INVITED REVIEW

Evoked and Event-Related Potentials as Biomarkers of Consciousness State and Recovery

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Summary: The definition of consciousness has been the subject of great interest for many scientists and philosophers. To better understand how evoked potentials may be identified as biomarkers of consciousness and recovery, the different theoretical models sustaining neural correlates of consciousness are reviewed. A multimodal approach can help to better predict clinical outcome in patients presenting with disorders of consciousness. Evoked potentials are inexpensive and easy-to-implement bedside examination techniques. Evoked potentials are an integral part of prognostic evaluation, particularly in cases of cognitive motor dissociation. Prognostic criteria are well established in postanoxic disorders of consciousness, especially postcardiac arrest but are less well determined in other etiologies. In the early examination, bilateral absence of N20 in disorder of consciousness patients is strongly associated with unfavorable outcome (i.e., death or unresponsive wakefulness syndrome) especially in postanoxic etiologies. This predictive value is lower in other etiologies and probably also in children. Both N20 and mismatch negativity are proven outcome predictors for acute coma. Many studies have shown that mismatch negativity and P3a are characterized by a high prognostic value for awakening, but some patients presenting unresponsive wakefulness syndrome also process a P3a. The presence of long-latency event-related potential components in response to stimuli is indicative of a better recovery. All neurophysiological data must be integrated within a multimodal approach combining repeated clinical evaluation, neuroimaging, functional imaging, biology, and neurophysiology combining passive and active paradigms.

Key Words: Coma, Unresponsive wakefulness syndrome, Minimally conscious state, Mismatch negativity, Auditory oddball, P3.

(J Clin Neurophysiol 2022;39: 22–31)

The definition of consciousness has been the subject of great interest for many scientists and philosophers: understanding its origin and its relationships with the body are long-standing questions in philosophy, psychology, and neuroscience.[1]

The neural correlates of consciousness are defined as the minimal neural mechanisms jointly sufficient for any conscious perception.[2] Comparison between neural activities elicited by a stimulus and neural activities when the stimulus is unperceived is fundamental to identify neural correlates of consciousness. Neural correlates of consciousness are usually identified through state-based approaches contrasting brain activity when consciousness is present, typically in awake healthy participants performing no task, with brain activity when consciousness is severely diminished—for example, during dreamless sleep or disorders of consciousness (DOC) such as coma and vegetative states.[1]

In a classical neurological view, brain stem lesions typically cause immediate coma by damaging the reticular activating system and its associated neuromodulatory system. However, neurological patients with a severely damaged cortex, but with relatively spared brain stem function, typically remain in an unresponsive wakefulness syndrome (UWS). This suggests that brain stem activity is insufficient to sustain consciousness in a clinical sense.

From a neurological point of view, consciousness is defined as the simultaneous presence of arousal and awareness.[3] Awareness could be distinguished in terms of external (of the environment) and internal (i.e., imagery, dreaming) aspects.[4] In a recent review, Naccache[5] mentions that empirical and theoretical studies over the past 20 years have demonstrated that conscious states do not rely on a single cortical area or network, but they require a brain-scale communication that must be sustained, complex, and differentiated. Several theoretical models emphasize these properties (Fig. 1):

1. the global neuronal workspace theory (for complete review see[6]);
2. the frontoparietal network of consciousness[4] and the meso-circuit hypothesis[7];
3. the integrated information theory[8]; and
4. the recently highlighted posterior hot zone.[9]

The global neural workspace is one model of conscious access: it posits that the function of conscious awareness is the broadcasting of information in the brain. Perceptual signals, information processed by localized cortical areas (i.e., primary

The authors have no funding or conflicts of interest to disclose.
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ISSN: 0736-0258/21/3901-0022
DOI 10.1097/WNP.0000000000000762

sensory or visual cortices) become conscious only if they reach a second computational space, composed of widely distributed excitatory neurons (called global neuronal workspace neurons) with long-range axons, connected to other processors across the brain (working memory, motor plans, language). Global neuronal workspace acts as a "router" and has the ability to receive bottom-up information and to transmit top-down information to any of the various processors, thus selecting and broadcasting information. The prefrontal cortex plays a key role in this model, but it is not the exclusive territory for conscious access. The global neuronal workspace model emphasizes the feed-forward and feedback connections as fundamental principles of conscious access. This model has been supported over the past 20 years by several experimental protocols: conscious and unconscious processing of briefly flashed words using a visual masking procedure,[10] presence of the event-related potential (ERP) P3b, and apparition of an error negativity if the subject is conscious, respectively, of the stimuli and of his error. According to global neuronal workspace, consciousness emerges from large-scale functional integration. Interestingly, humans can only have a single conscious content at a time.[11] In case of sensory consciousness, the conscious broadcast commences about 200 to 280 milliseconds (ms) post stimulus.[11] Using a sparse event-related functional MRI design, it has been demonstrated that unconscious auditory stimuli activate only auditory cortices, whereas conscious auditory stimuli activate auditory cortices at a higher level, plus a system comprising anterior insula, anterior cingulate, and thalamus.[12] More recently, several functional MRI, magnetoencephalography, and high-resolution electroencephalography studies demonstrated a disruption in long-range functional connectivity network in UWS patients versus patients presenting minimally conscious state (MCS) or locked-in syndrome.[6]

