associated to reduced commission error rates during Go-Nogo tasks [185], corroborating the right-lateralized proactive inhibition hypothesis [202]. Further, in self-paced motor tasks [203], a neural efficiency hypothesis for the pN has also been accounted, reflecting decreased recruitment of prefrontal areas in experienced performance. The hypothesis can be made that the BP and the pN might reflect a sort of accelerator/brake system that, based on predictive internal models, plans and anticipates future actions [19, 38]

Clinical applications Regarding the clinical applications, changes in the BP occur in several movement disorders, especially in those diseases including a failure of SMA activation. Indeed the presence (or absence) of a clear BP can also have diagnostic importance for certain movement disorders [86]. For instance, compared with healthy controls, Parkinson's disease patients showed delayed BP latency during a simple spontaneous thumb-pacing task. This result has been interpreted as impaired planning, preparation, and initiation of volitional acts [200]. In severe traumatic brain injury (TBI) with good recovery, the BP amplitude has been found reduced especially for self-paced movements, but not the motor potential [204]. These results indicate the presence of a selective deficit in motor preparation and a relatively spared pattern of activation during and following movement. Since the BP does not occur before involuntary movements, this component can be used for detecting the participation of the voluntary motor system in the generation of apparently involuntary movements in patients with psychogenic movement disorders [180]. Patients with paraplegia due to spinal cord injury (SCI) showed reduced BP and pN components in a discriminative visuo-motor task, independently from time from lesion (TFL). On the other hand, the TFL modified the BP topography, which showed a more posterior focus in subacute and chronic groups than healthy controls [205]. These results are in line with growing evidence of brain changes after SCI, in particular focusing on cognitive effects and evidencing possible functional mechanisms related to motor and cognitive readiness processing, relevant for SCI rehabilitation programs.

Advantages and limits In the pre-stimulus stage of processing, crucial hints of future action performance occur. Given the high temporal resolution of the ERP technique, it would be particularly useful segmenting the EEG signal into large epochs to unveil the proactive BP and pN components. Indeed, the modulation of these preparatory components can be investigated considering their crucial correlation with motor and cognitive preparation of upcoming actions. However, when building an ERP experiment aimed at measuring motor behavior and these preparatory components, some issues need to be addressed. Firstly, the interstimulus interval (ISI) should not be too short, given the slow nature and the pre-stimulus occurrence of these ERPs; ISI of more than 1 s are recommended to prevent overlapping with adjacent trials, which might seriously compromise BP and pN development. Secondly, ERP recordings are very sensitive to ocular movements, especially blinks, which represent the most common artifact to deal with. To overcome this issue, an independent

component analysis (ICA) procedure is recommended to remove ocular artifacts from EEG signal [206]. Thirdly, the amplitude and duration of the BP are influenced by movement features, muscle force, intention, and movement selection; thus, interpretations should be limited to standardized tasks and instructions, especially when considering between-subjects designs (Table 1).

Perspectives Evidence suggests that the "pre-movement" stage, namely the time when no task-related muscle movement is evident and the subject is aware of the action he/she is going to perform (or not) in the near future, uncovers crucial information for upcoming action performance; the analysis of both BP and pN reveals the complex interplay between motor and cognitive preparation to internally generated or externally triggered tasks.

As repeatedly shown, the pre-stimulus interval comprises components related to several putative motor planning and execution processes [207] and the study of the pN and the BP components might disclose in advance the covered intention for a future task performance. Therefore, a deeper understanding of these specific ERPs deserves further exploration, given the high potential for rehabilitation purposes in both healthy and motor-impaired populations; specifically, these activities might present novel non-muscular control channel brain-computer interfaces (BCIs) for delivering messages and commands to the external world. Within this framework, the BP and the pN might represent possible promising predictors of action performance. Also, the possibility of introducing ERP activities in neuro-feedback training might deserve further exploration; indeed, previous work suggested a successful impact of EEG biofeedback on event-related potentials (ERPs) in attention-deficit hyperactivity (ADHD) children [208], since EEG feedback affected the process of selection of action and decision making by means of P3 modifications.

