Pearl and pitfalls in brain functional analysis by event–related potentials: position statement of Italian Psychophysiology and Cognitive Neuroscience Society on methodological limits and clinical reliability-Part I

ABSTRACT

Event-Related Potentials (ERPs) is a method to extract, from the Electroencephalogram (EEG) or the Magnetoencefalogram (MEG-Event Related Fields-ERF), 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 the most of procedures. The aim of the present review is to establish limits and reliability of ERP medical application, summarizing main methodological issues, 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), with a chapter dedicated to laser evoked potentials (LEPs). One section is dedicated to proactive preparatory brain activity as the Bereitschaftspotential or readiness potential (BP/pN).

The P300 and 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 used in normal and pathological cases and well standardized, are still confined to the research field. Both CNV and BP/pN deserve to be largely tested in movement disorders to explain possible functional changes in motor preparation circuits subtending different clinical pictures and response to treatments.

Key words: event-related potentials, P300, mismatch negativity, Contingent Negative Variation, Bereitschaftspotential, Laser evoked potentials, limits, reliability, clinical application

Introduction

The Event-Related Potential (ERP) is a method to extract, from the whole electroencephalographic (EEG) 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) exogenous brain responses to stimuli requiring passive perception only, while ERPs may refer to late (more than 100 ms) endogenous brain responses to stimuli requiring more complex cognitive functions as stimulus discrimination and behavioral responses. However, giving that endogenous and exogenous responses usually coexist, together with motor responses, in any task (e.g. the P100 attention effects; [1], including passive perception e.g. [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, Braren, Zubin and John [5] made another advancement with the discovery of the P3 component. Over the next fifteen 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, the 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 applicaton [9]. Main indices as the latency of a given component, the mean amplitude across a time window, or 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 the most of procedures. Key reasons are the different recording and analysis methods, the different expertise in clinical neurophysiology or psychology, 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, 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], chronic pain [17].

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

The first part of the review, focuses on main standardized ERP methods, including P300, CNV, 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 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 needs to be better defined in order to improve reliability [19, 20].

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); 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 sec 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 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 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 10kOhms. 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/sec sampling rate) whereas a bandpass from 0.01 to 100 c/sec is optimal, being that ERPs are slow waves. Trials contaminated by non-cerebral artefacts 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 of 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 18-20 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 yrs. 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 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 to be 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, 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 preclinical 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 [59].

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) [60].

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) [61-64]. 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 [65].

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 [66].

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 [67]. However, data across studies are 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 [68]. P3b amplitude abnormalities emerged also in children with autism spectrum disorder, suggesting the presence of deficit in the domain of attention and working memory [69].

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 spatiotemporal 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 [70].

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 sec) [71], 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 [72]) is necessary to elicit the expectancy wave [4].
The inter-trial interval randomly could vary between 3-10 sec [4]. CNV can be evoked by combining visual and auditory stimuli or using stimuli consisting of a single sensory modality [4, 73]. For most healthy adult subjects, maximum CNV amplitude occurs after about 30 trials [74].
In order to obtain a better reproduction of this brain electrical signal very long-time constants (at least > 6 sec) are required [75]. Usually, the analysis epoch for each CNV is 5 sec with a 500ms 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 700ms following S1), and the late window (late CNV) (200ms preceding S2) compared with the pre-stimulus baseline [71, 76]. The minimum equipment to record a reliable CNV, consists of 3 recording electrodes on Fz,Cz and Pz derivations, referred to the linked mastoids. The band pass filter is 0.1-03-30-100 Hz. The electroculogram 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 [75]. A moderate-to-high reliability has been reported for all the three CNV components, especially the early CNV [77]. A relationship between CNV amplitude and reaction time following S2 is present: larger CNV amplitude, the shorter the response time [73, 78] (Fig.3). Developmental research demonstrated that children tend to have smaller, less negative CNV components compared to adults [79-80]. Additional data indicate that the CNV amplitudes gradually become more negative throughout development into young adulthood [81]. Moreover, a progressive amplitude reduction for CNV waves was found in the older subjects [82]. 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 subclinical 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 [83-84]. This “expectancy wave” is associated with selective behavioral functions, such as attention, preparation, estimation, and voluntary motor control [85, 73, 86]. When the interval between S1 and S2 is sufficiently long (>1,5 sec) [71], 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 [87].

Several studies have demonstrated that frontal regions are important in genesis of the CNV, especially the dorsolateral prefrontal cortex [88-90]. Additional neural influences have been suggested, such as the supplementary motor cortex, primary motor cortex, anterior cingulated cortex, basal ganglia, thalamus, orbitofrontal cortex, and even parietal areas [91-96].

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 of increased amplitude in migraineurs, and a deficit of habituation, specifically again in the early CNV, was also found [97]. These alterations are proven to worsen intercritically, especially during the days preceding the attack, and to normalize both during the attack [98-101]. 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 [102-105]. This data supports the hypothesis that the hyperresponsivity in stimulus processing, and the consequent enhanced neuronal energy demand [106-107] could contribute to the pathophysiology of migraine; moreover, the normalization of the CNV in migraine could reflect the improvement of its clinical course.

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 [108- 116], and this reduction can be restored by dopaminergic medication [117] and subthalamic nucleus deep brain stimulation [116], thus giving evidence that the basal ganglia deficit has consequences on the activity of prefrontal cortex functioning [118]. Moreover, they suggested that CNV is modulated by dopamine. Many studies confirmed these observations [119-121], 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 [122].

Lastly, CNV amplitude resulted decreased also in dystonic syndromes such as writer's cramp and cervical dystonia, with movement-specific abnormalities. 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) [123-125]. This finding point 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.

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 CNV amplitude, schizophrenic patients may display an enhanced negative potential after S2, which has been called Post-Imperative Negative Variation (PINV) [126-128]. 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" [129]. These patients, in fact, display a difficulty to correctly prepare for incoming stimulus and response evaluation [130] reflecting a problem of movement control [128] during the resolution of the task request at S2. This psychophysiological pattern is compatible with the prefrontal cortical dysfunction of schizophrenia.

Advantages and Limits. 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 evaluate 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 inter-stimulus 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

General description. Originally described by Näätänen et al [131], 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 [132]. 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 [133].

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 [94, 134-135]. There seems to be a small delay in the frontal activation compared to the activation of the auditory cortex [136], which supports the hypothesis that the detection change signal generated by the auditory cortex may induce the frontal addressing mechanism of attention [137].

Moreover, the first report of a visual MMN was published by Cammann in 1990 [138]. This section mainly concerns the best-known auditory MMN and includes some hints on the visual MMN.

Methods of recording and analysis. MMN is more evident when the subjects ignore the stimuli [139] and can be administered, for example, while the participant reads or watches videos. The auditory MMN can occur in response to deviance in pitch, intensity, or duration [140]. 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 [141]. 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 [142]. 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 0.1-0.3–30-100 Hz and sampled at twice than the high pass filter; responses must be averaged separately for each stimulus type in each subject and 0 μV baseline must be determined as the mean amplitude of the pre-stimulus period [143]. 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 [143]; it is usually evident on the frontal sites and on the mastoids due to the inversion of the dipole [144-145]. Recording several scalp derivations and mapping data certainly allows a clearer identification of the evoked potential concerned [144].

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 [133, 146-147]. The latency and the amplitude are the most important parameters to identify the possible auditory processing disorders [146]. 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 [148].

Main contribution in cognitive neurosciences and neurological diseases. The auditory MMN is an index of pre-attentive processing [149]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 [150-152]. 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 [146]. 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 [148,153-154].

Kimura et al. [155] 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 [156] and states of coma, in the latter becoming a measure of the prediction of its outcome and of the pharmacological effects [157-158]. 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 [159], of patients with oppositional character in association to difficulties in understanding a task such as young individuals with autism with mental retardation [143] or adults with dementia [160], and of subjects with incapacity to perform standard neuropsychological tests because of speech or motility problems, such as amyotrophic lateral sclerosis sufferers [161-162].

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 [163] and schizophrenia [164-165]. 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 help explain major clinical and pathophysiological aspects of schizophrenia and other psychotic disorders [166-167].

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 [168]. Hence, cognitive decline can now be objectively measured with the MMN [132].

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 [169]; this is the case, for instance, of narcolepsy [170-171].

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 [172].

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, hypertension, and in physiological aging [173].

Advantages and Limits. To 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 [174-176], despite the encouraging inputs by Näätänen et al. [168]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 [177].

Within the arrangement of normative data that might prove to be sensitive for the detection of subtle and pre-clinical 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 [148].

In a much 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 [178].