The frontoparietal network of consciousness[4] and the mesocircuit hypothesis[7] could be grouped in a common model identifying the core of the consciousness within a widespread frontoparietal network, associating medial (i.e., anterior cingulate/medio-rontal and posterior cingulate/precuneus) and lateral (i.e., prefrontal and posterior parietal) associative cortices. Functional connectivity, as well as metabolic activity, across both anterior forebrain and medial parietal cortex increase via the activation of the thalamocortical projections through the central thalamus. This hypothesis is supported by positron emission tomography, functional MRI, and magnetoencephalography studies, showing an impaired frontoparietal network in UWS versus MCS patients. In addition, an improvement of arousal and behavioural responsiveness has been observed in DOC patients treated using deep brain stimulation of central thalamus or dopaminergic drugs (i.e., amantadine), along with an activation of the frontoparietal network.[4]

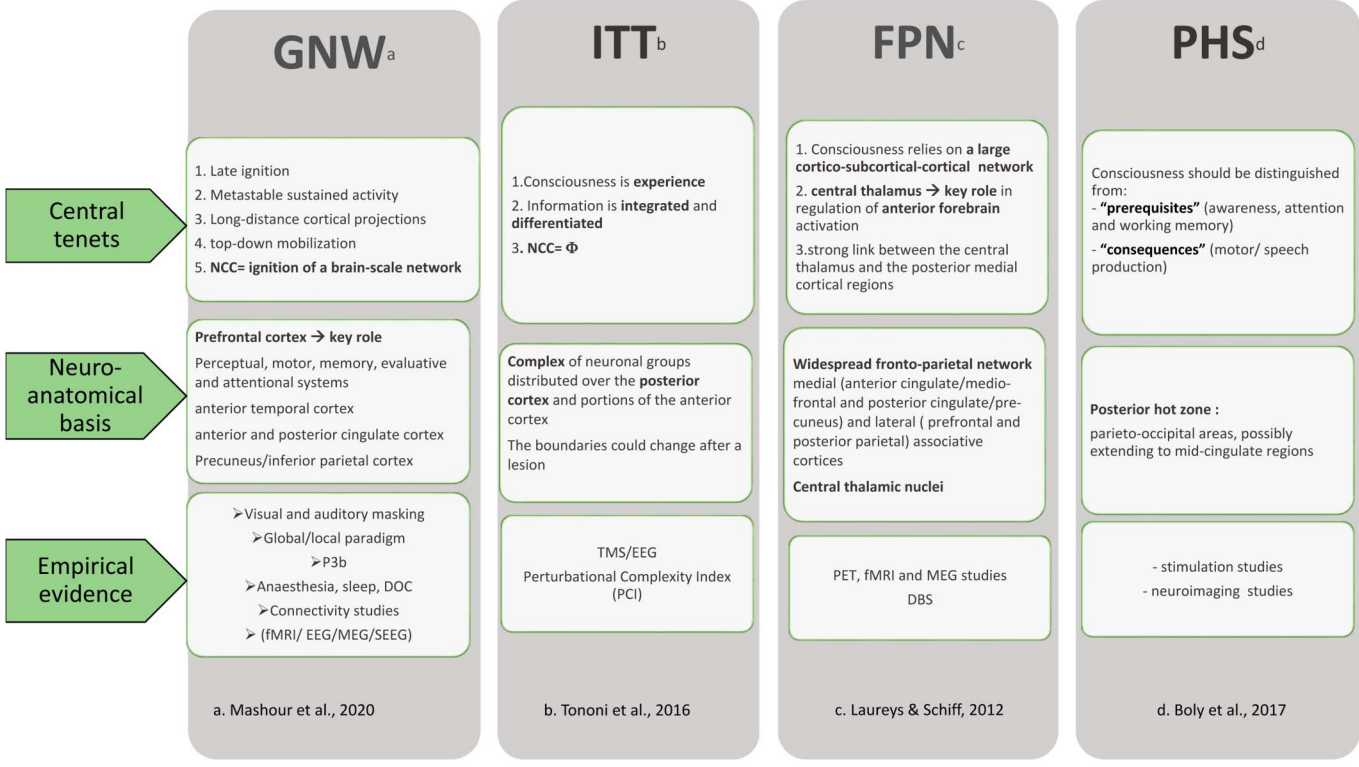

FIG. 1. Several theoretical models of consciousness are synthetized (central tenets, neuroanatomical basis, and empirical evidence). FPN, frontoparietal network of consciousness[4]; GNW, global neuronal workspace theory of consciousness[6]; ITT, Integrated Information theory[8]; PHS, posterior hotspot theory.[9]