The laser evoked potentials (LEP)

General description Laser-evoked potentials were introduced more than 40 years ago [209] and now represent the most validated neurophysiological technique for the functional assessment of the nociceptive pathway. Whether galvanic stimuli at painful intensity are used to activate nerve fibers or nervous receptors, both nociceptive and non-nociceptive afferents are stimulated. Since this simultaneous activation raises inhibitory mechanisms at both cortical [210] and spinal [211, 212] level, galvanic stimuli are not suitable to evoke brain responses specifically related to the nociceptive input. As demonstrated by an early microneurographic study, laser pulses applied on the hairy skin stimulate the thin myelinated (Aδ) and the unmyelinated (C) fibers selectively, without a concurrent activation of the non-nociceptive Aβ fibers [213]. The main LEP component is represented by a negative/positive complex (N2/P2), widely distributed over the scalp and reaching its maximal amplitude at the vertex. While the negative component has a mean latency of 200 ms, the positive response peaks at around 350 ms after hand stimulation. The N2/P2 component is preceded by a negative potential (N1) distributed in the temporal region contralateral to the stimulation and a simultaneous positive response (P1) recorded in the frontal region at around 150 ms to hand stimulation [17]. While several cerebral regions contribute to the N2/P2 complex generation, including the middle cingulate gyrus and the bilateral insular cortex, the N1 and P1 components are probably generated by a dipole source in the opercular region [214] (Fig. 6).

Methods of recording and analysis Three recording electrodes are enough to record LEPs for clinical applications [17]. An electrode at the Cz vertex, referred to the ipsilateral earlobe or to the nose, can pick up the N2/P2 complex, while the N1 potential is reliably obtained by a contralateral temporal lead, referred to Fz. Since LEPs can be easily contaminated by eye movement artifacts, an electrooculographic derivation should be always added, in order to exclude such a kind of artifacts from the final average. Reliable LEP waveforms are obtained by averaging 20–30 trials. The intensity of laser pulses should be settled just over the painful threshold to ensure us that all the stimuli are felt as painful pinpricks. Using this stimulation intensity, all the LEP components are related to the Aδ fiber input, while ultra-late responses, generated by C fibers, can be obtained by lowering the laser pulse intensity so that the subject perceives them as a diffused warmth [216]. However, this method can provide reliable results only to stimulation of the face or body midline, where the C thermoreceptors are highly represented [217, 218].

Normative data Latency and amplitude of laser-evoked potentials were standardized by different groups, with a good concordance in regard to the variability with age and height. Although several types of laser stimulators are available, normal data are available mostly for CO_2 laser-evoked responses. Truini et al. [219] recorded CO2 LEPs to perioral, hand, and foot stimulation in 100 normal subjects in the 14–82 age range. The N2 and P2 latencies were found increased and amplitudes decreased from the face to the foot. For all LEPs, regardless of the stimulation site, N2/P2 amplitude correlated negatively with age, whereas LEP latency did not.

The latency of hand and foot LEPs, but not that of face LEPs, strongly correlated with body height. In about 15% of normal subjects, all older than 69 years, laser stimulation of the foot failed to evoke reproducible brain potentials bilaterally. Amplitude and latency of LEPs were similar between genders, while females showed a slight reduction of laser pain