The Bereitshaftpotential and the Prefrontal Negativity

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, the Event-Related Potentials (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,[179]), and the recently discovered prefrontal negativity (pN, [180]). The BP reflects the progressive cortical excitability of supplementary and cingulate motor areas in self-paced [181] and externally-triggered motor tasks [19, 182], which was interpreted as an index of motor readiness [183]. The pN, whose source has been localized in the pars opercularis of the inferior frontal gyrus (fig; [38, 2, 184]), has been associated with proactive top-down cognitive control (especially inhibition) of an upcoming response for both externally-triggered [38] and self-paced [185] tasks. There is increasing evidence that the BP and the pN modulations might predict motor and cognitive action performance, respectively [186-189]. Differently from the contingent negative variation (CNV, 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 fronto-polar scalp sites (Fp1, Fpz, Fp2) with medial radial distribution in the later phase [187]. The pN initiates 800 ms before stimulus onset and peaks concomitantly to it [19] (Figure 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 [190-192]. In externally-triggered response tasks, the BP and the pN can be similarly obtained triggering the EEG on both events or responses [19,193]. 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, 192, 194] with sufficient inter-stimulus interval (minimum one second) 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. [181]). 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 [180, 188, 190,191, 192]. In externally-triggered tasks, its amplitude has been consistently associated with response speed: the larger the BP, the

shorter the response time (RT) [185, 187, 189]. Further, whilst the BP showed reduced amplitudes (~1μV) in pre-adolescent children compared to adults [188], this component seems to be not affected by ageing [192].

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 [187]. The pN is robustly affected by age: in children, it is almost absent, and response accuracy and consistency are low [188], 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 [192]. In SRTs, the pN is usually absent in young people but becomes evident after the 50th year [192]. Nonetheless, both pN and BP are enhanced in young-adults multiple sclerosis patients [195].

Main contribution in cognitive neurosciences and neurological diseases The BP component has been largely explored both in 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 [196-197]. Conversely, in externally-triggered response tasks, increased motor readiness has been associated to improved behavioral performance [186, 198-199]. 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 [189, 200]. 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 [201].

The pN component has been associated to proactive top-down control and proactive inhibition, according to its bilateral or right-lateralized distributions [38, 185, 202]. The pN amplitude has been associated with enhanced sustained attention on the task [189]. Further, increased right-lateralized pN activity has been found in self-decided inhibition during self-paced motor tasks [185] , and associated to reduced commission error rates during Go-Nogo tasks [186], corroborating the right-lateralized proactive inhibition

hypothesis [203]. Further, in self-paced motor tasks [204], a neural efficiency hypothesys for the pN has also been accounted, reflecting decreased recruitment of prefrontal areas in experienced performance. According to Di Russo et al. [38], the BP and the pN might reflect a sort of accelerator/brake system that, based on predictive internal models, plans and anticipates future actions. A review on the pN component can be found in Di Russo et al. [19].

Clinical applications. Regarding the clinical applications, changes in the BP occur in several movement disorders, expecially in those deseases including a failure of SMA activation. Indeed the presence (or absence) of a clear BP can also have diagnostic importance for certain movement disorders [87]. For istance, 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 [201]. In severe traumatic brain injury (TBI) with good recovery the BP amplitude has been found reduced expecially for self-paced movements, but not the motor potential [205]. These results indicate the presence in TBI patients 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 [181]. Patients with paraplegia due to spinal cord injury (SCI) showed reduced BP and pN components in a discrimative 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 [206]. 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 inter-stimulus interval (ISI) should not be too short, given the slow nature and the pre-stimulus occurrence of these ERPs; ISI of more than 1 second 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 [207]. 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 [208] 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 [209], since EEG feedback affected the process of selection of action and decision making by means of P3 modifications.

Laser Evoked Potentials

General description. Laser evoked potentials were introduced more than 40 years ago [210] 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 [211] and spinal [212-213] 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 [214]. 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 [215] (Figure 7).

Methods of recording and analysis. Three recording electrodes are enough to record LEPs for clinical applications [17]. An electrode at 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 diffuse 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 from perioral, hand and foot in 100 normal subjects in the 14-82 age range. The N2 and P2 latencies were found increased and amplitudes decreased from face to foot. For all LEPs, regardless of the stimulation site, N2P2 amplitude correlated negatively with age, whereas LEP latency did not.

The latency of hand and foot-LEPs, though 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 threshold. Another study in forty normal subjects in the 20-68 age range confirmed the age related changes of all the main LEPs waves amplitudes obtained from thigh and foot, including the N1 component [220]. Age dependent changes involved distal LEPs 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 correlated 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, with a progressive decline of hand vertex LEPs amplitudes with age. Authors suggested an age related facilitation of the cortical circuits subtending the

later LEPs at the trigeminal level [215]. 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 waves 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 N2P2 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 seemed to provoke an inhibitory action on the vertex complex [105, 231], indicating an interference effect between contexts of cognitive attraction and arousal, and pain.

Both in PNS and CNS 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 dysrythmia 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, LEPs study lead 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 LEPs generators networks [18]. The physiological significance of LEPs remains

considerable, as the specific a-delta-C fibers activation refers to the nociceptive pathways and central networks, whenever the latter have a multimodal way of function.

Clinical applications. LEPs are commonly used for the diagnosis of neuropathic pain [234, 219], 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 (pshycogenic) etiologies [237]. Finally, LEPs offer also an unique opportunity to explore distinct cortical areas, which are differently activated by medial and lateral nociceptive systems [17, 215, 238].

Overall, LEPs are altered in disorders affecting either the peripheral (PNS) or the central nervous system (CNS)[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 and sparing of unmyelinated fibres, have absent Adelta- but normal C-related potentials, whereas those with Wallenberg syndrome or other CNS pain syndromes have impaired both Adelta- and C-related responses [217].

LEPs are of particular interest also in the diagnosis of pain of non-organic origin [215]. 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 high-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 A-delta LEP N2/P2 responses, when compared to

minimally-conscious state (MCS) [248]. However, C-LEP 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 under 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. Studies underlining the scarce specificity of the vertex N2P2 complex and their cortical generators for pain, seemed to reduce the reliability of laser evoked responses [18]. Nevertheless, the specificity of laser stimulators for A-delta 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 the other stimulators as the Yap and argon 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].

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 the life. Also, LEPs have 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 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.

Figures Legends

Figure 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: mentally count the rare targets.

Figure 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.

Figure 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: 1000Hz, target: 2000Hz).

(B) Scalp potential maps at 600ms (mean value of W1-CNV) for T0, T1 and T2.

(modified from [78]).

Figure 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.

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

Figure 6 Laser evoked responses obtained by hand and foot stimulation. On the right, the vertex complex N2P2 and the temporal N1 are reported. On the left, 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, the P2 in the anterior cingulate (modified by Valeriani et al. [251]).

REFERENCES

1. Courchesne E, Hilliard SA, Galambos R (1975) Stimulus novelty, task relevance and the visual evoked potential in man. Electroencephalogr Clin Neurophysiol 39:131–143.
2. Ragazzoni A, Di Russo F, Fabbri S, Pesaresi I, Di Rollo A, Perri RL, Barloscio D, Bocci T, Cosottini M Sartucci F (2019) "Hit the missing stimulus". A simultaneous EEG-fMRI study to localize the generators of endogenous ERPs in an omitted target paradigm. Sci Rep 9:3684.
3. Luck, SJ (2014) An introduction to the event-related potential technique. MA: MIT Press, Cambridge.
4. Walter WG, Cooper R, Aldridge VJ, WC, Winter AL (1964) Contingent negative variation: an electric sign of sensorimotor association and expectancy in the human brain. Nature 203:380-384.
5. Sutton S, Braren M, Zubin J, John ER (1965) Evoked-Potential Correlates of Stimulus Uncertainty. Science 150:1187–1188
6. Murta T, Leite M, Carmichael DW, Figueiredo P, Lemieux L (2015) Electrophysiological correlates of the BOLD signal for EEG-informed fMRI. Hum Brain Mapp 36(1):391-414. doi: 10.1002/hbm.22623.