The integrated information theory[8,13] rather addresses the phenomenology of consciousness. This model posits two key properties of consciousness: differentiation (uniqueness of any conscious event) and information integration (unity of a conscious experience). From a neurophysiological point of view, it is defined as the ability of specialized functional areas (segregation or differentiation processes) to interact and communicate efficiently (integration). Integrated information theory presents a mathematical framework for evaluating the quality and quantity of consciousness. This model, primarily mathematical, introduces a quantity called Φ, which represents the degree of consciousness of any system, biological or artificial. Consciousness-supporting networks should present an optimal balance between functional integration and differentiation. This hypothesis has been tested using transcranial magnetic stimulation coupled with high-density EEG. The EEG responses to perturbational transcranial magnetic stimulation across different cortical areas and along time are measured by an empirical measure: the perturbational complexity index. This index is able to differentiate distinct states of consciousness (wakefulness, nonrapid eye movement and rapid eye movement sleep, anaesthesia) and to highlight a subgroup of UWS patients who may retain a capacity for consciousness that is not expressed in behavior.[14]

The posterior hotspot theory: Although it has been widely assumed that prefrontal circuits are essential for consciousness, either alone[15] or in conjunction with parietal areas,[4] Koch et al.[2] postulated that the anatomical neural correlates of consciousness are primarily localized in a posterior cortical hotspot that includes sensory areas. Boly et al.[9] critically reviewed all the evidence to define the role of the "front of the brain" (most prefrontal regions) versus the "back of the brain" (temporal, parietal, and occipital areas) in supporting consciousness. The posterior hotspot model is sustained by electrical stimulations and neuroimaging studies.[9] Electrical stimulation of most of the frontal cortex does not elicit content-specific changes in experience, whereas electrical stimulation of posterior cortex more reliably induces discrete changes in the content of consciousness.[9] Finally, studies contrasting dreaming versus nondreaming sleep have pointed to a posterior hot zone in parieto-occipital areas, possibly extending to midcingulate regions as a reliable neural correlates of consciousness.[9]

The loss of consciousness during epileptic seizures can provide important insights to our knowledge of the brain circuitry engaged in the normal conscious state. Although the structural and functional changes observed in partial seizures have been largely studied, the mechanisms leading to loss of consciousness are poorly known. A major hypothesis involves alteration of the global neural workspace.[6] In favour of this hypothesis, loss of consciousness occurring during temporal lobe seizures was correlated with a nonlinear increase of neural synchrony within distant corticocortical and corticothalamic networks.[16] It has been hypothesized that excessive synchrony may prevent this distributed network from encoding conscious representations. Similar data were obtained in parietal lobe seizures with the loss of consciousness.[17,18] Those results from epileptic seizures are in agreement with hypotheses linking DOC to disruptions on a large-scale network of frontoparietal associative systems.[18]

PROGNOSTIC EVALUATION IN ACUTE COMA SETTING: EVIDENCE AND LIMITATIONS

In the acute phase of coma, awakening and return of consciousness may be delayed because of neurological intensive care management and the severity of brain injury. A multimodal approach combining repeated clinical evaluations, neuroimaging, and neurophysiology (Fig. 2) can help to better predict neurologic outcome of these patients.[19] EEG and evoked potentials form an integral part of the clinical and prognostic evaluation of patients with DOC from the early phase in intensive care units.[20] Prognostic criteria are well established in postanoxic coma, especially postcardiac arrest,[21,22] but are less well determined in other etiologies, particularly in brain-damaged patients.

WHAT ARE THE NEUROPHYSIOLOGICAL TOOLS FOR NEUROPROGNOSTICATION?

Neurophysiological tests (EEG and EPs) are useful for assessing the degree of awareness especially in the difficult context of withdrawal of life-sustaining treatments. They can highlight signs of consciousness and thus help to assess the patient's ability to interact with his or her environment, particularly in cases of cognitive motor dissociation (patients who are unable to respond to stimuli despite still having conscious experiences).[23] In addition, showing the integrity of sensory tracts may encourage caregivers and relatives to continue care and to develop appropriate communication strategies.

BIOMARKERS

As a method of functional investigation of changes in brain electrical activities, EEG appears at first sight as a unique and optimal way to assess cerebral functions in DOC patients. The most widely used classifications are those from Synek and Young, which classify EEGs by severity according to background organization and reactivity to external stimuli.[20,24] Van Putten et al.[25] reported results of postmortem brain histopathology in relation to EEG and somatosensory evoked potentials (SSEPs) abnormalities in a cohort of postanoxic DOC patients. EEG burst-suppression patterns were associated with lesions in hippocampus, cerebellum, and cortices. In patients with additional thalamic involvement, burst suppression with identical bursts was observed.