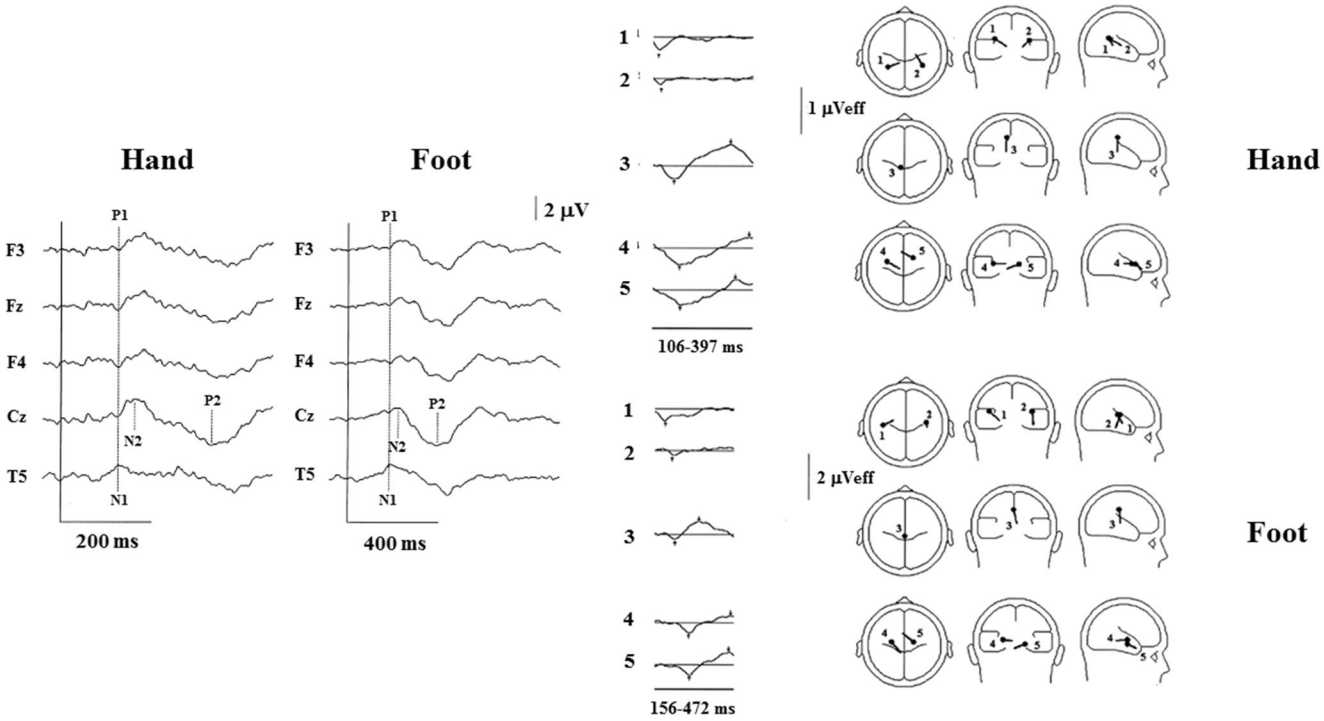

Fig. 6 Laser-evoked responses obtained by hand and foot stimulation. On the left, the vertex complex N2/P2 and the temporal N1 are reported. On the right, the dipolar source analysis by BESA method shows the source of the early temporal response in the bilateral S2, the N2 component in the bilateral operculo-insular cortex, and the P2 in the anterior cingulate gyrus (modified from [215])

threshold. Another study in 40 normal subjects in the 20–68 age range confirmed the age-related changes of all the main LEP waves' amplitudes obtained from the thigh and foot, including the N1 component [220]. Age-dependent changes involved distal LEP latencies as well, a result of a length-dependent functional deterioration of small myelinated fibers. The pain threshold was not age-dependent and not correlated with LEPs' amplitude decline, according to the theory that LEPs are not a direct correlation of subjective pain sensation and that amplitude and subjective perception are complex and not interrelated phenomena [221]. A following study considered normative data of trigeminal LEPs in 170 and hand LEPs in 237 healthy subjects, including children in the 7–17 age range [222]. This study reported a clear reduction of trigeminal N2 and P2 latencies and increased amplitude in the children group as compared to other ages. Authors suggested an age-related facilitation of the cortical circuits subtending the later LEPs at the trigeminal level [214]. The N1 amplitude and latency remained stable across ages, indicating a reliable pattern of potential utility in the assessment of nociceptive system integrity. This study assessed for the first time the normative range of habituation index, which is the ratio between the amplitude of the first and the last series of consecutive stimulations. The habituation phenomenon was clear in all the considered ages, especially at the trigeminal level. This pattern could be standardized and used to detect possible abnormal habituation patterns in chronic pain syndromes [223, 224] and migraine disorders [225, 226] when taking the normal ranges into consideration. Finally, the study by Tudor et al. in 51 adults [227] further outlined the correlations between age and height and N2 and P2 wave latencies and amplitudes. Summarizing, though the LEPs are well standardized for age, sex, and height, the clear variability due to these factors requests single-laboratory normative ranges.

