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Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group

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HIGHLIGHTS

- We provide an overview of EEG-based techniques in the prognostic and diagnostic assessment of DoC.
- We highlight bridging principles between conventional and investigational approaches.
- We share expert opinions and considerations on the technical and conceptual caveats.

ABSTRACT

The analysis of spontaneous EEG activity and evoked potentials is a cornerstone of the instrumental evaluation of patients with disorders of consciousness (DoC). The past few years have witnessed an unprecedented surge in EEG-related research applied to the prediction and detection of recovery of consciousness after severe brain injury, opening up the prospect that new concepts and tools may be available at the bedside. This paper provides a comprehensive, critical overview of both consolidated and investigational electrophysiological techniques for the prognostic and diagnostic assessment of DoC. We describe conventional clinical EEG approaches, then focus on evoked and event-related potentials, and finally we

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Abbreviations: α, alpha; β, beta; δ, delta; γ, gamma; θ, theta; AAN, American Academy of Neurology; BCI, Brain-Computer Interface; CI, confidence intervals; CMD, cognitive motor dissociation; CPC, cerebral performance category; CRS-R, Coma-Recovery Scale-revised; cEEG, continuous electroencephalography; CSD, cortical spread depolarization; DoC, disorders of consciousness; EAN, European Academy of Neurology; EEG, electroencephalography; EMCS, emergence from minimally conscious state; EP, evoked potential; ERD, event-related desynchronization; ERP, event-related potential; ERSP, event-related spectral perturbation; GOS, Glasgow Outcome Scale; GOS-E, Glasgow Outcome Scale Extended; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; FPR, false positive rate; HIE, hypoxic-ischemic encephalopathy; HMD, higher-order cortex motor dissociation; ICU, intensive care unit; IIC, ictal-interictal continuum; K, Kolmogorov complexity; LIS, locked-in syndrome; LFP, local field potential; MCS, minimally conscious state; ML, machine learning; MMN, mismatch negativity; NCSz, non-convulsive seizures; NCSE, non-convulsive status epilepticus; NREM, non-rapid eye movement; OPJ, occipito-parietal junction; PCI, perturbational complexity index; PHG, parahippocampal gyrus; PLF, phase locking factor; PMC, premotor cortex; PPV, positive predictive value; PSD, power spectral density; qEEG, quantitative EEG; REM, rapid eye movement; SAH, subarachnoid hemorrhage; SEP, somatosensory evoked potential; SIRPIDs, stimulus-induced rhythmic, periodic, or ictal discharges; SMA, supplementary motor area; SPES, single pulse electrical stimulation; TEP, TMS-evoked potential; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; TMS/EEG, TMS combined with EEG; TTM, targeted temperature management; UWS, unresponsive wakefulness syndrome; VS, vegetative state; wSMI, weighted symbolic mutual information.

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analyze the potential of novel research findings. In doing so, we (i) draw a distinction between acute, prolonged and chronic phases of DoC, (ii) attempt to relate both clinical and research findings to the underlying neuronal processes and (iii) discuss technical and conceptual caveats. The primary aim of this narrative review is to bridge the gap between standard and emerging electrophysiological measures for the detection and prediction of recovery of consciousness. The ultimate scope is to provide a reference and common ground for academic researchers active in the field of neurophysiology and clinicians engaged in intensive care unit and rehabilitation.

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Contents

1. Introduction

This decade will mark the first 100 years of electroencephalography (EEG), a relatively simple, inexpensive tool for the non-invasive measurement of brain activity. Early EEG recordings in humans performed by Hans Berger between 1929 and 1938 already suggested a link between levels of consciousness and brain electrical oscillations (Niedermeyer and Lopes da Silva, 2005). Since then, EEG has considerably evolved and, where available, it now represents a cornerstone for the instrumental assessment of patients with disorders of consciousness (DoC).

DoC stands for a class of severe neurological conditions that can essentially be categorized into coma, vegetative state (VS), also termed unresponsive wakefulness syndrome (UWS), or minimally conscious state (MCS). The classification is based on well-established, standardized neurobehavioral rating scales such as the Coma Recovery Scale Revised (CRS-R) (Giacino et al., 2004). Recent clinical guidelines on DoC endorsed by the American Academy of Neurology (AAN) (Giacino et al., 2018b, 2018a) also drew an important nosological distinction between acute, prolonged and chronic conditions based on defined temporal criteria (Table 1). Since these distinctions are important and used as a reference throughout this review, we specify them in Table 1.

The pathophysiology of DoC is heterogeneous (Bernat, 2006) and probably the result of a combination of factors whose role and interplay still need to be fully clarified (Giacino et al., 2014; Naccache, 2018). So, while DoC categories may superficially appear quite homogeneous, important distinctions exist in terms of diagnosis, prognosis and clinical management. In this vein, the AAN endorsed the use of EEG-based tools to evaluate DoC patients whose behavioral evidence is ambiguous regarding the presence of conscious awareness (Giacino et al., 2018b, 2018a). Further recommendations for the use of EEG-based techniques, including event-related potentials (ERPs) and a combination of transcranial magnetic stimulation (TMS) and EEG (TMS/EEG), to evaluate consciousness in DoC patients were specified by the recent European

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Table 1
Definition of DoC and related conditions.

According to behavioral criteria	Coma (Plum and Posner, 1966)	State of unresponsiveness characterized by absence of arousal (patients lie with their eyes closed) and, hence, of awareness. Of note, this definition is not based on the Glasgow Coma Scale criterion of a score < 8 which can erroneously include VS/UWS, MCS and conscious patients.
	VS (Jennett and Plum, 1972) also known as UWS (Laureys et al., 2010)	State defined by the recovery of arousal in an unresponsive patient who does not show any evidence of awareness.
	MCS (Giacino et al., 2002)	Condition of severely impaired consciousness in which there is minimal, discernible but fluctuating evidence of awareness. This state can be further subdivided into MCS plus (indicating high-level behavioral responses such as command following or specific responses to linguistic content) and MCS minus (indicating low-level non-reflex behavior such as visual pursuit, localization of pain or appropriate smiling to emotional stimuli) (Bruno et al., 2011).
According to temporal criteria (Giacino et al., 2018a, 2018b)	acute	DoC present for less than 28 days.
	prolonged	After at least 28 days from the brain injury.
	chronic	After 3 months in non-traumatic and after 12 months in traumatic cases. The term denotes the stability of a previous prolonged condition.
Conditions without impairment of consciousness	Locked-in syndrome (LIS) (Plum and Posner, 1966)	State in which the patient is completely de-efferented resulting in paralysis of all four limbs and lower cranial nerves.
	Emergence from a MCS (EMCS) (Giacino et al., 2002)	Condition characterized by a reliable and consistent demonstration of functional interactive communication and/or functional use of two different objects.
Conditions of clinical-paraclinical dissociations in DoC	Covert awareness (Owen et al., 2006, 2007)	Patients with no, or very limited, behavioral evidence of awareness who nonetheless demonstrate empirical evidence of command-following via functional MRI (fMRI), quantitative EEG (qEEG) or similar indirect measurements of brain response to spoken language. These terms denote a dissociation between behavioral motor dysfunction and the preserved higher cognitive functions only measurable by functional techniques. Despite the similar clinical presentation, these conditions differ in term of measured evidence (definite in case of covert awareness and CMD versus indefinite in functional LIS) and in term of awareness (binary in case of covert awareness and functional LIS versus graded in CMD).
	Cognitive-motor dissociations (CMD) (Schiff, 2015)	
	Functional LIS (Giacino et al., 2009; Bruno et al, 2011; Formisano et al., 2013).	
	MCS* (Gosseries et al, 2014a; Bodart et al., 2017)	
	Non-behavioral MCS (Stender et al., 2014)	
	Higher-order cortex motor dissociation (HMD) (Edlow et al., 2017).	HMD indicates evidence of physiological dissociation of cortical function and behavior without evidence of command following or other proxies of language comprehension.