Absence of EEG reactivity for poor outcome prediction had a specificity of 82% and a sensitivity of 73%.[26] However, the EEG reactivity does not benefit from a precise consensus. There is no gold standard for stimulation procedures or EEG reactivity assessment. Moreover, several studies have shown high interrater variability in the assessment of EEG reactivity.[27]

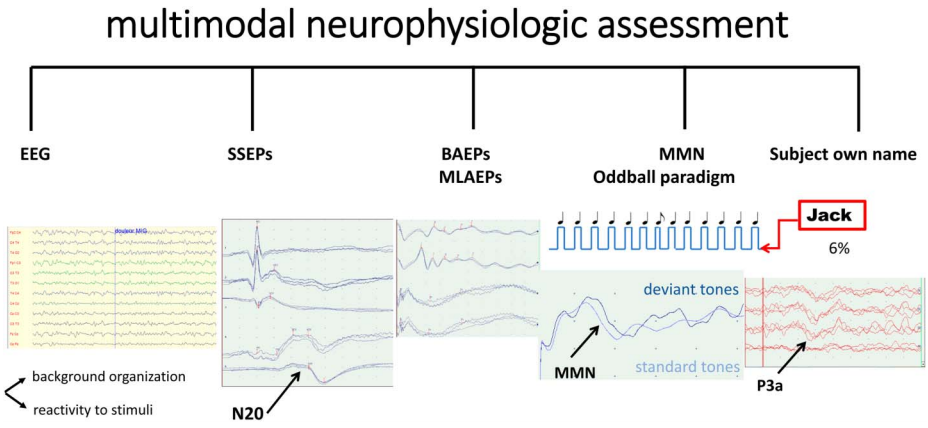

FIG. 2. Multimodal neurophysiologic evaluation comprises EEG (background analysis, characterization of reactivity to external stimuli), SSEPs (N20), BAEPs, MLAEPs, N100, MMN, and P3. BAEP, brain stem auditory evoked potential; MLAEP, middle latency auditory evoked potential; MMN, mismatch negativity; SSEP, somatosensory evoked potential.

N20

Somatosensory evoked potentials allow the evaluation of functional integrity of the somatosensory pathways in critically ill patients.[20] Several meta-analyses provide strong evidence for the value of bilateral absent N20 in predicting poor neurologic outcome or death.[28–30] Median nerve SSEPs assess the functional state of the proximal portion of the median nerve, the posterior columns of the spinal cord, the lemniscal somatosensory afferent pathways via the brain stem, the diencephalon, the thalamocortical tracts and the primary somatosensory cortex S1. Bilateral absent N20 in patients experiencing postanoxic coma after a cardiac arrest is invariably associated with a poor outcome.[31] The specificity is close to 100% in terms of prognosis for postanoxic coma, with grade B level of evidence provided in the American Academy of Neurology recommendations for evaluating the outcome of anoxic–ischemic encephalopathy.[32] However, preservation of N20 in these patients is not an indicator of good recovery.[33]

Bilateral absent N20 within the first week of anoxia is a robust predictor of poor outcome or death.[21,34] Adults in coma from anoxic–ischemic encephalopathy with bilateral absent N20 have $<1\%$ chance of awakening.[35] However, this predictive value is lower in other etiologies of coma and probably also lower in children whatever the etiology of coma.[20] Van Putten et al[25] reported results of postmortem brain histopathology in relation to EEG and SSEP abnormalities in a cohort of post-anoxic DOC patients. Absent N20 were always accompanied by thalamic damage. A few studies, encompassing small samples, have focused on SSEP response as an early predictor of poor outcome in patients with severe acquired brain injuries. These studies showed interest in repeated or continuous monitoring of SSEP.[36,37]

In practice, it is recommended to use equipment with four channels to record the four main components of median nerve SSEPs (N9, N13, P14, and N20, Fig. 3A). A fifth channel (C′3-C′4) can be useful to differentiate the N20 cortical component from the N18 subcortical component. When the equipment has only two channels, it is recommended to use one channel to record the peripheral response N9 and the other to record the N20 cortical component.[20]

Peripheral nerve lesions or spinal cord dysfunctions can lead to the absence of N20. An equipment with four channels is thus highly recommended. The N20 potentials require documentation at the brachial plexus level and at the cervical cord to be considered as reliably absent (Fig. 3B). Intravenous sedative drugs have little impact on SSEP amplitude and latency, whereas hypothermia has a depressant effect on SSEP cortical responses. Thus, to avoid any confounding effect, SSEPs should not be used for prognosis in the presence of hypothermia.[20,30]

A systematic review reported 14 cases of good neurologic outcomes in patients with hypoxic–ischemic coma despite bilateral absent N20. The authors hypothesized that the prognostic value of absent N20 may be biased by self-fulfilling prophecies and recommended that decisions regarding early withdrawal of life-sustaining treatment should not be solely determined by SSEP results.[38] However, Rothstein[30] reexamined these cases and concluded that when confounding factors (such as hypothermia, technical issues) are eliminated, the bilateral absence of N20 remains one of the most reliable and reproducible predictors of negative outcome.