7. Hari R, Baillet S, Barnes G, Burgess R, Forss N, Gross J, Hämäläinen M, Jensen O, Kakigi R, Mauguière F, Nakasato N, Puce A, Romani GL, Schnitzler A, Taulu S (2018) IFCN-endorsed practical guidelines for clinical magnetoencephalography (MEG). Clin Neurophysiol 129(8):1720-1747. doi: 10.1016/j.clinph.2018.03.042
8. Tallon-Baudry C, Bertrand O (1999) Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 3:151–162
9. Thigpen NN, Kappenman ES, Keil A (2017) Assessing the internal consistency of the event-related potential: An example analysis. Psychophysiology 54: 123–138. doi: 10.1111/psyp.12629.
10. Kappenman ES, Luck SJ (2012) Manipulation of orthogonal neural systems together in electrophysiological recordings: the MONSTER approach to simultaneous assessment of multiple neurocognitive dimensions. Schizophr Bull 38(1):92-102. doi: 10.1093/schbul/sbr147.
11. Dien J, Spencer KM, Donchin E (2003) Localization of the event related potential novelty response as defined by principal components analysis. Brain Research: Cognitive Brain Research 17 (3):637–650.
12. Sur S, Sinha VK (2009) Event-related potential: an overview. Ind Psychiatry 18(1):70-73.
13. Kotchoubey B (2017) Evoked and event-related potentials in disorders of consciousness: A quantitative review. Conscious Cogn 54:155-167. doi: 10.1016/j.concog.2017.05.002.
14. Bennys K, Gabelle A, Berr C, De Verbizier D, Andrieu S, Vellas B, Touchon J (2017) Cognitive Event-Related Potential, an Early Diagnosis Biomarker in Frail Elderly Subjects: The ERP-MAPT-PLUS Ancillary Study. J Alzheimers Dis 58(1):87-97. doi: 10.3233/JAD-161012.
15. Luck SJ, Mathalon DH, O'Donnell BF, Hämäläinen MS, Spencer KM, Javitt DC, Uhlhaas PJ (2011) A roadmap for the development and validation of event-related potential biomarkers in schizophrenia research. Biological Psychiatry 70:28–34. doi: 10.1016/j.biopsych.2010.09.021
16. Foti D, Kotov R, Hajcak G (2013) Psychometric considerations in using error-related brain activity as a biomarker in psychotic disorders. Journal of Abnormal Psychology 122:520–531.

17. Valeriani M, Pazzaglia C, Cruccu G, Truini A (2012) Clinical usefulness of laser evoked potentials. Neurophysiol Clin 42(5):345-353. doi: 10.1016/j.neucli.2012.05.002.
18. Legrain V, Iannetti GD, Plaghki L, Mouraux A (2011) The pain matrix reloaded: a salience detection system for the body. Prog Neurobiol 93(1):111-24. doi: 10.1016/j.pneurobio.2010.10.005
19. Di Russo F, Berchicci M, Bozzacchi C, Perri RL, Pitzalis S, Spinelli D (2017) Beyond the "Bereitschaftspotential": Action preparation behind cognitive functions. Neurosci Biobehav Rev 78:57-81. doi: 10.1016/j.neubiorev.2017.04.019
20. Belardinelli P, Biabani M, Blumberger DM, Bortoletto M, Casarotto S, David O, Desideri D, Etkin A, Ferrarelli F, Fitzgerald PB, Fornito A, Gordon PC, Gosseries O, Harquel S, Julkunen P, Keller CJ, Kimiskidis VK, Lioumis P, Miniussi C, Rosanova M, Rossi S, Sarasso S, Wu W, Zrenner C, Daskalakis ZJ, Rogasch NC, Massimini M, Ziemann U, Ilmoniemi RJ (2019) Reproducibility in TMS-EEG studies: A call for data sharing, standard procedures and effective experimental control. Brain Stimul 12(3):787-790. doi: 10.1016/j.brs.2019.01.010.
21. Sutton S, Braren M, Zubin J, John ER (1965) Evoked potentials correlates of stimulus uncertainty. Science 150:1187-1188.
22. Katayama J, Polich J (1999) Auditory and visual P300 topography from a 3 stimulus paradigm. Clin Neurophysiol 110:463-468.
23. Sutton S, Tueting P, Zubin J, John ER (1967) Information delivery and the sensory evoked potential. Science 155:1436-1439.
24. Donchin E, Ritter W, McCallum C (1978) Cognitive psychophysiology: the endogenous components of the ERP. In: Callaway E, Tueting P, Koslow S, eds. Brain event-related potentials in man. Academic Press, New York, pp 349-411.
25. Dien J, Spencer KM, Donchin E (2004) Parsing the late positive complex: mental chronometry and the ERP components that inhabit the neighborhood of the P300. Psychophysiology 41:665-678.
26. Kutas M, McCarthy G, Donchin E (1977) Augmenting mental chronometry: P300 as a measure of stimulus evaluation time. Science 197:792-795.

27. Ragazzoni A, Matà S, Grippo A, Pinto F (1996) Dual task performance: effects of increasing difficulty on auditory ERPs and RTs. In: Barber C, Celesia G, Comi GC, Mauguière F, eds. Functional Neuroscience (EEG Suppl. 46). Elsevier: 253-260.
28. Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L (2009) Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci U S A 106(5):1672-1677. doi:10.1073/pnas.0809667106.
29. Oostenveld R, Praamstra P (2001) The five percent electrode system for high-resolution EEG and ERP measurements. Clin Neurophysiol 112:713-719.
30. Picton T, Bentin S, Berg P, Donchin E, Hillyard SA, Johnson R Jr, Miller GA, Ritter W, Ruchkin DS, Rugg MD, Tajlor MJ (2000) Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. Psychophysiology 37:127-152.
31. Polich J, Kok A (1995) Cognitive and biological determinants of P300: an integrative review. Biol Psychol 41:103-146.
32. Polich J (1997) EEG and ERPs in normal aging. Electroenceph clin Neurophysiol 104:228-243.
33. Reinvang I (1999) Cognitive Event-Related Potentials in Neuropsychological assessment. Neuropsychol Rev 9:231-248.
34. Donchin, E (1981), Surprise!…Surprise?. Psychophysiology 18:493-513. doi:10.1111/j.1469-8986.1981.tb01815.x
35. Verleger R, Smigasiewicz K (2016) Do rare stimuli evoke large P3s by being unexpected? A comparison of the oddball effects between standard-oddball and prediction-oddball tasks. Adv Cogn Psychol 12:88-104.
36. Friston K A (2005) A theory of cortical responses. Phil Trans R Soc B 360:815-836.
37. Naatanen R, Paavilainen P, Rinne T, Alho K (2007) The mismatch negativity (MMN)0 in basic research of central auditory processing: a review. Clin Neurophysiol 118:2544-2590.
38. Di Russo F, Lucci G, Sulpizio V, Berchicci M, Spinelli D, Pitzalis S, Galati G (2016) Spatiotemporal brain mapping of the preparation, perception and action phases. Neuroimage 126:1-14.

39. Snyder E, Hillyard SA (1976) Long-latency evoked potentials to irrelevant, deviant stimuli. Behav Biol 16:319-331.
40. Squires NK, Squires KC, Hillyard SA (1975) Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroenceph clin Neurophysiol 38:387-401.
41. Halgren E, Marinkovic K, Chauvel P (1998) Generators of the late cognitive potentials in auditory and visual oddball tasks. Electroenceph clin Neurophysiol 106:156-164.
42. Polich J (2007) Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol 118:2128-2148.
43. Valeriani M, Fraioli L, Ranghi F, Giaquinto S (2001) Dipolar source modeling of the P300 event-related potential after somatosensory stimulation. Muscle Nerve 24(12):1677-1686.
44. Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Naatanen R, Polich J, Reinvang I, Van Petten C (2009) Event-related potentials in clinical research: Guidelines for eliciting, recording and quantifying mismatch negativity, P300 and N400. Clin Neurophysiol 120:1883-1908.
45. Goodin DS, Squires KC, Starr A (1978) Long latency event-related components of the auditory evoked potential in dementia. Brain 101:635-648.
46. Polich J, Corey-Bloom J (2005) Alzheimer's disease and P300: review and evaluation of task and modality. Curr Alzheimer Res 2:515-525.
47. Frodl T, Hampel H, Juckel G, Bürger K, Padberg F, Engel RR, Möller HJ, Hegerl U (2002) Value of event-related P300 subcomponents in the clinical diagnosis of mild cognitive impairment and Alzheimer's Disease. Psychophysiology 39:175-81.
48. Golob EJ, Irimajiri R, Starr A (2007) Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. Brain 130(Pt 3):740-752.
49. Golob EJ, Ringman JM, Irimajiri R, Bright S, Schaffer B, Medina LD, Starr A (2009) Cortical event-related potentials in preclinical familial Alzheimer disease. Neurology 73:1649-1655.
50. Ally BA, Jones GE, Cole JA, Budson AE (2005) The P300 component in patients with Alzheimer's disease and their biological children. Biol Psychol 72:180-187.