Abbreviations: CMD, Cognitive-motor dissociations; DoC, disorders of consciousness; EMCS, emergence from minimally conscious state; fMRI, functional magnetic resonance imaging; HMD, higher-order cortex motor dissociation; LIS, locked-in syndrome; MCS, minimally conscious state; qEEG, quantitative EEG; UWS, unresponsive wakefulness syndrome; VS, vegetative state.

Academy of Neurology (EAN) guideline on the diagnosis of coma and DoC (Kondziella et al., 2020). Following up on these AAN and EAN directions, this narrative review aims to provide an integrated overview of both conventional clinical and advanced EEG-based techniques for the bedside assessment of DoC patients.

The past few years have witnessed a formidable growth of EEG-related research applied to the prediction and detection of recovery of consciousness after severe brain injury. A rapid succession of scientific papers has generated, on one side, great interest and enthusiasm but also some doubts and questions. How do the various EEG-based measures differ one from another? Are they complementary or alternative to each other? What is the relationship between standard neurophysiological approaches and new research-driven proposals? Can we transform this dynamic, at times haphazardly growing, field into a more organized landscape for the practical benefit of patients?

The aim of this review is to offer a first basis for the reader to address these questions. Three basic principles have guided us. First, to provide a balanced and accessible presentation of both consolidated clinical applications and new emerging approaches, in order to bridge a potential divide between the reality of clinical assessment and the enthusiasm of research reports. Second, to relate both clinical and research findings to the underlying neuronal and network processes, in an attempt to provide a common reference framework. Third, to share expert opinions and considerations based on our hands-on experience, regarding technical and conceptual caveats that might be overlooked in the limited space of typical research or review papers.

Our overview of the various neurophysiological approaches to DoC patients is structured in three main parts. The first part describes conventional clinical EEG and its implications in terms of prognosis and diagnosis, the second focuses on the role of both consolidated and investigational evoked potentials (EP) and ERP applications, and the third part deals with novel research findings that may be of clinical use in the near future. Rather than representing another consensus or a recommendation report, this paper intends to offer a reasoned taxonomy encompassing both old and new electrophysiological measures for the prediction and detection of recovery of consciousness. Its ultimate ambition is to be useful to both clinicians and academic researchers. We hope that the former will be interested to learn about the potential of upcoming research-driven applications, the latter to discover (or re-discover) the rationale and value of consolidated EEG clinical approaches. Hopefully, the broader audience will get the best of both worlds and become interested in this vibrant translational field.

2. Conventional clinical EEG in acute and chronic DoC

Spontaneous EEG activity represents a simple measure of the global brain state that is supported by internationally standardized methods of acquisition and interpretation in the time and frequency domain (Niedermeyer and Lopes da Silva, 2005). The main advantage of EEG is its widespread availability and applicability in both intensive care unit (ICU) and clinical rehabilitation settings. The challenge is that relevant information carried by the EEG signal is often embedded in a multidimensional space (i.e. time-varying activity at several electrodes) and can be difficult to extract. In this first part, we highlight how with clinical practice one can use

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visual inspection to detect EEG features that provide crucial information for the assessment of acute, prolonged and chronic DoC patients.

2.1. EEG-based assessment of acute DoC

We here focus on the description of EEG features that can be used in the acute setting to specifically predict recovery of consciousness. In the ICU, EEG-based techniques can also be employed to detect conditions that can immediately mask recovery of consciousness or affect the clinical evolution and that can be reverted if promptly recognized. This latter aspect, which is not directly related to the prognosis and diagnosis of DoC but it is crucial for directing initial patient management, is discussed in Box 1.

Box 1. EEG-based monitoring of acute DoC in the ICU

In the initial phase, comatose patients may suffer complications that can hinder the recovery of consciousness and affect the clinical evolution. These conditions need to be promptly identified and treated.

In the acute setting, the EEG is routinely recorded primarily to detect non-convulsive seizures (NCSz) or non-convulsive status epilepticus (NCSE) that might explain the patient's unresponsiveness. The vast majority of seizures encountered in the ICU are nonconvulsive and a reliable diagnosis is not possible without an EEG. In retrospective case series, NCSz with minimal or absent clinical signs were detected in up to 30% of comatose patients in a neurological ICU (Claassen et al., 2004; Young et al., 1996), and in 10–25% of comatose patients with transitions from convulsive status to NCSE, even with adequate benzodiazepine treatment. In patients with acute brain injury, EEG is required to make the diagnosis of NCSz, in cases where clinical signs are nonspecific. In general, NCSz and NCSE are most frequently observed in patients admitted for central nervous system infections (i.e. encephalitis, meningitis, brain abscesses), slightly less frequent in hemorrhages (i.e. subarachnoid hemorrhage, SAH and subdural hemorrhage), TBI and least frequent in ischemic strokes. In these patients, unconsciousness may be secondary both to the seizures as well as the underlying acute brain injury that caused the seizure. Therefore, adequate treatment of seizures may or may not lead to recovery of consciousness. It was estimated that, in the ICU setting, NCSE may occur in up to 10% of unconscious patients, excluding those with evidence of brain injury (Towne et al., 2000; Oddo et al., 2009; Kurtz et al., 2014).

Notably, almost all seizures that are refractory to initial antiepileptic management are nonconvulsive and patients treated with anesthetic drips frequently have seizures during and immediately after weaning off anesthetic antiepileptic infusions (Claassen et al., 2002). In this context, EEG recordings are fundamental as continuous drips are typically titrated to EEG endpoints, such as seizure suppression or burst-suppression.

The optimal recording length for detecting seizures in comatose or unconscious patients is still a matter of debate. A routine EEG recording lasts about 20–30 min, a time window that may be insufficient to detect seizures (especially NCSz) in critically ill patients (Pandian et al., 2004; Nguyen-Michel et al., 2016). Indeed, it has been demonstrated that at least 24h of continuous EEG (cEEG) monitoring is needed to detect 95% of critical events (Claassen et al., 2004). On the other hand, the lack of epileptiform transients within the first 30 minutes has been suggested to render subsequent seizures very unlikely (Shafi et al., 2012; Alvarez et al., 2013b).

Nevertheless, the eventual presence of an ictal-interictal continuum (IIC) could dictate the need for a longer recording window. The IIC encompasses patterns that do not qualify as unequivocal seizure but are clearly abnormal and often observed in ICU brain-injured patients. While the clinical significance of these patterns is somewhat controversial, their presence is suggestive of a higher risk of NCSz (Rodriguez Ruiz et al., 2017). Particularly interesting among these latent patterns are those induced by exogenous stimulation; these abnormal reactive patterns, termed stimulus-induced rhythmic periodic ictal discharges (SIRPIDs), can herald a transition to a NCSE and can be accurately identified and classified only with cEEG, best by video EEG. There are conflicting data on the mortality rate associated with NCSE due to the large variability of the patients involved (e.g. non-comatose versus comatose patients). Risk factors leading to a worse outcome include acute brain disease, severe mental status impairment, and long seizure duration (Young et al., 1996; Shneker and Fountain, 2003). Compared with clinically overt status epilepticus, NCSE appears to be associated with a worse prognosis (DeLorenzo et al., 1998; Treiman et al., 1998); in a large randomized multicenter drug trial comparing benzodiazepines, phenytoin and phenobarbital, the mortality for NCSE (here defined as subtle status epilepticus) was reported to be 65%, compared to 27% mortality for overt generalized status epilepticus (Treiman et al., 1998).

In addition to its utility in seizure monitoring, the EEG can detect characteristic changes that parallel progressive stages of ischemia. In these cases, spectral analysis of serial EEG (Landau-Ferey et al., 1984; Rivierez et al., 1991) or cEEG (Vespa et al., 1997) typically evidences loss of fast electrical activity and an increase of low frequencies, which are helpful in detecting delayed cerebral ischemia in coma due to SAH (Landau-Ferey et al., 1984; Rivierez et al., 1991; Vespa et al., 1997). In patients with SAH, invasive brain monitoring suggests an uncoupling of neuronal activity and perfusion (Foreman et al., 2018) and an increase in the lactate pyruvate ratio and glutamate (Sarrafzadeh et al., 2002). Thus, the detection of IIC abnormalities (Kim et al., 2017) along with the application of automated algorithms for spectral analysis of the EEG (Wickering et al., 2016) are valid tools for predicting delayed cerebral ischemia in the ICU.