To enhance sensitivity of SSEP response to negative outcome, some recent studies explored the SSEP amplitude in postanoxic encephalopathy. The peak-to-peak amplitude of the N20/P25 complex was defined as being pathological below a discordant cutoff (0.2–0.65 μV) among studies. Interestingly, SSEP amplitude showed a positive correlation with other prognostic variables used in decision making with regards to potential withdrawal of life-sustaining treatment (EEG findings, present motor response, and absence of myoclonus). However, caution is mandatory in clinical practice to avoid premature withdrawal of life-sustaining treatment. Furthermore, among patients with present N20, no correlation was demonstrated between N20 amplitude and outcome.[39]

Multivariate logistic regression analysis of multimodal prognostication variables (EEG reactivity, neuron-specific enolase level, myoclonus, brain stem reflexes) showed that the other variables are independent predictors of absent N20. Some authors suggested that SSEPs could be redundant in multimodal prediction.[40] Neverthless, the association of EEG and SSEP results increases sensitivity in the prediction of the outcome.[31]

Application of SSEPs for positive prognostication has been proposed investigating the long-latency SSEPs components (P25, N35, N70) when N20 is present.[41–43] Their amplitude positively correlate with good outcome but with a wide confidence range.[43]

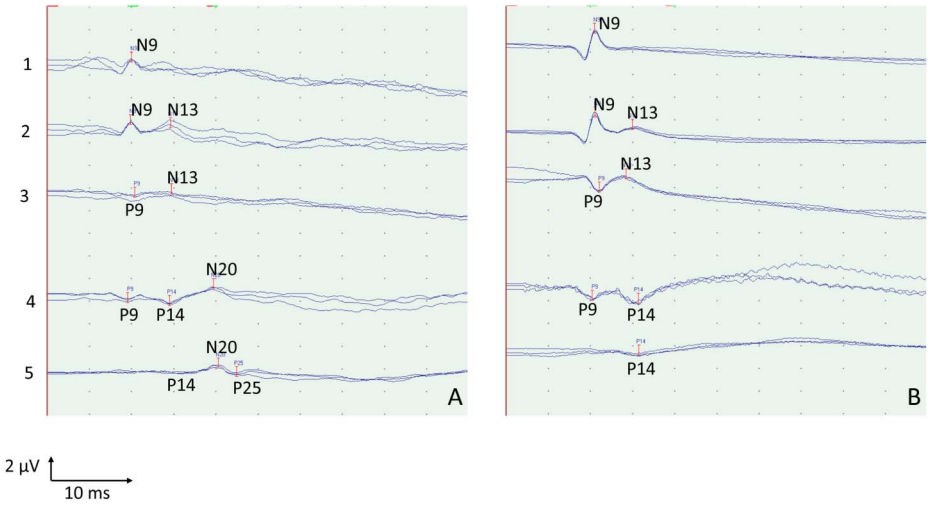

FIG. 3. SSEPs are performed using a five-channel montage: 1: ipsilateral Erb's point—contralateral Erb's point (N9); 2: ipsilateral Erb's point—Fz (N9, N13); 3: spinous process of C6—anterior neck (P9, N13); 4: C4—shoulder contralateral to the stimulation (P9, P14, N20, P25); 5: C4-C3 (N20, P25). **A**, Normal median nerve SSEP. **B**, Absent N20: the N20 is considered absent when no reproducible cortical component could be identified, although extracranial components (N9 and N13) are obtained. SSEP, somatosensory evoked potential.

Determination of the N70 in patients with postanoxic coma gives additional information. However, good outcome could not be predicted reliably with SSEP components because only 28% of patients with normal N20 and N70 had a good outcome.[42]

BRAIN STEM AUDITORY EVOKED POTENTIALS

There is less evidence of the usefulness of auditory evoked potentials for predicting coma outcome than for N20, although the alteration of auditory evoked potentials has been associated with poor outcome.[44] Brain stem auditory evoked potentials are evoked in the first 10 ms revealing the activity from the auditory nerve to the inferior colliculi. Brain stem auditory evoked potentials are elicited by monaural clicks (1,500–2,000 stimuli, duration 100 microseconds, intensity 80–90 dB, frequency: 7–10 Hz). Brain stem auditory evoked potentials are recorded using the active electrode placed at the earlobe (or mastoid) ipsilateral to the stimulation and Cz as reference. The assessment of brain stem function requires at least a present wave 1. In postanoxic coma, brain stem auditory evoked potentials are usually preserved and have no prognostic value. Conversely, in traumatic brain injury, the preservation of brain stem auditory evoked potentials is a good prognostic indicator while the absence of all waves beyond the wave 1 is ominous.[20]

MIDDLE LATENCY AUDITORY EVOKED POTENTIALS

Middle latency auditory evoked potentials are near-field responses, originating in the auditory pathways from the medial geniculate body to the primary auditory cortices. Middle latency auditory evoked potentials are elicited by monaural clicks and consist of several responses occurring within 100 ms. Middle latency auditory evoked potentials are recorded using an active electrode F3 (or F4) and the reference electrode placed at the ipsilateral mastoid (or earlobe). Middle latency auditory evoked potentials consist of two waves with frontal maximal amplitude: Na (probably thalamic origin) and Pa (primary auditory cortices). In postanoxic coma, the abolition of middle latency auditory evoked potentials has been associated with poor outcome.[44] A four-channel montage allows simultaneous recording of brain stem auditory evoked potentials and middle latency auditory evoked potentials, using a time scale of 10 ms for brain stem auditory evoked potentials and 100 ms for middle latency auditory evoked potentials. Benzodiazepines or other sedative drugs have a depressant effect on auditory evoked potentials. Brain stem auditory evoked potentials and middle latency auditory evoked potentials data are useful to efficiently interpret the subsequent N100 and auditory mismatch negativity (MMN).