51. Goodin DS, Aminoff MJ (1986) Electrophysiological differences between subtypes of dementia. Brain 109:1103-1113

52. Johnson R Jr, Litvan I, Grafman J (1991) Progressive supranuclear palsy: altered sensory processing leads to degraded cognition. Neurology 41:1257-1262.

53. Bonanni L, Franciotti R, Onofrj V, Anzellotti F, Mancino E, Monaco D, Gambi F, Manzoli L, Thomas A, Onofrj M (2010) Revisiting P300 cognitive studies for dementia diagnosis: early dementia with Lewy bodies (DLB) and Alzheimer disease (AD). Neurophysiol Clin 40:255-265.

54. Patterson JV, Michalewski HJ, Starr A (1988) Latency variability of the components of auditory event-related potentials to infrequent stimuli in aging, Alzheimer-type dementia, and depression. Electroenceph clin Neurophysiol 71:450-460.

55. Polich J, Herbst KL (2000) P300 as a clinical assay: rationale, evaluation and findings. Int J Psychophysiol 38:3-19.

56. Heinze HJ, Munte TF, Kutas M, Butler SR, Naatanen R, Nuwer M, Goodin DS (1999) Cognitive event-related potentials. In : Recommendations for the Practice of Clinical Neurophysiology: Guidelines of the International Federation of Clinical Neurophysiology. G. Deuschl, A. Eisen (Eds.). Electroenceph clin Neurophysiol, Suppl 52:91-95.

57. Farwell LA, Donchin E (1991) The truth will out: interrogative polygraphy (‘‘lie detection’’) with event-related brain potentials. Psychophysiology 28:531–547.

58. Meijer EH, Ben-Shakhar G, Verschuere B, Donchin E (2013) A comment on Farwell (2012): brain fingerprinting: a comprehensive tutorial review of detection of concealed information with event-related brain potentials. Cogn Neurodyn 7:155–158

59. Meijer EH, Ben-Shakhar G, Verschuere B, Donchin E (2013) A comment on Farwell (2012): brain fingerprinting: a comprehensive tutorial review of detection of concealed information with event-related brain potentials. Cogn Neurodyn 7(2):155-158. doi: 10.1007/s11571-012-9217-x.

60. Wolpaw, JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM (2002) Brain-computer interfaces for communication and control. Clin Neurophysiol 113:767–791.

61. Kotchoubey B, Lang S, Mezger G, Schmalohr D, Schneck M, Semmler A, Bostanov V, Birbaumer N (2005) Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin Neurophysiol 116:2441-2453.
62. Chennu S, Finoia P, Kamau E, Monti MM, Allanson J, Pickard JD, Owen AM, Bekinschtein TA (2013) Dissociable endogenous and exogenous in disorders of consciousness. Neuroimage Clin 3:450-461.
63. Ragazzoni A, Pirulli C, Veniero D, Feurra M, Cincotta M, Giovannelli F, Chiaramonti R, Lino M, Rossi S, Miniussi C (2013) Vegetative versus minimally conscious states: a study using TMS-EEG, sensory and event-related potentials. PLoS One 8:e57069.
64. Ragazzoni A, Cincotta M, Giovannelli F, Cruse D, Young GB, Miniussi C, Rossi S (2017) Clinical neurophysiology of prolonged disorders of consciousness: From diagnostic stimulation to therapeutic neuromodulation. Clin Neurophysiol 128:1629-1646.
65. Daltrozzo J, Wioland N, Mutschler V, Kotchoubey B (2007) Predicting coma and other low responsive patients outcome using event-related brain potentials: A meta-analysis. Clin Neurophysiol 118:606–614.
66. Jeon YW, Polich J (2003) Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40:684-701.
67. Karaaslan F, Gonul AS, Oguz A, Erdinc E, Esel E (2003) P300 changes in major depressive disorders with and without psychotic features. J Affect Disord 73:283-287.
68. Johnstone SJ, Barry RJ, Clarke AR (2013) Ten years on: a follow-up review of ERP research in attention-deficit/hyperactivity disorder. Clin Neurophysiol 124:644-667.
69. Cui T, Wang PP, Liu S, Zhang X (2017) P300 amplitude and latency in autism spectrum disorder: a meta-analysis. Eur Child Adolesc Psychiatry 26:177-190.
70. Dale AM, Halgren E (2001) Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. Curr Opin Neurobiol 11:202-208.
71. Gaillard AW (1976) Effects of warning-signal modality on the contingent negative variation (CNV). Biol Psychol 4:139–154.

72. Bareš M, Nestrasil I, Rektor I (2007) The effect of response type (motor output versus mental counting) on the intracerebral distribution of the slow cortical potentials in an externally cued (CNV) paradigm. Brain Res Bull 71(4):428-435.
73. Tecce JJ (1972) Contingent negative variation (CNV) and psychological processes in man. Psychol Bull 77(2):73–108.
74. Cohen J (1969) Very slow brain potentials relating to expectancy: the CNV. In Donchin E and Lindsley DB (ed), Average evoked potentials; methods, results, and evaluations. US Government Printing Office, Washington, DC, pp 143-198.
75. Walter WG (1968) The contingent negative variation: an electro-cortical sign of sensori-motor reflex association in man. Prog Brain Res 22:364-377.
76. Travis F, Tecce JJ (1998) Effects of distracting stimuli on CNV amplitude and reaction time. Int J Psychophysiol 31: 45–50.
77. Taylor BK, Gavin WJ, Davies PL (2016) The Test–Retest Reliability of the Visually Evoked Contingent Negative Variation (CNV) in Children and Adults. Dev Neuropsychol 41(3)162-175.
78. Pauletti C, Mannarelli D, Grippo A, Currà A, Locuratolo N, De Lucia MC, Fattapposta F (2014) Phasic alertness in a cued double-choice reaction time task: a Contingent Negative Variation (CNV) study. Neurosci Lett 581:7-13.
79. Hämmerer D, Li SC, Müller V, Lindenberger U (2010) An electrophysiological study of response conflict processing across the lifespan: Assessing the roles of conflict monitoring, cue utilization, response anticipation, and response suppression. Neuropsychologia 48:3305–3316.
80. Jonkman LM (2006) The development of preparation, conflict monitoring and inhibition from early childhood to young adulthood: A Go/Nogo ERP study. Brain Research 1097:181–193.
81. Segalowitz SJ, Davies PL (2004) Charting the maturation of the frontal lobe: An electrophysiological strategy. Brain and Cognition 55:116–133.

82. Zappoli R (2003) Permanent or transitory effects on neurocognitive components of the CNV complex induced by brain dysfunctions, lesions and ablations in humans. Int J Psychophysiol 48(2):189-220.
83. Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience 3(3):201–215.
84. Gomez CM, Flores A (2011) A neurophysiological evaluation of a cognitive cycle in humans. Neuroscience and Biobehavioral Reviews 35(3):452–461.
85. McCallum WC, Walter WG (1968) The effects of attention and distraction on the contingent negative variation in normal and neurotic subjects. Electroencephalography and Clinical Neurophysiology 25(4):319–329.
86. Birbaumer N., Elbert T, Canavan AGM, Rockstroh B (1990) Slow potentials of the cerebral cortex and behavior. Physiological Reviews 70(1):1–41.
87. Colebatch JG (2007) Bereitschaftspotential and movement-related potentials: origin, significance, and application in disorders of human movement. Mov Disord 22(5):601-610.
88. Bareš M, Rektor I, Kanovský P, Streitová H (2003) Cortical and subcortical distribution of middle and long latency auditory and visual evoked potentials in a cognitive (CNV) paradigm. Clin Neurophysiol 114(12):2447-2460.
89. Basile LF, Baldo MV, de Castro CC, Gattaz WF (2003) The generators of slow potentials obtained during verbal, pictorial and spatial tasks. Int J Psychophysiol 48(1):55-65.
90. Mannarelli D, Pauletti C, Grippo A, Amantini A, Augugliaro V, Currà A, Missori P, Locuratolo N, De Lucia MC, Rinalduzzi S, Fattapposta F (2015) The Role of the Right Dorsolateral Prefrontal Cortex in Phasic Alertness: Evidence from a Contingent Negative Variation and Repetitive Transcranial Magnetic Stimulation Study. Neural Plast 2015:410785. doi: 10.1155/2015/410785.
91. Basile LF, Ballester G, de Castro CC, Gattaz WF (2002) Multifocal slow potential generation revealed by high-resolution EEG and current density reconstruction. Int J Psychophysiol 45(3):227-240.