2.1.1. EEG classifications in the acute setting

The first attempt to correlate the outcome of coma patients with the level of EEG abnormality dates back more than 50 years ago, when a classification of EEG patterns based on background frequencies and amplitudes was proposed in post-anoxic coma (Hockaday et al., 1965). A consistent finding was the association of worsening brain function with a progressive slowing and dampening of EEG background oscillations. This notion was further refined by Synek (Synek, 1988) who proposed an EEG classification in five grades ranging from dominant reactive alpha activity (grade 1), through a progressive background slowing to an isoelectric EEG (grade 5). Notably, this classification included EEG reactivity, defined as changes in frequency and/or amplitude in the background activity induced by auditory, visual or noxious stimulations. This is important, as jointly considering EEG background and reactivity may improve the prognostic value; for example, grade 2 patterns of a "reactive type" were associated with favorable outcomes and survival, whereas unreactive alpha and theta

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coma were associated with unfavorable outcome. EEG reactivity was given further importance in the classification proposed by Young (Young et al., 1997) which specified in detail each EEG pattern to improve inter-observer reliability.

Following on the proposals by Synek (Synek, 1988) and Young (Young et al., 1997), the quest for improved generalizability has led to a standardized description of EEG terminology proposed by the American Clinical Neurophysiology Society (Hirsch et al., 2013) which has been validated by two independent groups (Gaspard et al., 2014; Westhall et al., 2015). For example, EEG background is described according to precisely defined characteristics such as symmetry, predominant frequency, reactivity, amplitude, the presence of sleep transients, and continuity. In addition, this classification incorporates proper definitions of major transients defined according to both their spatial distribution (generalized, lateralized, bilateral independent, or multifocal) and temporal features (periodic, rhythmic delta activity, or spike-waves). Hence, most of the observations reported in the following two sections can be framed within the standardized critical care EEG terminology proposed by Hirsch and colleagues (2013).

2.1.2. EEG-based prognosis of hypoxic-ischemic encephalopathy

We start by describing the prognostic value of EEG features in post-anoxic patients, in whom the reliability of this technique is widely recognized. In hypoxic-ischemic encephalopathy (HIE), the prognostic role of EEG is typically established with a multimodal protocol (including clinical examination, blood biomarkers and brain imaging) to minimize false positive predictions of poor outcome (Sandroni et al., 2014; Rossetti et al., 2016). In this context, a potential confounding factor is the targeted temperature management (TTM, induced mild hypothermia to 32 °C or strict normothermia at 36 °C for 24 h) and sedation often employed in post-anoxic patients. However, it has been shown that mild hypothermia, does not lead to significant EEG changes (Stecker et al., 2001) and also sedative infusions administered for TTM do not significantly impair the EEG prognostic accuracy at 24 h compared to recordings carried out after 2–3 days (Oddo and Rossetti, 2014; Sivaraju et al., 2015; Rossetti et al., 2017). Furthermore, it was found that early EEG recordings in HIE have a higher prognostic value than later recordings (after 24–48 h) (Hofmeijer et al., 2015) irrespective of sedation protocols. Indeed, in a large multicenter trial, Ruijter et al. (2019a) showed that propofol does not affect both favorable and unfavorable prognostic value of early EEG despite its effect of reduction on amplitude, background continuity, and dominant frequency.

In the majority of the cited studies, outcome was defined according the Cerebral Performance Category (CPC) (Booth et al., 2004) as good (CPC = 1–2; no or mild cerebral impairment) or poor (CPC = 3–5; moderate cerebral impairment, VS/UWS or death) at 3 or 6 months. Regarding EEG, findings are typically categorized according to three main dimensions which are background activity, reactivity and epileptiform features. As a rule, the decline of brain function in terms of background activity is paralleled by a progressive decrease in both the amplitude and frequency. Low voltage ($<20\ \mu V$) or suppressed ($<10\ \mu V$) background activity at 24 h (false positive rate FPR 0%, 95% confidence intervals CI: 0–17% Cloostermans et al., 2012; Sivaraju et al., 2015), burst-suppression (FPR 0%, 95%CI: 0–11% Sivaraju et al., 2015), burst-suppression with identical bursts (FPR 0%, 95% CI: 0–17% Hofmeijer et al., 2014b) and spontaneous discontinuous background (FPR 7%, 95%CI: 0–24% Rossetti et al., 2012) are apparently solid predictors of poor outcome. As an exception, burst suppression outlasting sedation for weeks has been associated in one subject with good outcome (Becker et al., 2017). In this patient and in two additional patients with a late emergence from coma, a θ (~4–7 Hz) peak intraburst spectral power similar to a cohort of patients with early recovery of consciousness was recently shown (Forgacs et al., 2020); however, all documented cases of burst-suppression with identical bursts have been associated with a poor outcome (Hofmeijer et al., 2014b; Hofmeijer and van Putten, 2016). Conversely, a continuous background appearing at 12 h may herald a good outcome (positive predictive value PPV 92%, 95% CI: 80–98% Hofmeijer et al., 2015). Further confirming the role of background continuity, two objective indexes (i.e. the background continuity index and the burst-suppression amplitude ratio) were recently proposed (Ruijter et al., 2018); their combination seems to provide accurate prognostic indications both for good and poor outcome. A peculiar condition where a continuous background has to be considered a malignant pattern is the alpha-coma which is characterized by rhythmic activity in the alpha frequency band that occur with a widespread or anterior distribution (Scollo-Lavizzari and Bassetti, 1987). This specific pattern has been strongly linked with a poor outcome (Synek, 1988; Berkhoff et al., 2000); however, it is encountered only a few days after cardiac arrest.

The role of EEG reactivity in predicting outcome still appears rather controversial. Absent reactivity has been reported to strongly correlate with poor outcome even during TTM (FPR 1.5%, 95% CI: 0–4% Rossetti et al., 2017), whereas a reproducible reactivity may indicate a subsequent good outcome (PPV 72%, 95% CI: 66–78% Rossetti et al., 2017). Interestingly, non-physiological reactivity, such as stimulus-induced rhythmic periodic ictal discharges (SIRPIDs), correlates with poor prognosis (FPR 2%, 95%CI: 0–11%) especially during TTM (Alvarez et al., 2013a). On the other hand, the reliability of EEG reactivity was recently questioned by a multicentric study (Admiraal et al., 2019) which reported a lower accuracy especially for poor outcome at 6 months. This study did not find a substantial added value of EEG reactivity with respect to EEG background, neurological examination and somatosensory evoked potentials (SEPs). Different methodological issues (e.g. the avoidance of nipple pinch for ethical concerns) should be taken into account to explain these controversial results (Lee, 2019). Indeed, a generalization of these findings is mainly hampered by the variability of inter-rater agreements (Noirhomme et al., 2014; Westhall et al., 2015; Admiraal et al., 2018; Duez et al., 2018). A standardized stimulation protocol may help to improve this aspect (Tsetsou et al., 2015; Fantaneanu et al., 2016). However, current guidelines do not state which stimuli to use, nor do they define clearly how to interpret EEG reactivity (Admiraal et al., 2019).

Epileptiform features such as sharp waves, (poly-) spikes, spike and waves (defined according to Hirsch et al., 2013) are rarely recorded in isolation, as they typically occur in repetitive (periodic or rhythmic) patterns over at least 10% of the recording. If these features are present during TTM, under sedation with antiepileptic properties, the FPR for poor outcome is low (0–3%, 95% CI: 0–30% Sadaka et al., 2015; Rossetti et al., 2017).