N100

The N100 is a negative inflection that appears around 100 ms, at the level of midline central and parietal electrodes in response to any auditory stimulus, showing an activation of auditory cortices (Fig. 4). The presence of the N100 in DOC patients indicates that primary auditory cortices are functionally preserved. The absence of the N100 is considered to be predictive of a negative outcome. A clear N100 response (to frequent and deviant tones, cf infra) is mandatory to search for an auditory MMN.

ODDBALL PARADIGM

An oddball paradigm is made of frequent identical and irrelevant stimuli mixed with some rare and relevant stimuli (Fig. 4A). Auditory tone oddball paradigms where standard and deviant stimuli differed by their duration or their frequency are the most frequently used in assessing DOC. If heard, standard and deviant stimuli both elicit N100 (Fig. 4) and P200 automatic components but also elicit different components later because of the differences between stimuli.

In visual masking protocols, an early negative component, N200 or visual awareness negativity, has been described as correlate of awareness but also of ignition (reverberation) because

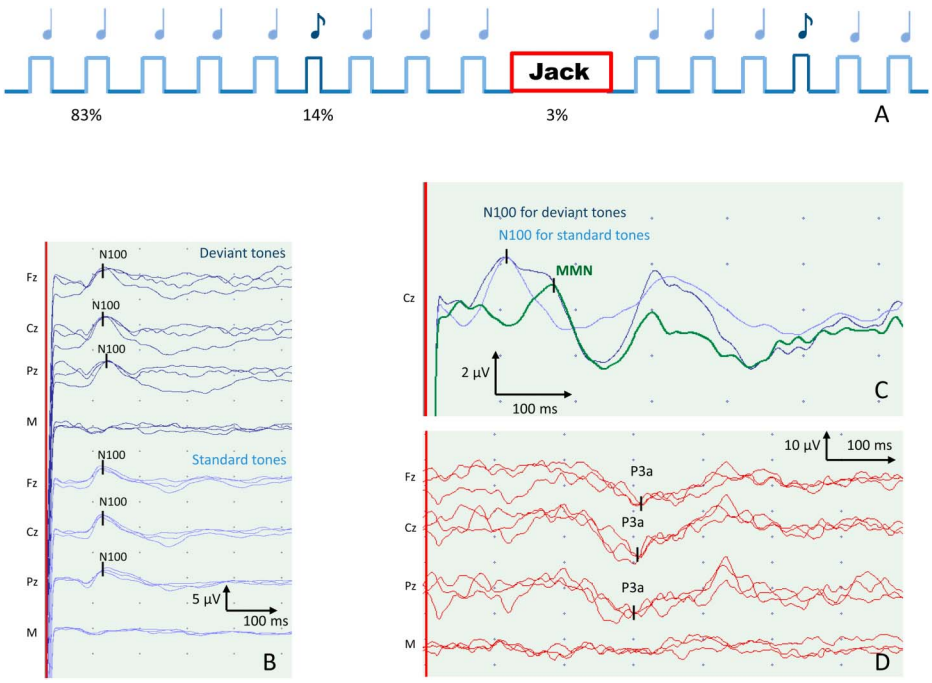

FIG. 4. **A**, Standard tones (duration 75 ms) are intermixed with deviant tones (duration 35 ms; occurrence 14%) and the subject's own name (occurrence 3%), (**B**) N100 are obtained for deviant tones (dark blue) and standard tones (light blue), (**C**) the MMN (in green) is obtained by subtracting the deviant tones EPs (dark blue) and the standard tones EPs (light blue), (**D**) P3a is obtained for the patient own name at the level of midline electrodes. EP, evoked potential; MMN, mismatch negativity.

it correlates with P3b. Components occurring within the first 200 ms correspond to early perceptual processing and can be fully preserved in unconscious perception. Attention is a necessary prerequisite for consciousness, but possible dissociation between attention and consciousness has been widely demonstrated.[6,11]

MMN

Auditory MMN is recorded between 100 and 250 ms after stimulus mainly on the frontocentral electrodes. Mismatch negativity reflects an automatic process because of acoustic differences between the two discriminated stimuli presented (i.e., frequency, duration, or intensity differences). As subjects do not need to be voluntarily attentive to the sound to detect an MMN, it indicates an automatic response generated by a comparison process between the afferent input and a memory trace developed by the repetitive stimulation.