92. Bender S, Resch F, Weisbrod M, Oelkers-Ax R (2004) Specific task anticipation versus unspecific orienting reaction during early contingent negative variation. Clinical Neurophysiology 115:1836–1845.
93. Falkenstein M, Hoormann J, Hohnsbein J, Kleinsorge T (2003) Short-term mobilization of processing resources is revealed in the event-related potential. Psychophysiology 40:914–923.
94. Giard MH, Perrin F, Pernier J, Bouchet P (1990) Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. Psychophysiology 27:627–640.
95. Knott VJ, Lapierre YD, De Lugt D, Griffiths L, Bakish D, Browne M, Horn E (1991) Preparatory brain potentials in major depressive disorder. Progress in Neuro-Psychopharmacology & Biological Psychiatry 15:257–262.
96. Zimmer H, Demmel R (2000) Habituation and laterality of orientating processes as reflected by slow negative waves. Biological Psychology 53:161–176.
97. Schoenen J, Ambrosini A, Sándor PS, Maertens de Noordhout A (2003) Evoked potentials and transcranial magnetic stimulation in migraine: published data and viewpoint on their pathophysiologic significance. Clin Neurophysiol 114(6):955-972.
98. Schoenen J, Timsit-Berthier M (1993) Contingent negative variation: methods and potential interest in headache. Cephalagia 13:28–32
99. Kropp P, Gerber WD (1995) Contingent negative variation during migraine attack and interval: evidence for normalization of slow cortical potentials during the attack. Cephalalgia 15(2):123–8.
100. Kropp P, Gerber WD (1998) Prediction of migraine attacks using a slow cortical potential, the contingent negative variation. Neurosci Lett 257(2):73–76.
101. Siniatchkin M, Kropp P, Gerber WD, Stephani U (2000) Migraine in childhood – are periodically occurring migraine attacks related to dynamic changes of cortical information processing? Neurosci Lett 279(1):1–4.

102. Schoenen J, Maertens de Noordhout A, Timsit-Berthier M, Timsit M (1986) Contingent negative variation and efficacy of beta-blocking agents in migraine. Cephalalgia 6(4):229-233.

103. Siniatchkin M, Gerber WD, Vein A (1998) Clinical efficacy and central mechanisms of cyclandelate in migraine: a double-blind placebo-controlled study. Funct Neurol 13(1):47–56.

104. Siniatchkin M, Andrasik F, Kropp P, Niederberger U, Strenge H, Averkina N, Lindner V, Stephani U, Gerber WD (2007) Central mechanisms of controlled-release metoprolol in migraine: a double-blind, placebo-controlled study. Cephalalgia 27(9):1024-1032.

105. de Tommaso M, Guido M, Sardaro M, Serpino C, Vecchio E, De Stefano G, Di Claudio T, Specchio LM, Livrea P (2008) Effects of topiramate and levetiracetam vs placebo on habituation of contingent negative variation in migraine patients. Neurosci Lett 442(2):81-85.

106. Di Clemente L, Coppola G, Magis D, Fumal A, De Pasqua V, Di Piero V, Schoenen J (2007) Interictal habituation deficit of the nociceptive blink reflex: an endophenotypic marker for presymptomatic migraine? Brain 130(Pt 3):765–770

107. Coppola G, Parisi V, Di Lorenzo C, Serrao M, Magis D, Schoenen J, Pierelli F (2013) Lateral inhibition in visual cortex of migraine patients between attacks. J Headache Pain 14(1):20.

108. Wright MJ, Geffen GM, Geffen LB (1993) Event-related potentials associated with covert orientation of visual attention in Parkinson’s disease. Neuropsychologia 31:1283–1297.

109. Cunnington R, Iansek R, Bradshaw JL, Phillips JG (1995) Movement-related potentials in Parkinson’s disease: presence and predictability of temporal and spatial cues. Brain 118:935–950.

110. Cunnington R, Iansek R, Johnson KA, Bradshaw JL (1997) Movement-related potentials in Parkinson's disease. Motor imagery and movement preparation. Brain 120(Pt 8):1339-1353.

111. Cunnington R, Iansek R, Bradshaw JL (1999) Movement-related potentials in Parkinson's disease: external cues and attentional strategies. Mov Disord 14(1):63-68.

112. Pulvermüller F, Lutzenberger W, Muller V, Mohr B, Dichgans J, Birbaumer N (1996) P3 and contingent negative variation in Parkinson’s disease. Electroencephalogr Clin Neurophysiol 98:456–467.

113. Praamstra P, Meyer AS, Cools AR, Horstink MW, Stegeman DF (1996) Movement preparation in Parkinson's disease. Time course and distribution of movement-related potentials in a movement precueing task. Brain 119:1689–704.

114. Wascher E, Verleger R, Vieregge P, Jaskowski P, Koch S, Kömpf D (1997) Responses to cued signals in Parkinson's disease. Distinguishing between disorders of cognition and of activation. Brain 120:1355–1375.

115. Ikeda A, Shibasaki H, Kaji R, Terada K, Nagamine T, Honda M, Kimura J (1997) Dissociation between contingent negative variation (CNV) and Bereitschaftspotential (BP) in patients with Parkinsonism. Electroencephalogr Clin Neurophysiol 102(2):42–51.

116. Gerschlager W, Alesch F, Cunnington R, Deecke L, Dirnberger G, Endl W, Lindinger G, Lang W (1999) Bilateral subthalamic nucleus stimulation improves frontal cortex function in Parkinson's disease. An electrophysiological study of the contingent negative variation. Brain 122:2365–2373.

117. Amabile G, Fattapposta F, Pozzessere G, Albani G, Sanarelli L, Rizzo PA, Morocutti C (1986) Parkinson disease: electrophysiological (CNV) analysis related to pharmacological treatment. Electroencephalogr Clin Neurophysiol 64(6):521-524.

118. Verleger R (2002) Event-related EEG potential research in neurological patients. In: Zani A, Proverbio AM, Posner MI (ed) The cognitive electrophysiology of mind and brain. Elsevier Science, USA pp 309–341.

119. Strollo F, Amabile G, Fattapposta F, Strollo G, More M, Riondino G (1988) Thyrotropin-releasing hormone enhances event-related brain potentials and growth hormone release in man. Neurosci Lett 93(2-3):346-353.

120. Tecce JJ (1991) Dopamine and CNV: studies of drugs, disease and nutrition. Electroencephalogr Clin Neurophysiol Suppl 42:153-164.

121. Linssen AM, Vuurman EF, Sambeth A, Nave S, Spooren W, Vargas G, Santarelli L, Riedel WJ (2011) Contingent negative variation as a dopaminergic biomarker: evidence from dose-related

effects of methylphenidate. Psychopharmacology (Berl) 218(3):533-542. doi: 10.1007/s00213-011-2345-x.

122. de Tommaso M, Difruscolo O, Sciruicchio V, Specchio N, Livrea P (2007) Abnormalities of the contingent negative variation in Huntington's disease: correlations with clinical features. J Neurol Sci 254(1-2):84-89.

123. Kaji R, Ikeda A, Ikeda T, Kubori T, Mezaki T, Kohara N, Kanda M, Nagamine T, Honda M, Rothwell JC, Shibasaki H, Kimura J (1995) Physiological study of cervical dystonia: task-specific abnormality in contingent negative variation. Brain 118:511-522.

124. Ikeda A, Shibasaki H, Kaji R, Terada K, Nagamine T, Honda M, Hamano T, Kimura J (1996) Abnormal sensorimotor integration in writer's cramp: study of contingent negative variation. Mov Disord 11(6):683-690.

125. Hamano T, Kaji R, Katayama M, Kubori T, Ikeda A, Shibasaki H, Kimura J (1999) Abnormal contingent negative variation in writer's cramp. Clin Neurophysiol 110(3):508-515.

126. Timsit-Berthier M, Delaunoy J, Koninckx N, Rousseau JC (1973) Slow potential changes in psychiatry. I. Contingent Negative Variation. Electroenceph clin Neurophysiol 35:355-361.

127. Klein C, Rockstroh B, Cohen R, Berg P (1996) Contingent negative variation (CNV) and determinants of the post-imperative negative variation (PINV) in schizophrenic patients and healthy controls. Schizophr Res 21(2):97-110.

128. Verleger R, Wascher E, Arolt V, Daase C, Strohm A, Kömpf D (1999) Slow EEG potentials (contingent negative variation and post-imperative negative variation) in schizophrenia: their association to the present state and to Parkinsonian medication effects. Clin Neurophysiol 110(7):1175-1192

129. Timsit M, Koninckx N, Dargent J, Fontaine O, Dongier M (1970) Contingent negative variation in psychiatry [in French]. Electroencephalogr Clin Neurophysiol 28(1):41-47.