However, a subset of patients with epileptiform patterns appearing only after stopping sedation (especially when brainstem reflexes, EEG reactivity and SEPs are also preserved) may have a good outcome if subsequently treated (Rossetti et al., 2009). Yet, whether the treatment of epileptiform discharges in patients with HIE is beneficial for improving outcome is still debated (Ruijter et al., 2014). An elegant study (Elmer et al., 2016) highlighted the poor outcome heralded by generalized myoclonic status epilepticus (characterized by high-voltage, diffuse discharges on a suppressed background), as opposed to Lance-Adams syndrome (a stimulus-sensitive myoclonus with epileptiform EEG characterized by low-voltage, vertex discharges on a continuous background). Also, the earlier the epileptiform features appear after cardiac arrest, the worse the prognosis (Westhall et al., 2018). Recently, an EEG score including findings on recordings performed during and shortly after TTM (epileptiform features; background continu-

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ity, reactivity, amplitude; SIRPIDs after TTM) has been proposed to identify patients who may regain consciousness after an early epileptiform EEG (Barbella et al., 2020a).

2.1.3. EEG-based prognosis of traumatic, hemorrhagic and toxic-metabolic encephalopathies

Regarding other etiologies (other than post-anoxic), the wide range of pathophysiology and lesional load complicates the relationship between EEG features and outcome.

In patients with a traumatic brain injury (TBI), seizures have been associated with a higher early mortality (Hesdorffer et al., 2009), and may worsen the cerebral damage (Vespa et al., 2007); similar findings apply to subarachnoid hemorrhage (SAH) (Dennis et al., 2002; Claassen et al., 2006), probably more so than to intracranial hemorrhage (Passero et al., 2002; Vespa et al., 2003; Claassen et al., 2007).

As already mentioned, in SAH the EEG can predict the onset of vasospasm: spectral analysis of continuous EEG (cEEG) can reveal a decreasing α variability or α/δ ratio up to 48 h in advance (Vespa et al., 1997). However, the extent to which EEG findings influence prognosis in this setting remains unclear. In acute brain-injured patients with SAH, distinctive features (such as an increase in central γ and posterior α) can also help predict the behavioral state (Claassen et al., 2016).

Similarly to HIE, EEG reactivity can be important in patients with TBI; the majority of patients showing a transitory increase of slow waves or suppression to sensory stimuli seem to have a favorable outcome, compared to those without any EEG reaction; in these cases, the discriminative power of EEG reactivity appears better than that of SEPs (Gütling et al., 1995).

Metabolic or toxic encephalopathies, like other impairments of brain function primarily induced by extracerebral causes, are seen on the EEG as progressive slowing (Kaplan, 2004; Amodio and Montagnese, 2015). In some cases, these encephalopathies are characterized by the appearance of rhythmic delta or sharp waves with triphasic appearance (Sutter et al., 2013). Here, again, EEG reactivity seems to play a key role in defining the prognosis (Kaplan, 2004).

2.2. EEG-based assessment of prolonged and chronic DoC

Beyond the acute window, the distinction between diagnostic and prognostic aspects becomes unclear since the evidence regarding outcome is less systematic in prolonged and chronic DoC. This is partly a result of the rather coarse mode in which outcome from the comatose state is defined in the prognostic behavioral scales (Glasgow Outcome Scale, GOS, or its extended version, GOS-E and CPC) (Jennett et al., 1981; Wilson et al., 1998; Booth et al., 2004). For example, a GOS-E grade 3 refers to conscious patients with severe disability but still able to follow commands, a definition which may only implicitly correspond to "MCS plus" but that does not specifically include "MCS minus" (Formisano et al., 2018) (see Table 1 for definitions).

In all cases, a key message of this section is that an educated inspection of basic EEG features in prolonged DoC can provide relevant information about the functional integrity of thalamo-cortical networks (Schiff, 2016). In this vein, we outline in Box 2 the putative relationships between scalp EEG patterns and basic neuronal processes occurring as a consequence of a severe brain damage.

2.2.1. The EEG during wakefulness

2.2.1.1. Prognosis. Several studies have explored the value of clinical EEG features in the prognosis of prolonged DoC (Bagnato et al., 2010, 2015, 2017; Arnaldi et al., 2016). Bagnato and colleagues (2010) first highlighted the utility of EEG in predicting 3-month

Box 2. The EEG in DoC: putative neuronal and network mechanisms

As basic EEG features can be traced back to time-varying synaptic activity in cortical circuits and to the influences of subcortical structures (Nunez et al., 2006), it is possible to make inferences from clinical EEG traces about the functional integrity of thalamo-cortical networks in DoC (Schiff, 2016). Our current understanding of the mechanisms of brain oscillations (Nunez et al., 2006; Steriade, 2006; Sanchez-Vives et al., 2017) suggests that at least some of the EEG patterns observed in DoC may reflect disconnection (or deafferentation) within and among cortical and subcortical structures (Schiff et al., 2014; Schiff, 2016).

Specifically, relating the slowing of the EEG background often found in DoC to structural and functional deafferentation of both vertical subcortico-cortical connection and horizontal cortico-cortical connections seems particularly relevant in the light of animal, in vitro and in silico experiments. For example, deafferentation may occur during acute ischemia due to disruption of presynaptic processes (Hofmeijer and van Putten, 2012; van Putten and Hofmeijer, 2016). Hence, mild to moderate ischemia may impair synaptic transmission whereas the ability to generate action potentials remains intact. In this condition, synaptic failure is frequently associated with an increase of EEG slowing in the δ band (Bolay et al., 2002; Hofmeijer et al., 2014a; van Putten and Hofmeijer, 2016). If ischemia becomes more severe, neuronal functional changes are replaced by structural changes such as cytotoxic edema and cell death secondary to changes in membrane potential and the abolition of action potentials (Rungta et al., 2015).

Macroscopic structural disconnections of cortical circuits are also expected to play a major role. White matter lesions are indeed known to produce an EEG pattern dominated by oscillations in the δ range (Gloor et al., 1977). Experimental models, such as cortical slabs, in which all afferent inputs are removed from the cerebral cortex (Timofeev et al., 2000) produce EEG patterns not unlike those observed in severe DoC patients (Schiff et al., 2014). In these experiments, the deafferentation of small cortical volumes results in depressed EEG and intracellular activity with only sporadic depolarizing events occurring at a frequency of 0.03–0.1 Hz, resembling burst suppression. Intriguingly, this pattern evolves toward a sleep-like slow oscillation in the δ range (at nearly 1 Hz) if the volume of the cortical slab is larger, allowing for more recurrent cortico-cortical excitatory activity. Slow oscillations at 1 Hz or less can also be found in cortical slices in vitro (an extreme model of cortical deafferentation) and have been recently interpreted as the default-mode pattern of activity expressed by isolated cortical circuits (Sanchez-Vives et al., 2017). Notably, such slow EEG oscillations at around 1 Hz correspond to the "A"-type spectral pattern of the "ABCD" model (Schiff 2016) (Fig. B.1). In this framework, the "A"-type may represent the complete functional cortico-thalamic deafferentation which can be found in some VS/UWS patients with severe anoxic injury (Forgacs et al., 2017).

The model also predicts that if some level of cortical activation through ascending afferents can be recovered, but thalamic neurons remain strongly hyperpolarized, intrinsic membrane properties of the cortical circuits will allow oscillations in the θ range (around 7 Hz) to emerge (Silva et al., 1991; Williams et al., 2013). These oscillations generated by cortical neurons under a condition of relative disfacilitation may cor-

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respond to the “B”-type EEG pattern observed in some patients.

Severe brain injury of varying etiology can produce a direct (thalamo-cortical and brainstem-thalamic) or indirect (cortico-striatal-thalamic) reduction of the neuronal activity in the central thalamus, which is part of the ascending activating system and is known to play a key role in sustaining arousal, working memory, attention and motor intentional networks (Giacino et al., 2014; Gent et al., 2018). According to this framework, called the mesocircuit hypothesis (Schiff 2010, 2016), there is a rough graded relationship between the degree of deafferentation, the mode of thalamic activity and EEG patterns (Fig. B.1). Hence, depending on the degree of deafferentation, neurons of the central thalamus can be either quiescent (“A-type”, “B-type”), enter in a bursting mode (“C-type”) or progress towards a tonic mode of activity (“D-type”). These modalities are thought to reflect a progressive increase of excitatory drive especially to anterior forebrain thalamo-cortical circuits (Liu et al., 2015). The coexistence of bursting and tonic modes in different sectors of the thalamus may thus result in a pattern characterized by co-localized β and θ, corresponding to the “C-type” patterns shown in Fig. B.1. Full recovery of thalamic facilitation and a shift to ubiquitous tonic firing restores the typical wakeful EEG activity, characterized by α and β oscillations corresponding to the “D-type” pattern (Schiff, 2016). Notably, this latter pattern can be observed in patients who are behaviorally minimally responsive, but are able to successfully engage in active fMRI and EEG active paradigms (see Section 4.3), signaling a CMD (Schiff, 2015; Curley et al., 2018).