Main contribution in cognitive neurosciences and neurological diseases LEPs are suitable for the study of attentional mechanisms of pain, as the vertex component N2/P2 changes in amplitude with relation to distraction [228]. They were thus employed in the study of the complex relationship between motor cortex activation and pain [229, 230]. Different factors of potential attention deviation from painful stimuli seem to provoke an inhibitory action on the vertex complex [104, 231], indicating an interference effect between contexts of cognitive attraction and arousal, and pain.

In both peripheral and central nervous system disorders, studies have demonstrated a reduced LEP-habituation as a result of an abnormal central pain processing [226, 232]: the loss of habituation likely represents the neurophysiological correlate of the central sensitization, a complex phenomenon comprising spinal and brain maladaptive changes, including phenotypic switch in the expression of spinal neuropeptides, thalamocortical dysrhythmia, and functional reorganization of cortical maps, thus progressively

leading to the chronization of pain [233]. The loss of habituation, as assessed by LEPs, may constitute the hallmark of a pharmacoresistant pain syndrome.

In the last years, LEP studies led to new theory about the pain matrix, largely superimposed to the "salience matrix." In fact, stimuli of the same relevance as the painful ones could recruit the same cortical areas comprised in the LEP generator networks [18]. The physiological significance of LEPs remains considerable, as the specific Adelta-C fiber activation refers to the nociceptive pathways and central networks, whenever the latter have a multimodal way of function.

Clinical applications The LEPs are commonly used for the diagnosis of neuropathic pain [219, 234], as well as for the assessment of the efficacy of putative therapies in chronic pain syndromes [235, 236]. LEPs evaluate small fibers that are commonly excluded from the routinary electrodiagnostic evaluation. They are also useful to differentiate organic from functional (psychogenic) etiologies [237]. Finally, LEPs offer also a unique opportunity to explore distinct cortical areas, which are differently activated by medial and lateral nociceptive systems [17, 214, 238].

Overall, LEPs are altered in disorders affecting either the peripheral or the central nervous system [239]: a significant reduction of the amplitudes, paralleled by a marked increase of LEP latencies, has been described in several diseases, ranging from diabetic neuropathy [240]and post-herpetic neuralgia [241] to Wallenberg's syndrome [217] and spinal cord lesions [242]. The use of "new generation" stimulators (e.g., the "solid-state" Nd-YAG laser) allows to study the involvement of myelinated and unmyelinated fibers separately, by modifying stimulation intensities and laser spot diameters [243]. In particular, patients with trigeminal neuropathy, characterized by loss of myelinated fibers and sparing of unmyelinated fibers, have absent Adelta- but normal C-related potentials, whereas those with Wallenberg syndrome or other central pain syndromes show impairment of both Adelta- and C-related responses [217].

The LEPs are of particular interest also in the diagnosis of pain of non-organic origin [214]. Compared to organic pain syndromes, LEPs are not attenuated in patients with non-organic (functional) forms of pain, in whom LEPs could even be enhanced by stimulation of the painful territory. Increased responses in non-organic pain are in line with the cognitive modulation observed in healthy subjects who direct attention to a laser stimulus [244, 245].

An interesting application of LEPs refers to the diagnosis of disorders of consciousness (DOC), although their significance and reliability are still debated. Some authors have shown that highly relevant painful stimuli may be processed even in patients with severe brain damage [246, 247], while others have reported that vegetative state (VS) patients do not show reliable Adelta LEP N2/P2 response, when compared to those who are in minimally conscious state (MCS) [248]. However, C-LEPs are often preserved also in VS, possibly suggesting a residual cortical pain arousal in these patients. Further studies are needed to confirm that cortical arousal toward pain salience may be a primary function for life persistence, possibly evolving our knowledge about DOC.