In practice, using a duration difference, standard tones (duration 75 ms, incidence 86%; 80 dB; 800 Hz) and deviant tones (duration 35 ms; incidence 14%; 80 dB; 800 Hz) are delivered binaurally. Several stimulation series are recommended. Recording electrodes are placed at Fz, Cz, and Pz. The most commonly used reference in auditory ERPs is the mathematically linked mastoids.[45] In some other studies, recording electrodes are placed at Fz, Cz, Pz, and linked mastoids. An electrode placed on the nose served as reference[20]. The temporal window of analysis is 600 ms. Event-related potentials are averaged separately for the standard and deviant tones. The MMN is obtained by subtracting the response to deviant tones and the response to frequent tones (Fig. 4).

Recording an MMN is a good predictor of awakening, mainly in postanoxic DOC: in the study of Fischer et al.[28] of 62 patients with postcardiac arrest DOC, MMN was present in all patients who were awake at 1 year. Positive predictive value of MMN in other DOC etiologies is still interesting but less powerful. In a cohort of 30 patients with DOC, Naccache et al.[46] reported that MMN recorded between the fourth day and the 96th day after the onset of DOC had a positive predictive value for awakening (defined as a conscious state on the Glasgow Outcome Scale, i.e., between 3–5) of 90%. In a large cohort of 346 patients with DOC (defined as Glasgow coma scale < 8) of various etiologies (stroke, traumatic brain injury, anoxia, post-neurosurgery, encephalitis), Luauté et al.[47] reported that MMN recorded in the first 3 months after the onset of DOC was the

FIG. 5. The active local-global paradigm evaluates cerebral responses to violations of temporal regularities that are either local in time (within trial) or global (across trials).[59] The patient is asked to count the global violations.

highest predictor of good outcome at 1 year with a positive predictive value of 69.8% (good outcome being defined as a recovery of consciousness with no or moderate disability according to the Glasgow Outcome Scale[48] in this study).

Some authors have described that the appearance of the MMN or an increase in MMN amplitude should predict an improvement in consciousness state, such as the emergence of a MCS.[49–51] Moreover, MMN can be observed in deeply sedated critically ill patients and could help predict subsequent awakening.[52] Interestingly, based on the concept of auditory discrimination in MMN, some authors have tried to explore DOC with sensory discrimination. In the study of Pfeiffer et al.,[53] patients with postanoxic DOC underwent an auditory discrimination paradigm and then a sensory discrimination paradigm. The somatosensory discrimination paradigm consisted in a vibrotactile stimulation on the left index finger (standard stimulus of 100 ms and deviant stimulus of 150 ms) presented in a pseudorandom order in two blocks with 80% of standard stimuli and 20% of deviant stimuli. Evoked related potentials were extracted from EEG acquisitions. An improvement in the auditory discrimination task was a good predictor of consciousness recovery with a positive predictive value of 73% but a lower negative predictive value (45%). However, the tactile discrimination task was not predictive of the clinical outcome.

P3

Fifty years ago, a later positive wave was discovered using a similar oddball paradigm: the P3 component.[54] The P3 corresponds to the activation of a frontoparietal network. This wave can be recorded if the patient focuses on the deviant stimuli and if these deviant stimuli occur rarely and randomly.[55] This component is considered as endogenous, reflecting a cognitive attention task. The recording of this P3 depends on the arousal and the attention of the patient but is independent of the acoustic differences between stimuli. Mismatch negativity seems to reflect an involuntary detection of differences between stimuli, whereas P3 seems to reflect the orientation of the attention toward the novel stimulus.[56]

The P3 is a complex positive response that includes two components around 350 ms: an earlier one, called P3a, passively recorded and a later one, called P3b, which can be recorded with a parietal maximum in active paradigms (cf. infra). This P3b component may constitute a reliable indicator of consciousness.[57] It is important to note that in DOC patients, probably because of the presence of brain lesions, topographies and latencies of P300 components can vary: in a study by Wijnen et al.[58] where passive ERPs paradigms were repeated every 2 weeks in the early stages of coma (mostly because of traumatic brain injuries), patients who recovered to consciousness displayed a P3 wave with delayed latencies (around 650–700 ms) and a maximum central topography.

LOCAL GLOBAL PARADIGM

Mismatch negativity and P3a are recorded with passive paradigm, whereas eliciting the P3b seems to need an active task with attention and conscious awareness of the stimuli. In 2009, Bekinschtein et al.[59] developed a different active paradigm trying to distinguish conscious and nonconscious processes. In this paradigm, on each ERP trial, a series of five brief sounds is presented: the first four sounds are all identical (low or high pitched) but the fifth sound can be either identical or different. When all fifth sounds are identical, it is called a "locally standard trial" and when the fifth sound is different, it is called a "locally deviant trial." Twenty to 30 series of fifth sounds are presented to the subject to define a global regularity. Then, violation to this global regularity is introduced with 20% of different series (locally standard trial in a regularity of locally deviant trials; Fig. 5). During the paradigm, patients are asked to actively count the number of global deviant trials. In this study, in healthy volunteers, global violations induced a late and largely distributed response in central regions only when subjects were aware of the violations (and this response disappeared if the subject performed a distractive task). In eight noncommunicating patients explored with this paradigm in the same study, the global violation was only detected in conscious patients. A larger cohort of 49 noncommunicating patients confirmed these results: only conscious patients processed a response to global violations.[60] However, these results were challenged by Tzovara et al.[61] who demonstrated in 24 acute anoxic–ischemic DOC patients (with Glasgow Coma Scale < 6) that 10 of them could detect a global violation in auditory sequences. Nevertheless, the authors gave possible explanations for these results: (1) differences in the type of patients being recorded and (2) differences in the analyses conducted on the EEG signals.