A spectral-based assessment according to the “ABCD” model was recently applied to DoC patients, early after HIE (Forgacs et al., 2017). Interestingly, the predicted transitions of neocortical dynamics represented by spectral features correlated well with a higher level of consciousness and positive clinical outcome (see also Kustermann et al., 2019 for similar findings in coma).

In this perspective, basic EEG features observed in DoC can be traced back, albeit indirectly, to neuronal (e.g. presynaptic damage) and network (e.g. structural disconnection) alterations previously studied in experimental models. A key notion is that the disconnection of cortical neurons from subcortical inputs is associated with slowing of EEG rhythms even in the presence of eyes opening in DoC patients. In this way, a critical level of deafferentation may lead to the widespread appearance of stereotypical sleep-like slow oscillations even during behavioral wakefulness, to loss of EEG reactivity and circadian modulation. As described in Section 4.2, TMS/EEG experiments showed that pathological slow waves and the associated neuronal events may further precipitate thalamo-cortical circuits into a state of functional disconnection and low complexity, possibly engendering a vicious circle (Rosanova et al., 2018).

outcome by applying the Synek classification. In follow-up studies, a restricted collection of standard EEG features was employed (i.e. overall amplitude, dominant frequency, and reactivity, called AFR score) and it correlated with 3-month outcome in prolonged DoC (Bagnato et al., 2015). Specifically, reduced overall EEG amplitudes and dominant δ (<4Hz) frequency content were significantly associated with worse outcomes; conversely, the presence of α dominant frequency and preserved EEG reactivity predicted recovery. Accordingly, a subsequent study looking at 6-month outcome found that recovery from VS/UWS was predicted by increases in the dominant frequency of the EEG background activity, emergence of EEG reactivity and higher AFR scores (Bagnato et al., 2017). Recently, a more standardized visual analysis based on the American Clinical Neurophysiology Society terminology confirmed the prognostic value of conventional EEG features in a large sample of patients (Scarpino et al., 2019).

The prognostic role of epileptiform abnormalities was explored by Bagnato and colleagues (2016). Although patients with bilateral epileptic features tended to have lower CRS-R scores, these features did not have a significant impact on recovery of consciousness. A parallel study (Pascarella et al., 2016) found that only the presence of epileptic seizure, but not of epileptiform activity, significantly hampered recovery of consciousness.

2.2.1.2. Diagnosis. The diagnostic value of conventional EEG descriptors is based on the simple observation that a well-organized EEG pattern during wakefulness corresponds to highly-preserved thalamo-cortical function, as assessed by fMRI and fluorodeoxyglucose positron emission tomography (FDG-PET) in MCS patients (Forgacs et al., 2014). As shown in Fig. 1, an intact waking EEG architecture, including dominant posterior α rhythm, is present in all DoC patients capable of fMRI correlates of mental imagery, indicating a state of CMD. This has led to a novel EEG classification for prolonged and chronic DoC based on three EEG descriptors (predominant background frequency, organization of the anteroposterior gradient, and presence of any diffuse/focal slowing). The classification consists of four possible EEG categories (i.e. normal, mildly abnormal, moderately abnormal and severely abnormal) (sensitivity of 61% for a diagnosis of MCS in prolonged DoC when considering a normal/mildly abnormal background; specificity of 75%). A fifth category, the low voltage pattern, was added to this classification by Estraneo and colleagues (2016), as it was found to be significantly more frequent in VS/UWS patients.

These two studies were critically reappraised in the recent guidelines on the diagnosis of DoC endorsed by EAN (Kondziella et al., 2020). According to this analysis, a normal or mildly abnormal background is able to detect MCS with very high specificity but low sensitivity (relative risk 11.25 95% CI 2.85–44.46; P = 0.0006) resulting in a strong recommendation for the use of standard clinical EEG in the diagnostic evaluation of DoC.

In line with these recent recommendations, we would reinforce the notion that a conventional clinical EEG (revealing the structure and the differentiation of coordinated EEG activity and reactivity patterns) remains a fundamental clinical tool to confirm a LIS or to suspect a state of CMD. This simple bedside tool should be performed in all patients with prolonged or chronic DoC since a reactive posterior alpha rhythm during wakefulness can rule out VS/UWS with high specificity. At the same time, it is important to stress the risk of false negative inherent to standard EEG inspection, as even a severely abnormal background cannot rule out a MCS condition (low sensitivity).

2.2.2. The EEG during sleep

According to the classical definition of coma by Plum & Posner (Plum and Posner, 1966), the recovery of ascending activating systems is a crucial hallmark for defining the end of the comatose phase and therefore of the acute phase of DoC. The importance of this system as an “on/off” switch for the transition between conscious wakefulness and sleep provides a solid rationale for sleep studies in DoC (Kotchoubey and Pavlov, 2018b). Most important, the preservation of specific sleep EEG features such as spindles, slow waves and their homeostatic regulation may reflect the sparing of fundamental neuronal and network processes within thalamic and cortical circuits. Landsness and colleagues (2011) found preserved sleep EEG features to be prevalent in MCS, while not typ-

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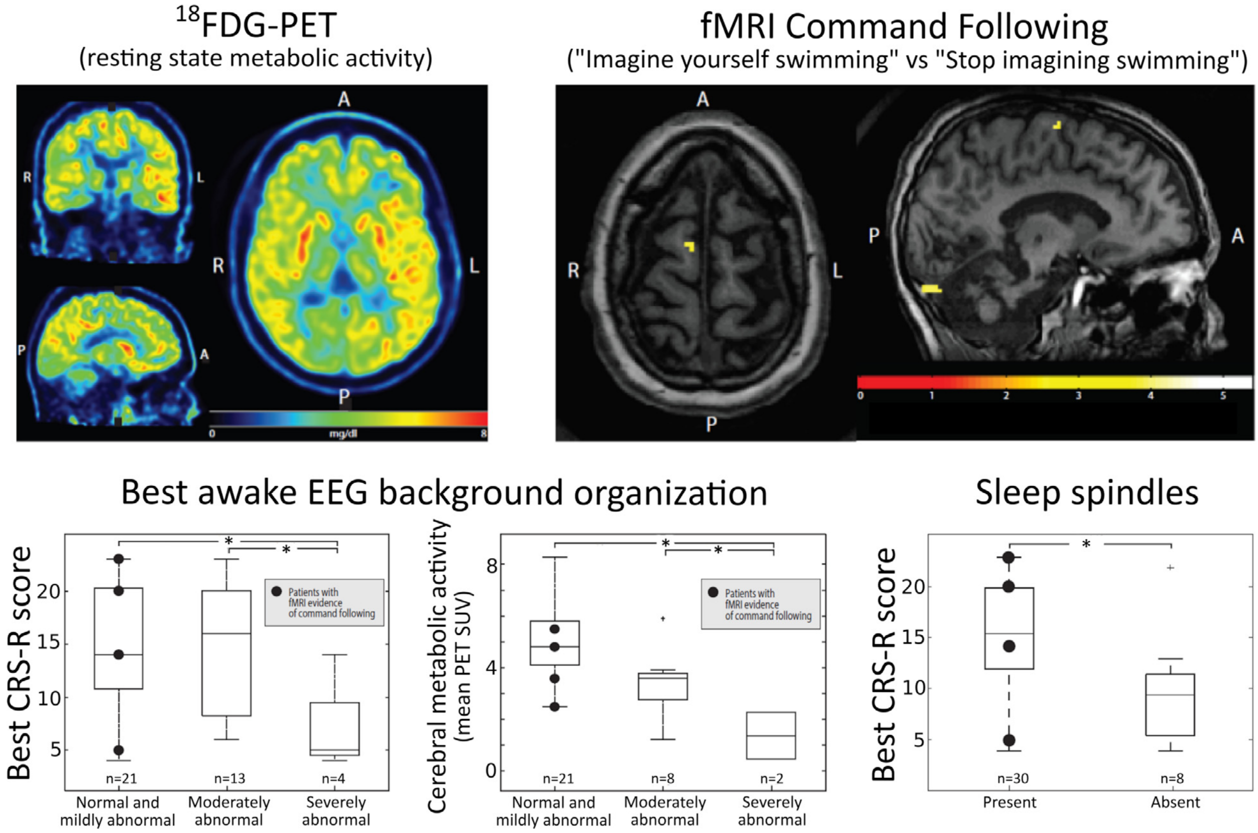