130. Klein C, Andresen B, Berg P, Krüger H, Rockstroh B (1998) Topography of CNV and PINV in schizotypal personality. Psychophysiology 35(3):272-282.

131. Näätänen R, Gaillard AW, Mäntysalo S (1978) Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst) 42(4):313-329.

132. Näätänen R, Kujala T, Kreegipuu K, Carlson S, Escera C, Baldeweg T, Ponton C (2011) The mismatch negativity: an index of cognitive decline in neuropsychiatric and neurological diseases and in ageing. Brain 134(Pt 12):3435-3453.

133. Näätänen R, Paavilainen P, Tiitinen H, Jiang D, Alho K (1993) Attention and mismatch negativity. Psychophysiology 30(5):436-450.

134. Näätänen R, Michie PT (1979) Early selective-attention effects on the evoked potential: a critical review and reinterpretation. Biol Psychol 8(2):81-136.

135. Restuccia D, Della Marca G, Marra C, Rubino M, Valeriani M (2005) Attentional load of the primary task influences the frontal but not the temporal generators of mismatch negativity. Brain Res Cogn Brain Res 25(3):891-899.

136. Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Näätänen R (2000) Separate time behaviors of the temporal and frontal mismatch negativity sources. Neuroimage 12(1):14-19.

137. Näätänen R (1990) The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. Behav Brain Sci 13(2):201-233.

138. Cammann, R. (1990). Is there a mismatch negativity (MMN) in visual modality? Behav Brain Sci 13(2):234-235.

139. Paavilainen P, Tiitinen H, Alho K, Näätänen R (1993) Mismatch negativity to slight pitch changes outside strong attentional focus. Biol Psychol 37(1):23-41.

140. Baldeweg T, Richardson A, Watkins S, Foale C, Gruzelier J (1999) Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. Ann Neurol 45(4):495-503.

141. Bardsley B, Parker D, Lockton E (2014) Implementation of integrated mismatch negativity in differentiating children with specific language impairment. Neuropediatrics 45(1):10-15.

142. Tervaniemi M, Kujala A, Alho K, Virtanen J, Ilmoniemi RJ, Näätänen R (1999) Functional specialization of the human auditory cortex in processing phonetic and musical sounds: A magnetoencephalographic (MEG) study. Neuroimage 9(3):330-336.

143. Ferri R, Elia M, Agarwal N, Lanuzza B, Musumeci SA, Pennisi G (2003) The mismatch negativity and the P3a components of the auditory event-related potentials in autistic low-functioning subjects. Clin Neurophysiol 114(9):1671-1680.

144. Alho K, Paavilainen P, Reinikainen K, Sams M, Näätänen R (1986) Separability of different negative components of the event-related potential associated with auditory stimulus processing. Psychophysiology 23(6):613-623.

145. Lang AH, Eerola O, Korpilahti P, Holopainen I, Salo S, Aaltonen O (1995) Practical issues in the clinical application of mismatch negativity. Ear Hear 16(1):118-130.

146. Näätänen R, Astikainen P, Ruusuvirta T, Huotilainen M (2010) Automatic auditory intelligence: an expression of the sensory-cognitive core of cognitive processes. Brain Res Rev 64(1):123-136.

147. Shiga T, Yabe H, Yu L, Nozaki M, Itagaki S, Lan TH, Niwa S (2011) Temporal integration of deviant sound in automatic detection reflected by mismatch negativity. Neuroreport 22(7):337-341.

148. Raggi A, Tasca D, Rundo F, Ferri R (2013) Stability of auditory discrimination and novelty processing in physiological aging. Behav Neurol 27(2):193-200.

149. Näätänen R, Alho K (1995) Mismatch negativity--a unique measure of sensory processing in audition. Int J Neurosci 80(1-4):317-337.

150. Paavilainen P (2013) The mismatch-negativity (MMN) component of the auditory event-related potential to violations of abstract regularities: a review. Int J Psychophysiol 88(2):109-123.

151. Saarinen J, Paavilainen P, Schöger E, Tervaniemi M, Näätänen R (1992) Representation of abstract attributes of auditory stimuli in the human brain. Neuroreport 3(12):1149-1151.

152. Sussman E, Ritter W, Vaughan HG Jr (1998) Attention affects the organization of auditory input associated with the mismatch negativity system. Brain Res 789(1):130-138.

153. Haenschel C, Vernon DJ, Dwivedi P, Gruzelier JH, Baldeweg T (2005) Event-related brain potential correlates of human auditory sensory memory-trace formation. J Neurosci 25(45):10494-10501.

154. Ruzzoli M, Pirulli C, Brignani D, Maioli C, Miniussi C (2012) Sensory memory during physiological aging indexed by mismatch negativity (MMN). Neurobiol Aging 33(3):625.e21-30. doi: 10.1016/j.neurobiolaging.2011.03.021

155. Kimura M, Schröger E, Czigler I (2011) Visual mismatch negativity and its importance in visual cognitive sciences. Neuroreport 22(14):669-673.

156. Ibáñez AM, Martín RS, Hurtado E, López V (2009) ERPs studies of cognitive processing during sleep. Int J Psychol 44(4):290-304.

157. Kane NM, Curry SH, Butler SR, Cummins BH (1993) Electrophysiological indicator of awakening from coma. Lancet 341(8846):688.

158. Kane NM, Butler SR, Simpson T (2000) Coma outcome prediction using event-related potentials: P(3) and mismatch negativity. Audiol Neurootol 5(3-4):186-191.

159. Cheour M, Ceponiene R, Lehtokoski A, Luuk A, Allik J, Alho K, Näätänen R (1998) Development of language-specific phoneme representations in the infant brain. Nat Neurosci 1(5):351-353.

160. Schroeder MM, Ritter W, Vaughan HG Jr (1995) The mismatch negativity to novel stimuli reflects cognitive decline. Ann N Y Acad Sci 769:399-401.

161. Raggi A, Consonni M, Iannaccone S, Perani D, Zamboni M, Sferrazza B, Cappa SF (2008) Auditory event-related potentials in non-demented patients with sporadic amyotrophic lateral sclerosis. Clin Neurophysiol 119(2):342-350.

162. Raggi A, Iannaccone S, Cappa SF (2010) Event-related brain potentials in amyotrophic lateral sclerosis: A review of the international literature. Amyotroph Lateral Scler 11(1-2):16-26.

163. Pekkonen E (2000) Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. Audiol Neurootol 5(3-4):216-224.

164. Javitt DC, Grochowski S, Shelley AM, Ritter W (1998) Impaired mismatch negativity (MMN) generation in schizophrenia as a function of stimulus deviance, probability, and interstimulus/interdeviant interval. Electroencephalogr Clin Neurophysiol 108(2):143-153.

165. Javitt DC (2000) Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. Audiol Neurootol 5(3-4):207-215.

166. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC (1996) Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. Proc Natl Acad Sci U S A 93(21):11962-11967.

167. Olney JW, Farber NB (1995) Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52(12):998-1007.

168. Näätänen R, Kujala T, Escera C, Baldeweg T, Kreegipuu K, Carlson S, Ponton C (2012) The mismatch negativity (MMN)--a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clin Neurophysiol 123(3):424-458.

169. Goodin DS, Aminoff MJ (1992) Evaluation of dementia by event-related potentials. J Clin Neurophysiol 9(4):521-525.

170. Naumann A, Bierbrauer J, Przuntek H, Daum I (2001) Attentive and preattentive processing in narcolepsy as revealed by event-related potentials (ERPs). Neuroreport 12(13):2807-2811.

171. Raggi A, Plazzi G, Pennisi G, Tasca D, Ferri R (2011) Cognitive evoked potentials in narcolepsy: a review of the literature. Neurosci Biobehav Rev 35(5):1144-1153.

172. Näätänen R, Kähkönen S (2009) Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int J Neuropsychopharmacol 12(1):125-135.

173. Kremláček J, Kreegipuu K, Tales A, Astikainen P, Põldver N, Näätänen R, Stefanics G (2016) Visual mismatch negativity (vMMN): A review and meta-analysis of studies in psychiatric and neurological disorders. Cortex 80:76-112.

174. Bishop DV, McArthur GM (2004) Immature cortical responses to auditory stimuli in specific language impairment: evidence from ERPs to rapid tone sequences. Dev Sci 7(4):F11-18.

175. Boly M, Garrido MI, Gosseries O, Bruno MA, Boveroux P, Schnakers C, Massimini M, Litvak V, Laureys S, Friston K (2011) Preserved feedforward but impaired top-down processes in the vegetative state. Science 332(6031):858-862.

176. Taylor MJ, Baldeweg T (2002) Application of EEG, ERP and intracranial recordings to the investigation of cognitive functions in children. Dev Sci 5(3):18-34.