Advantages and limits The major limits of LEPs in clinical practice could be the impossibility to express the peripheral conduction and the level of lesion. LEPs are comprised within the event-related potentials, and they represent the final result of peripheral conduction and central processing of pain. This could be an advantage from the psychophysiological point of view, as they summarize the general status of nociceptive system. For this reason, the standardization needs normative values by single laboratories. The scarce specificity of the vertex N2/P2 complex and LEP cortical generators for pain seems to reduce the reliability of laser evoked responses [18]. Nevertheless, the specificity of laser stimulators for Adelta and C afferents guarantees that the obtained responses are generated by pain-related circuits within not-pain–specific cortical regions. For this reason, the specificity of stimulators for nociceptive afferents is mandatory [224]. The most diffused stimulator, the CO2 one, is minimally invasive and dangerous for the superficial skin, while other stimulators, as the YAP and thulium lasers, are less available in clinical practice (Table 1).

Perspectives The LEPs should be increasingly used in the diagnosis of the different forms of pain syndromes, especially small fibers pathologies. They should be associated to other methods as quantitative sensory testing, skin biopsy, and vegetative study. New stimulators, as electrodes with properties for small afferents, or specific devices for cold receptors and related fibers, would promote the diffusion of pain-related responses in the clinical study of pain syndromes. The evaluation of the event-related spectral perturbation could clarify further psychophysiological features of the laser-related responses, including the study of the high-frequency bands [249] and the connectivity analysis within the cortical generators [250].

The N400

General description Kutas and Hillyard described for the first time the N400 response in 1980, adapting the typical P3b oddball paradigm to language materials [251]. In the following years, several studies assessed this ERP as a dependent measure in language and mimic processing and semantic and recognition memory. It is currently applied to different neurological and psychiatric disorders. In the original study, authors implemented a typical oddball paradigm, using 75% of congruent control sentences while a random 25% ended with an incoherent word. This manipulation of the oddball paradigm did not elicit a typical P3, but a large negativity peaking

around 400 ms, diffuse over the scalp with a prevalent bilateral parietal representation. The wave was thus called N400, and in the course of the years, it was well characterized as a response to semantic errors and unexpected and abnormal phrases ending [251]. The anatomical origin of this potential seems quite variable, as it does not appear as a response of specific cerebral areas to oddball tasks, rather it is an experiential tag for stimulus-related brain activity in the 200–600 ms post-stimulus interval with a characteristic morphology and different sensitivity to experimental conditions. In fact, small N400s are elicited by the second words of semantically related (e.g., red/yellow) compared to semantically unrelated (e.g., red/cold) pairs. In the semantic domain, N400 amplitude is sensitive to lexical and contextual characteristics in printed, spoken, and signed language [44].

Methods of recording and analysis In building the task for eliciting the N400, the evidence that it is not a simple signature of the violation of any arbitrary or over-learned pattern should be taken into account [252]. The generation and amplitude modulation of N400 response is thus dependent upon congruity, semantic relationship, and lexical factors. The repetition of stimuli should be avoided, as it could substantially reduce N400 amplitude [253]. Specific lexical variables should be texted, focusing to those of experimental interest [44].

There is not a fixed number of stimuli, as it could vary from 20 to 120 trials per condition, depending on the predictability of incongruity or lexical and semantic abnormalities. Probability of occurrence is not considered a significant variable, but equal probability of congruous and incongruous items is typical. Duration of stimuli depends upon the time of stimulus perception; interstimulus intervals are planned in accord to normal reading or listening of continuous speech. Concurrent behavioral task could guarantee the required attention level.

The N400 appears as a negative-going potential on particular scalp locations relative to a specific reference derivation. The minimal required recording electrodes are placed on Fz, Cz, Pz, F3/T3, F4/T4, P3/T7, and P4/T8, referred to bilateral mastoid/earlobe electrodes. A post-averaging with 0.01–100 Hz as band-pass filters, digitization rate 250 Hz, epoch length 100–200 ms pre-stimulus baseline, and at least 900 ms following stimulus onset, artifact reduction, EOG rejection or correction, and rejection of trials with voltages ± 70 micro V in any EEG channel are recommended.

Whereas predictable endings elicit a broad positive waveform from 200 to 600 ms, the incongruent words elicit a large negative wave in this latency range. Indeed, the N400 elicited by an unexpected item does not need to be negative in absolute terms, but it is thus typically examined in cross-condition comparisons with a point-by-point subtraction of, e.g., a congruent ERP from an incongruent one. This difference—or N400 effect—is a monophasic negativity between 200 and 600 ms, largest over left frontal or centro-parietal sites (Fig. 7). No single electrode is recommended for N400 analysis, but scalp distribution and prevalent anterior-posterior or lateral position, as well as hemispheric asymmetry should be taken into account. [44].