Fig. 1. Correlated performance of a fMRI mental imagery task with resting cerebral metabolism (FDG-PET), behavioral assessments and a clinical EEG classification. All patients with positive fMRI findings (black dots) demonstrated an intact wakeful EEG architecture and the presence of sleep spindles. CRS-R, Coma-Recovery Scale-revised; EEG, electroencephalography; FDG-PET, fluorodeoxyglucose positron emission tomography; fMRI, functional magnetic resonance imaging; SUV, standardized uptake value. Modified from (Forgacs et al., 2014).

ical of VS/UWS. In particular, all MCS patients demonstrated a transition from non-rapid eye movement (NREM) to rapid eye movement (REM) sleep as well as a pattern of overnight homeostatic decline of slow wave activity during the night. Conversely, VS/UWS patients exhibited only behavioral signs of sleep–wake cycles apparently not associated with electrophysiological features of sleep. These findings were, however, challenged by subsequent studies that found electrophysiological sleep-wake cycles also in VS/UWS with 24-h polysomnography (Cologan et al., 2013; de Biase et al., 2014) or with shorter recordings rated by 3 independent investigators and spectral analysis (Pavlov et al., 2017). Accordingly, Wislowska and colleagues (2017) reported a similar variability of sleep elements in MCS and VS/UWS patients without differences in the prevalence of sleep spindles or slow wave sleep. However, higher CRS-R scores were associated with the concurrent presence of sleep spindles and REM sleep (de Biase et al., 2014), with sleep spindles alone (Fig. 1) (Forgacs et al., 2014) or with longer duration of NREM sleep (Rossi Sebastiano et al., 2018). Overall, in spite of a large variability at the single-subject level, a partially preserved alternation of sleep-wake cycles with periods of consolidated slow wave sleep seems to be more prevalent in MCS patients (Rossi Sebastiano et al., 2015, 2018). Interestingly, all the patients with CMD (capable of fMRI correlates of mental imagery) also demonstrated preserved sleep spindles (Forgacs et al., 2014).

Future investigations in larger cohorts are necessary to identify the sources of variability among these studies. As pointed out by most authors, an unresolved limitation is that pathological sleep staging in DoC did not coincide with standard sleep scoring criteria (Cologan et al., 2013; Kotchoubey and Pavlov, 2018b; Rossi Sebastiano et al., 2018). Only a longer duration of polysomnography (at least 24 h) and additional physiological parameters (such as melatonin rhythm, temperature and actigraphy) (Wislowska et al., 2018) may allow a thorough evaluation of the abnormal circadian rhythms in DoC patients (Wislowska et al., 2017; Schabus et al., 2018; Wielek et al., 2018). Since a reliable characterization of sleep remains challenging in the absence of established staging criteria, complementary analysis of sleep EEG data by means of user-independent computational techniques might improve the diagnostic accuracy (Malinowska et al., 2013; Wislowska et al., 2017; Wielek et al., 2018).

2.3. Conventional clinical EEG in DoC: technical and conceptual caveats

In this section, we provide opinions and suggestions on how to improve the acquisition/interpretation of EEG data in clinical practice. A detailed characterization of the technical aspects involved in EEG recordings can be found in previous reports (American Clinical Neurophysiology Society, 2006a, 2006b; Alvarez and Rossetti, 2015) and is beyond the scope of this review.

1. Adapt the duration and timing of EEG to the specific context

When seizures are suspected in an unconscious patient, the recommended duration of EEG monitoring to record the first seizure is greater than 24 h (Claassen et al., 2004; Pandian et al., 2004). However, the absence of epileptiform activity in the first 30 min may provide a shorter monitoring window without a measurable decrease in sensitivity (Shafi et al., 2012; Alvarez et al., 2013b). A scoring system to quantify the risk of seizures according to EEG findings has been proposed (Struck et al., 2017). To date, there are only two retrospective studies based on discharge diagnosis, which reported a lower mortality associated with cEEG recording (Ney et al., 2013; Hill et al., 2019).

For prognosis in HIE, if cEEG is not available, serial EEGs are usually performed, since electrical activity evolves over the first 24–72 h (Rundgren et al., 2010; Cloostermans et al., 2012; Oh et al., 2013, 2015), taking into account changes of sedation during and after TTM. Indeed, the EEG within 24 h is a robust predictor of poor (unfavorable EEG pattern at 24 h) or good (favorable EEG pattern at 12 h) outcome of comatose patients after cardiac arrest (Cloostermans et al., 2012; Hofmeijer et al., 2015; Ruijter et al., 2019b).

In the ICU, several authors propose cEEG recording for up to 48 h (Hofmeijer et al., 2015; Sivaraju et al., 2015). However, two standard EEGs (<30 min) including reactivity, recorded within 48 h of cardiac arrest, might provide comparable prognostic information (Alvarez et al., 2013b) at lower cost (Crepeau et al., 2014); this approach does not seem to have any impact on prognosis (Fatuzzo et al., 2018). Thus, standard intermittent EEG recording should be considered, especially in centers with limited medical resources bearing in mind, nonetheless, its potential limitations.

2. Interpret EEG findings within a multi-modal framework in acute settings

EEG is part of the routine multi-modal approach (including clinical examination, neurophysiological evaluation, laboratory biomarkers and neuroimaging) applied in the ICU. In this setting, a multimodal evaluation for prognosis is warranted to reduce the possibility of false-positive predictions of poor outcome and of circular thinking resulting in self-fulfilling prophecies (Sandroni et al., 2014; Rossetti et al., 2016). Such assessment is also instrumental to achieve a better understanding of the underlying pathophysiological mechanisms, with direct impact on clinical decisions. For example, an epileptiform EEG on top of a severely damaged brain does not necessarily imply the need for aggressive antiepileptic therapy to increase the chances of awakening (Bauer and Trinka, 2010; Ruijter et al., 2014), especially if associated with negative findings from other prognostic markers such as clinical examination, SEPs and neuron-specific enolase.

3. Apply standardized behavioral scale and specific EEG cues in patients with chronic or prolonged DoC

A standardized neurobehavioral assessment based on the CRS-R scale is nowadays the gold standard for any EEG-based study on prognostic and diagnostic evaluation of DoC (Giacino et al., 2018b). The repetition of multiple CRS-R assessments has also been suggested to improve diagnostic accuracy (Wannez et al., 2017).

Given the impact of fluctuation in DoC, it is essential to check the vigilance state, rule out potential sedation confounders and constantly verify if the patient is awake. In this vein, an arousal protocol, similar to that employed during the CRS-R assessment, should be applied also during EEG recordings. Once the patient is awake, a passive eye opening/closing is mandatory to verify the preservation of posterior EEG background reactivity. Testing reactivity to exogenous stimuli such as acoustic and painful stimulation is also particularly important since the preservation of EEG reactivity may have a diagnostic role in distinguishing MCS from VS/UWS (sensitivity for MCS of 97%) (Estraneo et al., 2016). A prolongation of the clinical EEG recording time may also be useful both for sleep staging and for wakefulness characterization whenever clinical fluctuations or abundant muscle artifacts impair visual analysis.