177. Lee AK, Larson E, Maddox RK, Shinn-Cunningham BG (2014) Using neuroimaging to understand the cortical mechanisms of auditory selective attention. Hear Res 307:111-120.

178. Bartha-Doering L, Deuster D, Giordano V, am Zehnhoff-Dinnesen A, Dobel C (2015) A systematic review of the mismatch negativity as an index for auditory sensory memory: From basic research to clinical and developmental perspectives. Psychophysiology 52(9):1115-1130.

179. Kornhuber HH, Deecke L (1965) Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere 284(1):1-17.

180. Berchicci M, Lucci G, Pesce C, Spinelli D, Di Russo F (2012) Prefrontal hyperactivity in older people during motor planning. NeuroImage 62:1750-1760.

181. Shibasaki H, Hallett M (2006) What is the Bereitschaftspotential? Clinical Neurophysiology 117(11):2341-2356.

182. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ (1995) Self-initiated versus externally triggered movements: I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 118(4):913-933.

183. Vaughan Jr HG, Costa LD, Ritter W (1968) Topography of the human motor potential. Electroencephalography and Clinical Neurophysiology 25(1):1-10.

184. Sulpizio V, Lucci G, Berchicci M, Galati G, Pitzalis S, Di Russo F (2017) Hemispheric asymmetries in the transition from action preparation to execution. NeuroImage 148:390- 402.

185. Bianco V, Di Russo F, Perri RL, Berchicci M (2017) Different proactive and reactive action control in fencers' and boxers' brain. Neuroscience 343:260-268.

186. Bianco V, Berchicci M, Perri RL, Spinelli D,Di Russo, F (2017) The proactive self-control of actions: Time-course of underlying brain activities. NeuroImage 156:388-393.

187. Di Russo F, Berchicci M, Bianco V, Perri RL, Pitzalis S, Quinzi F, Spinelli D et al (2019). Normative Event-Related Potentials from sensory and cognitive tasks reveal occipital and frontal activities prior and following visual events. NeuroImage 196:173-187.

188. Quinzi F, Berchicci M, Bianco V, Perri RL, Di Russo F (2019) The independency of the Bereitschaftspotential from previous stimulus-locked P3 in visuomotor response tasks. Psychophysiology 56(3):e13296. doi: 10.1111/psyp.13296.

189. Perri RL, Berchicci M, Spinelli D, Di Russo F (2014) Individual differences in response speed and accuracy are associated to specific brain activities of two interacting systems. Frontiers in Behavioral Neuroscience 8:251.

190. Bozzacchi C, Giusti MA, Pitzalis S, Spinelli D, Di Russo F (2012) Awareness affects motor planning for goal-oriented actions. Biological Psychology 89(2):503-514.

191. Bozzacchi C, Giusti MA, Pitzalis S, Spinelli D, Di Russo F (2012b) Similar cerebral motor plans for real and virtual actions. Plos One 7(10):e47783

192. Berchicci M, Lucci G, Perri, RL, Spinelli D, Di Russo F (2014). Benefits of physical exercise on basic visuo-motor functions across age. Frontiers in Aging Neuroscience 6:48.

193. Berchicci M, Spinelli D, Di Russo F (2016) New insights into old waves. Matching stimulus- and response-locked ERPs on the same time-window. Biological psychology 117:202-215.

194. Berchicci M, Ten Brink AF, Quinzi F, Perri RL, Spinelli D, Di Russo F (2019) Electrophysiological evidence of sustained spatial attention effects over anterior cortex: Possible contribution of the anterior insula. Psychophysiology 56(7):e13369. doi: 10.1111/psyp.13369.

195. Di Russo F, Berchicci M, Perri RL, Ripani FR, Ripani M (2013) A passive exoskeleton can push your life up: application on multiple sclerosis patients. PloS One 8(10):e77348. doi: 10.1371/journal.pone.0077348.

196. Grabner RH, Fink A, Stipacek A, Neuper C, Neubauer AC (2004) Intelligence and working memory systems: evidence of neural efficiency in alpha band ERD. Cognitive Brain Research 20(2):212-225.

197. Di Russo F, Taddei F, Apnile T, Spinelli D (2006) Neural correlates of fast stimulus discrimination and response selection in top-level fencers. Neurosci Lett 408(2):113-118.

198. Del Percio C, Rossini PM, Marzano N, Iacoboni M, Infarinato F, Aschieri P, Lino A, Fiore A, Toran G, Babiloni C,Eusebi F (2008) Is there a “neural efficiency” in athletes? A high-resolution EEG study. NeuroImage 42(4):1544-1553.

199. Hung TM, Spalding TW, Maria DLS, Hatfield BD (2004) Assessment of reactive motor performance with event-related brain potentials: attention processes in elite table tennis players. Journal of Sport and Exercise Psychology 26(2):317-337.

200. Bogacz R, Wagenmakers EJ, Forstmann BU, Nieuwenhuis S (2010) The neural basis of the speed–accuracy tradeoff. Trends in Neurosciences 33(1):10-16.

201. Sefer AB, Krbot M, Isgum V, Cifrek M (2009) Movement related evoked potentials in Parkinson’s disease patients and healthy controls. In World Congress on Medical Physics and Biomedical Engineering, September 7-12, 2009, Munich, Germany. Springer, Berlin, Heidelberg, pp 2158-2161.

202. Gonçalves ÓF, Rêgo G, Conde T, Leite J, Carvalho S, Lapenta OM, Boggio PS (2018) Mind Wandering and Task-Focused Attention: ERP Correlates. Scientific reports 8(1):7608.

203. Aron AR (2011) From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biological psychiatry 69(12): e55-e68.

204. Berchicci M, Quinzi F, Dainese A, Di Russo F (2017) Time-source of neural plasticity in complex bimanual coordinative tasks: Juggling. Behavioral Brain Research 328:87-94.

205. Di Russo F, Incoccia C, Formisano R, Sabatini U, Zoccolotti P (2005) Abnormal motor preparation in severe traumatic brain injury with good recovery. Journal of Neurotrauma 22(2):297-312.

206. Lucci G, Pisotta I, Berchicci M, Di Russo F, Bonavita J, Scivoletto G, Spinelli D, Molinari M (2019) Proactive cortical control in spinal cord injury subjects with paraplegia. Journal of neurotrauma, Ahead of print doi: 10.1089/neu.2018.6307.

207. Jung TP, Humphries C, Lee TW, Makeig S, McKeown M.J, Iragui V, Sejnowski TJ (1998) Removing electroencephalographic artifacts: comparison between ICA and PCA. In Neural Networks for Signal Processing VIII. Proceedings of the 1998 IEEE Signal Processing Society Workshop (Cat. No. 98TH8378), pp 63-72. IEEE.

208. Crammond DJ, Kalaska JF (2000) Prior information in motor and premotor cortex: activity during the delay period and effect on pre-movement activity. Journal of Neurophysiology 84(2):986-1005.

209. Bakhtadze SZ, Dzhanelidze MT, Khachapuridze NS (2011) Changes in cognitive evoked potentials during non-pharmacological treatment in children with attention deficit/hyperactivity disorder. Georgian medical news 192(3)47-56.

210. Mor J, Carmon A (1975) Laser emitted radiant heat for pain research. Pain 1(3):233-237.

211. Testani E, Le Pera D, Del Percio C, Miliucci R, Brancucci A, Pazzaglia C, De Armas L, Babiloni C, Rossini PM, Valeriani M (2015) Cortical inhibition of laser pain and laser-evoked potentials by non-nociceptive somatosensory input. Eur J Neurosci 42(7):2407-2414.

212. Melzack R, Wall PD (1965) Pain mechanisms: a new theory. Science 150(3699):971-979.

213. Valeriani M, Pazzaglia C, Rizzo V, Quartarone A, Vollono C (2018) Laser evoked potential amplitude and laser-pain rating reduction during high-frequency non-noxious somatosensory stimulation. Clin Neurophysiol 129(5):920-925.

214. Bromm B, Treede RD (1984) Nerve fibre discharges, cerebral potentials and sensations induced by CO2 laser stimulation. Hum Neurobiol 3(1):33-40.

215. Garcia-Larrea L, Frot M, Valeriani M (2003) Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin 33(6):279-292.

216. Valeriani M, Restuccia D, Le Pera D, De Armas L, Maiese T, Tonali P (2002) Attention-related modifications of ultra-late CO(2) laser evoked potentials to human trigeminal nerve stimulation. Neurosci Lett 329(3):329-333.