Normative data Measures of N400 are recommended in the 300–700 latency range for adults, with earlier latency for continuous speech [254]. The amplitude of the response varies with stimuli expectation and behavioral reaction [252, 255]. Single-laboratory normative data are needed for the specific implemented tasks, taking into consideration the effect of age, education, and hemisphere dominance. In fact, there is a progressive amplitude decline from childhood forward. The left and right scalp distribution of the negative wave depends upon the bilateral activation of different cortical sources [256].

Main contribution in cognitive neurosciences and neurological diseases The N400 is one of the most salient ERPs modulated during language comprehension. According to the access/retrieval account, the N400 amplitude reflects the retrieving from memory of the conceptual issues connected to the test word, considering the preceding context. Increased N400 amplitudes refer to a difficulty in approaching lexical information [252, 255]. The integration interpretation is based on the general concept that the N400 amplitude expresses the effort in the integration of the target word with the preceding context. On this view, increased N400 amplitudes reflect increased integration difficulty. The hybrid hypothesis is a combination of the access/retrieval and integration theories, which consider N400 amplitude dependent upon the effort involved in recovering information from memory and integrate for the word interpretation. Recent findings in healthy volunteers supported the concept that N400 amplitude reflects context-sensitive lexical retrieval – but not integration – processes, while subsequent positive response-P600-could be reconciled with the integration view [257].

The N400, often in conjunction with neuropsychological measures, has been used to measure language and memory features in general populations across the lifespan.

Considering that it could be a descriptor of aspects of language and memory, there are a huge amount of studies showing application in neurological and psychiatric populations, including Alzheimer's disease, aphasia, autism, cerebral palsy, head injury, dyslexia (and other developmental language disabilities), epilepsy, mood disorders, Parkinson's disease, psychopathy, and schizophrenia [258]; in these diseases, it was useful in clarifying the nature of specific deficits, or language and memory processing in patients with limited abilities to be submitted to neuropsychological batteries [44].

Clinical applications Decrements in amplitude and delayed latencies of N400 elicited by semantic incongruities are

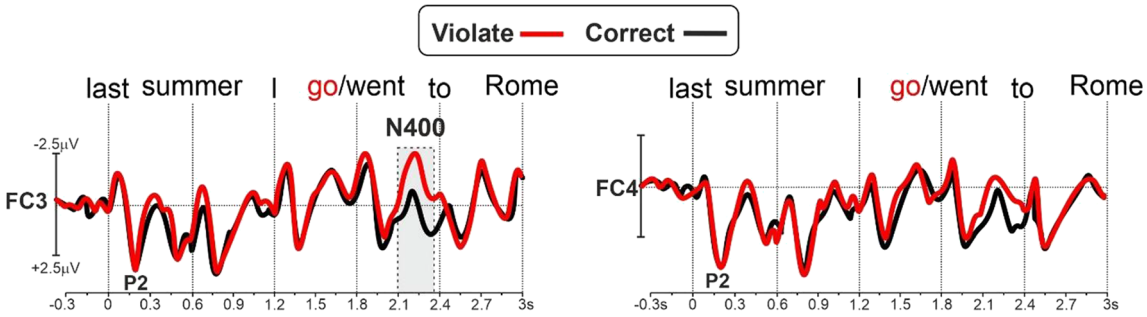

Fig. 7 N400 elicited in a visually presented sentence containing an adverb-verb temporal concord violation

observed in patients who have suffered form strokes in the left temporal lobe or temporo-parietal junction. In these populations, the N400 seems a reliable quantitative tool to assess the presence and severity of comprehension deficits [259]. In this recent study, application of a word picture verification task confirmed impairments at both phonological and semantic stages of comprehension in Wernicke's aphasia.