4. Consider the limitations of scalp EEG in reflecting underlying neuronal events

Discriminating between MCS and VS/UWS patients is not always reliable due to the low sensitivity of scalp EEG. Indeed, the general assumption that scalp EEG time-series represent the underlying average activity of neocortical neurons is not always correct. A dramatic example of such dissociation is the rare phenomenon in which a continuous spike-wave activity consistent with refractory absence seizures appears in an awake, conscious human subject (Gökyiğit and Calişkan, 1995) or when high voltage slow waves appear in conscious children with Angelman syndrome (Frohlich et al., 2020). In this case, powerful local sources of pathological activity may mask at the level of scalp voltages the presence of normal patterns of neuronal activity. A similar example is represented by the local EEG activations that can be observed during NREM sleep in intracranial recordings while scalp EEG is still dominated by slow waves (Nobili et al., 2012). More complex and unpredictable dissociations are likely to occur in cases of severe brain injury of traumatic, vascular or infective etiology, where intact tissue can coexist with islands of disconnected or damaged cortex.

3. EPs and ERPs in acute and chronic DoC

We move now from the conventional analysis of spontaneous EEG to the evaluation of EEG responses to sensory stimulation and consider the prognostic and diagnostic role of EPs and ERPs. According to a classical definition (Picton et al., 2000), EPs, also referred to as "exogenous responses", are largely dependent on the physical parameters of the incoming stimulus. Typically, these components peak early, within the first 100 ms after the stimulus onset and are tightly time-locked to stimulus onset. Conversely, ERPs, or "endogenous responses", capture neural activity more related to late stages of information processing and to the cognitive aspects of the task in which the stimulus is embedded (Fig. 2). These potentials typically show a more variable time relationship with the stimulus onset and a marked sensitivity to the specific experimental paradigm. A synthetic overview of the main EP/ERP paradigms employed in DoC is provided in Box 3.

As with spontaneous EEG activity, the analysis of evoked responses can either be descriptive, based on the operator's experience, or quantitative and automatic. In the first case, a classical approach based on visual inspection and voltage analysis of specific components with defined spatiotemporal and polarity features is provided (Fischer et al., 2010; Rohaut et al., 2015). The second approach involves a more advanced analysis, based on wavelet-transformed data (Kotchoubey et al., 2005; Steppacher et al., 2013) or statistical decoding algorithms and machine learning (ML) (King et al., 2013a; Sitt et al., 2014; Rohaut et al., 2015; Tzovara et al., 2016).

Below, we discuss the prognostic relevance of EPs and ERPs in the ICU versus rehabilitation settings and, finally, we focus on their diagnostic performance in distinguishing MCS from VS/UWS.

3.1. EP/ERP-based assessment of acute DoC

Similarly to spontaneous EEG, also for EPs/ERPs, the clinical outcome is classified in most studies as either poor (VS/UWS or dead, both frequently labelled as "non-awake") or good (ranging from severe disability to good recovery) according to the GOS (Jennett et al., 1981), GOS-E (Wilson et al., 1998) or the CPC (Booth et al., 2004; Rittenberger et al., 2011).

3.1.1. SEPs

The role of bilateral absence of N20 in predicting poor outcome of coma was first reported by Goldie (Goldie et al., 1981). Subsequently, a considerable body of literature confirmed this role by showing 100% prognostic specificity for VS/UWS or death in patients with HIE (Rothstein et al., 1991; Berek et al., 1995; Madl et al., 2000; Sherman et al., 2000; Logi et al., 2003). The specificity in predicting a poor outcome was also high (87–99%) for vascular and post-traumatic coma (Sleigh et al., 1999; Logi et al., 2003).

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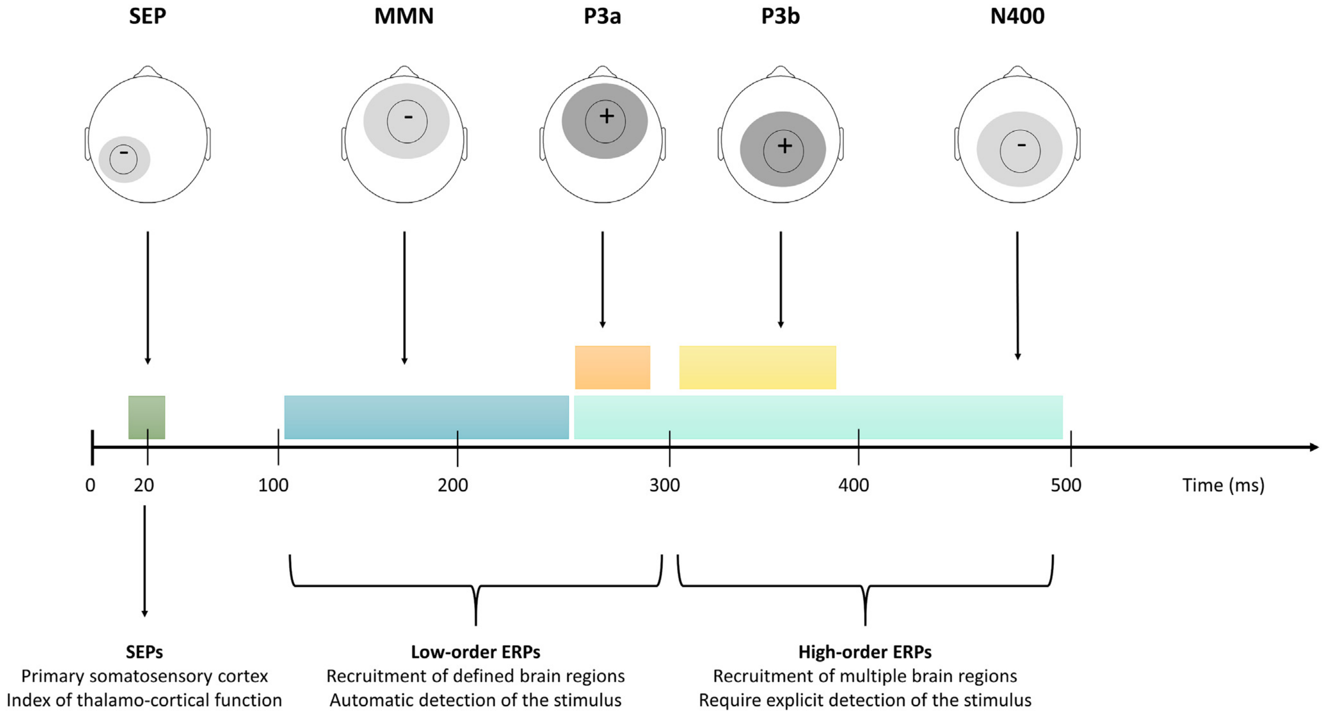

Fig. 2. Hierarchic and temporal representation of EPs and ERPs. Each component is associated with a scalp topography (topo-plots), rough time-domains (different color-coded horizontal bars) and putative significance. Of note, in case of SEPs, the contralateral somatosensory cortex to the side of median nerve stimulation is involved. ERP, event-related potential; MMN, mismatch negativity; SEP, somatosensory evoked potential.

Since this SEP pattern has been repeatedly recognized as one of the most powerful prognostic indicators of poor outcome (Zandbergen et al., 1998; Carter and Butt, 2005), it was included in major guidelines on HIE (Wijdicks et al., 2006; Guérit et al., 2009).

Notably, SEPs are only marginally influenced by hypothermia or mild-moderate sedation (Langeron et al., 1999; Kamps et al., 2013). Low dose sedation is usually required to improve the quality of SEP recording and to reduce possible periodic epileptiform discharge that may hamper a proper interpretation. In the therapeutic hypothermia era, the bilateral absence of N20 still correlated with poor outcome, not only after (FPR 0.5%, 95%CI: 0–2% Leithner et al., 2010; Samaniego et al., 2011; Bouwes et al., 2012; Oddo and Rossetti, 2014; Hofmeijer et al., 2015) but also during TTM (FPR 0%, 95%CI: 0–2% Leithner et al., 2010; Sandroni et al., 2014). This is significant given that hypothermia and sedation usually affect the neurologic examination of comatose patients.