P3A OWN NAME

Many studies have demonstrated the potency of hearing one's own name for commanding attention.[62] Some studies have demonstrated that P3 components were larger if the deviant stimulus was relevant.[63–65] Thus, to improve the relevance of deviant stimuli, a novel oddball paradigm was developed including a novel stimuli: the patient's own name, intermixed with standard and deviant tones.[66] In this paradigm, standard tones are intermixed with deviant tones (occurrence 14%) and the subject's own name (occurrence 3%). In DOC patients, as this paradigm is recorded passively without asking the patient to perform any task, only a P3a can be recorded, named "novelty-P3" by some authors (Fig. 4D).[20] This P3a seems to reflect an evaluation of novelty before behavioural reaction.[67]

One study, performed in healthy subjects, tried to improve the relevancy of the own name stimulus by recording it more personally with a familiar voice.[68] Only the late phase of the P3 was larger when the own name was recorded by a familiar voice, compared to a non-familiar voice. In another study, in DOC patients, the patient's favorite music was able to enhance the novelty P3 to the subject's own name.[69] These results have to be confirmed in larger DOC patient cohorts, and other protocols are still ongoing.

In DOC patients, recording a P3a to the subject's own name is highly correlated to the prognosis of awakening in some studies.[70] In a cohort of 34 patients with UWS posttraumatic

brain injury, P3 was recorded at 2 months after injury in 88% of patients who recovered from persistent vegetative syndrome at 1 year post injury. Conversely, P3 at 2 months post injury was not recorded in any patient with persistent UWS at 1 year.[71] Moreover, in a cohort of 50 severe comatose patients, compared with MMN, recording a P3a at 20 days from the beginning of the DOC was more sensitive for awakening at three months (sensibility P3a 0.71 vs. 0.42 for MMN) and as specific (specificity about 0.85).[66]

Looking for MMN and own name P3a provides complementary evidence, and passive paradigms of stimulation have been developed to record both stimuli at the same time.[72] This combination should help to better predict the prognosis,[73] but it should be borne in mind that some UWS patients can also process a P3a. Thus, neurophysiological data must be multimodal and integrated within the global clinical and paraclinical evaluation.[74]

N400, P600

Additional ERPs could be useful to disentangle UWS and MCS patients or to predict which patients will recover consciousness. N400 and P600 are obtained in cases of semantic violations in auditory (or visual) stimuli. N400 is suggested as an important tool to assess information-processing capacities that can predict the likelihood of recovery of patients in UWS or MCS.[75] N400 is present in conscious and unconscious processing of word in healthy subjects and is more represented in MCS than in UWS patients.[76] N400 and P600 may be better indicators of recovery than the P300.[75–77] N400 is more reliably obtained in MCS than in UWS patients, whereas P600 is obtained only in MCS and conscious patients.[71] It has been proposed that the P600 could reflect conscious access to semantic violation, whereas the N400 would reflect an earlier and nonconscious stage of semantic processing.[71]

COGNITIVE ERPS: LIMITS

Cognitive ERPs encompass several limits.[23] First, cognitive ERPs are not elicited in all healthy subjects. Moreover, vigilance and consciousness may fluctuate in DOC patients, both in the short term (seconds to hours) and longer term (days). Associated cognitive impairment (such as language or memory dysfunction) may also fluctuate, representing a potential interference in processing stimuli (and thus in recording ERPs). In addition, distinction between UWS and MCS or recovery of consciousness is not an "all or none" state but a continuum. Second, different methods are used for the analysis of ERPs (visual analysis, wavelet-transformed data, statistical, or machine learning analysis). Results could vary depending on this choice. Furthermore, diagnostic procedures, evaluation criteria (i.e., clinical scales for outcome), and intervals between (1) the accident and (2) the ERPs recording, this measurement and the follow-up assessment differ across studies. It thus seems important to create a network allowing a multicenter collaboration to share and validate protocols and data. Some meta-analyses have highlighted that neurophysiological data predicted the transition from UWS to MCS better than they predicted the recovery of consciousness and that ERPs have to be integrated in a multimodal evaluation of DOC patients.[23,78]

ACKNOWLEDGMENTS

The authors are very grateful to Dr Nathalie André-Obadia and to Dr Aileen McGonigal for revision of the English version.

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