The presence of N400 as an indicator of semantic comprehension and possible awareness was used to evaluate residual cognitive abilities in chronic disorder of consciousness. The response to semantic paradigms may be preserved in a minority of behaviorally unresponsive or low-responsive DOC patients, also in absence of ERPs by oddball tasks, confirming that such cortical response could be useful in the complete assessment of cognitive reserve [260, 261]. In focal seizure disorders, the N400 was used to evaluate language comprehension and verbal memory before surgery. A lack of N400 effect in temporal lobe epilepsy could indicate a deficit in semantic processing and a failure in the mechanisms of automatic access to lexicon [262]. In temporal epilepsy patients submitted to ERPs by language memory, phonological, and semantic decision tasks, the left hemisphere lateralization could be an important element to assess presurgery evaluation [263].

In Alzheimer's disease, the early involvement of temporal lobe functions suggested the use of N400. Results are quite contradictory, depending upon the stage of the disease and the semantic context of the task. Studies in small mild cognitive impairment patients' groups suggested that abnormalities of the N400 and subsequent P600 are associated with an increased risk of subsequent conversion to Alzheimer's disease (AD) [264]. The N400 was also modulated in amplitude in AD patients submitted to a cognitive training, so it could be a sign of plasticity due to language rehabilitation strategy [265].

Disorganized speech is a fundamental clinical symptom of schizophrenia. This symptom encouraged many ERP studies examining N400 semantic context effects in patients with this disorder. A recent review on N400 paradigms application in schizophrenia patients reported that patients with schizophrenia have deficits in using contextual information in combination with world knowledge to predict upcoming meaningful or semantic stimuli. A neurocognitive mechanism of delusions could thus subtend such abnormalities [266].

Divergent results are reported in studies on learning disabled subjects, for the different tasks implemented and the possible variability in specific developmental language deficits. However, the N400 could be a reliable tool in the early prediction of poor expressive language skills [267].

In ERP studies on reading, dyslexic readers have been found to exhibit deviant phonological priming in the N400 range [268]. In a study on dyslexic and skilled adult control readers, a N400 effect associated with semantically related pictures (vs. unrelated) was found in both groups, reflecting intact integration of semantic similarities. The attenuated N400 to objects preceded by phonemic-related primes vs. unrelated showed a more widespread distribution over the right hemisphere in the dyslexics, so authors concluded that topographic differences between groups might suggest different word form encoding process in dyslexics [269].

Advantages and limits The N400 is not a simple "language" measure, though it opened the scenario of the investigation of the neural bases of language comprehension. A major contribution of the N400 to psycholinguistic research was the almost immediate time of detection of semantic manipulations. The N400 is also reliable in the assessment of qualitative similarity between the effects of a word prime and those of a sentence context on word processing. However, the functional interpretation of these ERPs is often confusing. The tremendous number of N400 studies conducted in recent decades show a variety of findings, including monophasic N400 and subsequent P600 effects, but also bi-phasic N400/P600 patterns [252].

Perspectives The clinical use of such ERP is promising in the cognitive domain, though questions regarding the full interpretation of obtained signals in specific populations are hard in the absence of a unique theory of the neural and functional nature of the N400. Larger studies involving specific populations as the demented, epileptic, or focal lesion-affected patients could contribute to clarify

doubts regarding functional nature of the ERP and its possible diagnostic and predictive value.

General remarks

The first part of this review article dealt with the more commonly used event-related responses. For historical reasons, we began with the P300 potential, which can be considered as the progenitor of ERPs. This component has been largely studied in both healthy subjects and diseases. Although the cerebral mechanisms at the base of its generation are still partially unknown, P300 has proved useful in detecting cognitive decline in the different ages of life. Also, LEPs have a well-documented clinical usefulness, but their diffusion is limited by the cost of the equipment and legal limitations (e.g., LEPs are not approved by FDA). While P300 and MMN potentials are commonly used in the clinical practice, other ERP components mentioned here are still confined to the research field. However, these techniques (CNV, BP/pN, N400 recording) deserve to be tested also in clinical conditions, since they provide an information on the cognitive cerebral mechanisms which cannot be obtained with the neuroimaging methods. We hope that a larger diffusion of the different psychophysiological techniques will make them more reliable not only for the investigation of the physiological processes underlying the mental activities, but also for a possible contribution to the diagnosis and follow-up of patients.

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Compliance with ethical standards

Conflict of interest No author declared conflict of interest.

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