217. Cruccu G, Pennisi E, Truini A, Iannetti GD, Romaniello A, Le Pera D, et al (2003) Unmyelinated trigeminal pathways as assessed by laser stimuli in humans. Brain 126(Pt 10):2246-2256.

218. Valeriani M, Pazzaglia C, Ferraro D, Virdis D, Rotellini S, Le Pera D, Testani E, Minciotti I, Balestri M, Vigevano F, Vollono C (2011) Evidence of different spinal pathways for the warmth evoked potentials. Clin Neurophysiol 122(12):2469-2474. doi: 10.1016/j.clinph.2011.04.023.

219. Truini A, Galeotti F, Romaniello A, Virtuoso M, Iannetti GD, Cruccu G (2005) Laser-evoked potentials: normative values. Clin Neurophysiol 116(4):821-826.

220. Creac'H C, Bertholon A, Convers P, Garcia-Larrea L, Peyron R (2015) Effects of ageing on laser evoked potentials. Muscle Nerve 51:736–742.

221. Treede RD, Lorenz J, Baumgärtner U (2003) Clinical usefulness of laser-evoked potentials. Neurophysiol Clin 33:303–314.

222. de Tommaso M, Ricci K, Montemurno A, Vecchio E (2017) Age-related changes in laser-evoked potentials following trigeminal and hand stimulation in healthy subjects. Eur J Pain 21(6):1087-1097

223. Valeriani M, Sestito A, Le Pera D, De Armas L, Infusino F et al (2005) Abnormal cortical pain processing in patients with cardiac syndrome X. Eur Heart J 26:975–982.

224. de Tommaso M, Santostasi R, Devitofrancesco V, Franco G, Vecchio E, Delussi M, Livrea P, Katzarava Z (2011) A comparative study of cortical responses evoked by transcutaneous electrical vs CO(2) laser stimulation. Clin Neurophysiol 122(12):2482-7.

225. Valeriani M, de Tommaso M, Restuccia D, Le Pera D, Guido M et al (2003) Reduced habituation to experimental pain in migraine patients: A CO2 laser evoked potential study. Pain 105: 57–64.

226. de Tommaso M, Sciruicchio V, Ricci K, Montemurno A, Gentile F, Vecchio E, et al (2016) Laser-evoked potential habituation and central sensitization symptoms in childhood migraine. Cephalalgia 36(5):463-473.

227. Tudor KI, Petravić D, Krbot Skorić M, Išgum V (2018) Need for Thorough Standardization of CO2 Laser Evoked Potential Procedure.j Clin Neurophysiol 35(6):485-489. doi: 10.1097/WNP.0000000000000502.

228. Legrain V, Guérit JM, Bruyer R, Plaghki L (2002) Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. Pain 99(1-2):21-39.

229. Le Pera D, Brancucci A, De Armas L, Del Percio C, Miliucci R, Babiloni C, Restuccia D, Rossini PM, Valeriani M (2007) Inhibitory effect of voluntary movement preparation on cutaneous heat pain and laser-evoked potentials. Eur J Neurosci 25(6):1900-1907.

230. Lefaucheur JP, Jarry G, Drouot X, Ménard-Lefaucheur I, Keravel Y, Nguyen JP (2010) Motor cortex rTMS reduces acute pain provoked by laser stimulation in patients with chronic neuropathic pain. Clin Neurophysiol 121(6):895-901. doi: 10.1016/j.clinph.2009.12.028.

231. Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F, Valeriani M (2008) Learning potentiates neurophysiological and behavioral placebo analgesic responses. Pain 139(2):306-314. doi: 10.1016/j.pain.2008.04.021. Epub 2008 Jun 6. PubMed PMID: 18538928.

232. Hullemann P, von der Brelie C, Manthey G, Dusterhoft J, Helmers AK, Synowitz M, et al (2017) Reduced laser-evoked potential habituation detects abnormal central pain processing in painful radiculopathy patients. Eur J Pain 21(5):918-926.

233. Hsieh PC, Tseng MT, Chao CC, Lin YH, Tseng WY, Liu KH, et al (2015) Imaging signatures of altered brain responses in small-fiber neuropathy: reduced functional connectivity of the limbic system after peripheral nerve degeneration. Pain 156(5):904-916.

234. Iannetti GD, Leandri M, Truini A, Zambreanu L, Cruccu G, Tracey I (2004) Adelta nociceptor response to laser stimuli: selective effect of stimulus duration on skin temperature, brain potentials and pain perception. Clin Neurophysiol 115(11):2629-2637.

235. Truini A, Panuccio G, Galeotti F, Maluccio MR, Sartucci F, Avoli M, et al (2010) Laser-evoked potentials as a tool for assessing the efficacy of antinociceptive drugs. Eur J Pain 14(2):222-225.

236. Cruccu G, Leandri M, Iannetti GD, Mascia A, Romaniello A, Truini A, et al (2001) Small-fiber dysfunction in trigeminal neuralgia: carbamazepine effect on laser-evoked potentials. Neurology 56(12):1722-1726.

237. Garcia-Larrea L, Convers P, Magnin M, Andre-Obadia N, Peyron R, Laurent B, et al (2002) Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. Brain 125(Pt 12):2766-2781.

238. Valeriani M, Le Pera D, Restuccia D, de Armas L, Miliucci R, Betti V, et al (2007) Parallel spinal pathways generate the middle-latency N1 and the late P2 components of the laser evoked potentials. Clin Neurophysiol 118(5):1097-1104.

239. Bocci T, De Carolis G, Ferrucci R, Paroli M, Mansani F, Priori A, et al (2019)Cerebellar Transcranial Direct Current Stimulation (ctDCS) Ameliorates Phantom Limb Pain and Non-painful Phantom Limb Sensations. Cerebellum 18(3):527-535. doi: 10.1007/s12311-019-01020-w.

240. Di Stefano G, La Cesa S, Leone C, Pepe A, Galosi E, Fiorelli M, et al (2017) Diagnostic accuracy of laser-evoked potentials in diabetic neuropathy. Pain 158(6):1100-1107.

241. Truini A, Haanpaa M, Zucchi R, Galeotti F, Iannetti GD, Romaniello A, et al (2003) Laser-evoked potentials in post-herpetic neuralgia. Clin Neurophysiol 114(4):702-709.

242. Iannetti GD, Truini A, Galeotti F, Romaniello A, Manfredi M, Cruccu G (2001) Usefulness of dorsal laser evoked potentials in patients with spinal cord damage: report of two cases. J Neurol Neurosurg Psychiatry 71(6):792-794.

243. Iannetti GD, Truini A, Romaniello A, Galeotti F, Rizzo C, Manfredi M, et al (2003) Evidence of a specific spinal pathway for the sense of warmth in humans. J Neurophysiol 89(1):562-570.

244. Lorenz J, Garcia-Larrea L (2003) Contribution of attentional and cognitive factors to laser evoked brain potentials. Neurophysiol Clin 33(6):293-301.

245. Bocci T, Barloscio D, Parenti L, Sartucci F, Carli G, Santarcangelo EL (2017) High Hypnotizability Impairs the Cerebellar Control of Pain. Cerebellum 16(1):55-61.

246. de Tommaso M, Navarro J, Ricci K, Lorenzo M, Lanzillotti C, Colonna F, et al (2013) Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. Brain Inj 27(7-8):962-972.

247. de Tommaso M, Navarro J, Lanzillotti C, Ricci K, Buonocunto F, Livrea P, et al (2015) Cortical responses to salient nociceptive and not nociceptive stimuli in vegetative and minimal conscious state. Front Hum Neurosci 9:17.

248. Naro A, Russo M, Leo A, Rifici C, Pollicino P, Bramanti P, et al (2015) Cortical Responsiveness to Nociceptive Stimuli in Patients with Chronic Disorders of Consciousness: Do C-Fiber Laser Evoked Potentials Have a Role? PLoS One 10(12):e0144713.

249. Chien JH, Liu CC, Kim JH, Markman TM, Lenz FA (2014) Painful cutaneous laser stimuli induce event-related oscillatory EEG activities that are different from those induced by nonpainful electrical stimuli. J Neurophysiol 112(4):824-833.

250. de Tommaso M, Trotta G, Vecchio E, Ricci K, Van de Steen F, Montemurno A, Lorenzo M, Marinazzo D, Bellotti R, Stramaglia S (2015) Functional Connectivity of EEG Signals Under Laser Stimulation in Migraine. Front Hum Neurosci 9:640.

251. Valeriani M, Rambaud L, Mauguière F (1996) Scalp topography and dipolar source modelling of potentials evoked by CO2 laser stimulation of the hand. Electroenchephalogr Clin Neurophysiol 100(4):343-353.