Because of ease of recording, the bilateral absence of the N20 components is often used in the ICU as part of the multimodal paradigm for withdrawal of life-sustaining treatments (Rothstein, 2000). Conversely, the bilateral (or unilateral) preservation of SEPs does not imply a favorable outcome with a PPV ranging from 40% (29–50%) (Hofmeijer et al., 2015) to 58% (95%CI: 49–68%) (Oddo and Rossetti, 2014). As shown in Box 3 and Fig. 3, SEPs reflecting an intact "receiving mode" can be preserved even in case of severe impairment of the cortical "sending mode" as reflected by a suppressed EEG background (van Putten, 2012). Comparing their sensitivity for detecting a poor outcome, SEPs seem less reliable than absent EEG background reactivity during TTM (74%; 95%CI: 62–84%) (Oddo and Rossetti, 2014). Recent studies have suggested that not only the absence of the cortical N20 potential, but also a low amplitude (typically below 0.65 μV) may signal a poor prognosis (Endisch et al., 2015; Carrai et al., 2019; Barbella et al., 2020b).

The bilateral absence of SEPs in pediatric patients or after TBI does not necessarily indicate an irreversible loss of neural function (Pohlmann-Eden et al., 1997; Schwarz et al., 1999; Cruccu et al., 2008) (refer to Carrai et al., 2010 for a meta-analysis on the prognostic value of SEPs in comatose children). After TBI, a transient N20 disappearance may be secondary to focal midbrain dysfunction or focal cortical lesions. Therefore, in coma of traumatic and vascular etiology, it is essential to integrate SEPs with other tools (such as EEG and clinical examination) to improve the predictive power. Unlike HIE, in TBI and vascular brain injury the preservation of SEPs has been associated with a good recovery (Logi et al., 2003; Robinson et al., 2003; Zhang et al., 2011).

Of note, a recent systematic review (Amorim et al., 2018) reported few patients who had a good neurological outcome after HIE despite bilaterally absent N20 responses. Even if a small interobserver variability in the interpretation of SEPs for neurological prognosis has been described (Pfeifer et al., 2013), detailed reviews of case reports of recovery have generally identified confounders (Rothstein, 2019). To prevent inaccurate predictions, it is essential to verify the efficacy of peripheral stimulation and the absence of strategical lesion along the anatomical somatosensory pathway. Hence, the bilateral absence of SEPs requires the presence of normal responses over Erb's point (N9) and neck (N13) in order to demonstrate that somatosensory inputs have reached the central nervous system through an intact peripheral pathway (Cruccu et al., 2008).

A multimodal approach which also includes EEG evaluation can help to identify cases without chance of recovery (Glimmerveen et al., 2019; Scarpino et al., 2020) and benign EEG patterns where SEPs are not needed for outcome prediction (Fredland et al., 2019). Furthermore, new evidence (Lachance et al., 2020) suggests that novel quantitative methods of analyzing SEP may track cerebral recovery and might predict good outcomes.

Middle-latency SEP components have also been employed for prognostic purposes with promising results both for good and poor prognosis. The preservation of these components was first associ-

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ated with a high (97%) PPV for a good outcome (Madl et al., 2000) but then challenged by a subsequent study (Zandbergen et al., 2006) which reported a good outcome in only 28% of patients. Despite these contradictory findings, more recent studies (Zanatta et al., 2012, 2015; Del Felice et al., 2017) found that the preservation of the N70 component in HIE was associated with a good long-term functional recovery (PPV 100%, 95% CI 87–100%).

Box 3. Overview of the main EP/ERP paradigms in DoC

EPs and ERPs are a practical neurophysiological tool for the assessment of sensory information processing and covert basic cognitive functions in comatose (Kane et al., 1993; Fischer et al., 1999, 2004; Daltrozzo et al., 2009) and DoC patients (Neumann and Kotchoubey, 2004; Kotchoubey et al., 2005; Boly et al., 2011). Recorded at the bedside, they can be used to probe the integrity of different stages of information processing, ranging from basic sensory elaboration to conscious detection of specific complex sequences (see Fig. 2 for a schematic overview of the EP/ERP components).

SEPs

SEPs for clinical purposes are commonly elicited by bipolar transcutaneous electrical stimulation transiently applied (at 3-5Hz stimulation frequency) over the trajectory of a peripheral nerve (median nerve at the wrist and posterior tibial nerve at the ankle). Median SEP components include a series of positive and negative deflections which are generated in the plexus (N9), cervical spinal cord (N13), brainstem (P14) and in the contralateral primary somatosensory cortex (N20) (Chiappa and Ropper, 1982). Recording these waves at different levels of the somatosensory pathway allows to assess the transmission of the afferent volley from the periphery up to the cortex, and the general functioning of the whole somatosensory system.

It is well established that the N20 is generated in the posterior wall of the central sulcus of the somatosensory cortex (Allison et al., 1991) (Fig. 3); at this level, the excitatory thalamo-cortical volley produces active depolarizing sinks at the basal dendrites of the deep and superficial pyramidal cells. These currents extend along the apical dendrites of the pyramidal cells which have a horizontal position causing a tangential dipole with anterior positivity (Ikeda et al., 2005). According to this model, SEPs are mainly considered as an expression of glutamatergic thalamo-cortical function with somatosensory neurons reflecting the "receiving mode". Conversely, the spontaneous EEG signal would reflect the "sending mode" property of neurons, which depends on an intact synaptic transmission between pyramidal cells and requires a sufficient number of residual synapses. These different properties may explain some important dissociations, such as the observation that SEPs (reflecting an intact "receiving mode") can be preserved even in the case of severe EEG impairment (reflecting blockage of the "sending mode") secondary to a post-anoxic damage (van Putten, 2012). For this reason, the presence of SEPs does not necessarily predict the recovery of consciousness whereas their absence has a strong negative predictive power, as further described in Section 3.1.1.

Mismatch Negativity

The auditory modality provides the most straightforward sensory channel for recording ERPs, as it can be easily targeted in brain-injured patients, even in complex clinical settings. A simple, established protocol for assessing auditory processing is the mismatch negativity (MMN) (Näätänen et al., 1978; Garrido et al., 2009). In this paradigm, a small proportion (around 15 %) of tone bursts differing from the others in terms of one or several features (duration, intensity, or pitch) which are randomly introduced into the sequence. The MMN is elicited by these oddball stimuli (called deviants) deviating from the repetitive and frequent standard ones. It can be detected even if subjects are not aware of the auditory changes, but only if the deviance exceeds the subject's discrimination threshold (Näätänen et al., 1978; Morlet and Fischer, 2014).

This component peaks at 100–150 ms after stimulus onset with a prominent fronto-central distribution and can be identified by subtracting the response to standard stimuli from that to deviant ones (Garrido et al., 2009). MMN is a pre-attentive and preconscious marker of the brain ability to discriminate sounds and reflects the automatic detection of auditory violations (Näätänen et al., 2014).

MMN is generally held to be a necessary, albeit not sufficient, condition for conscious processing because is reliably elicited when stimuli are not consciously detected. Accordingly, MMN can be found even in conditions where top-down contributions to sensory processing can be ruled out, such as during sleep, anesthesia with propofol (Koelsch et al., 2006), and deep sedation in ICU patients (Azabou et al., 2018).

P3

P3 or P300 (Desmedt et al., 1965; Sutton et al., 1965) is a positive ERP component usually maximal in amplitude when recorded from centro-parietal derivations, occurring around 300ms after the presentation of a rare stimulus when the subject orients attention and reacts to it. Thus, in this paradigm, unexpected salient stimuli (called novel stimuli) are added to the passive auditory oddball paradigm, with a very low frequency of presentation. Originally called P300, this task-relevant component has been divided into two different components, P3a and P3b; the earlier P3a is elicited on fronto-central derivations when unexpected and highly deviant stimuli are presented to the subject who is not required to pay attention to it (Squires et al., 1975). Hence, P3a, or novelty P3, is considered to reflect an automatic detection of changes in the environment inducing a phenomenon of stimulus-driven attention switch. On the contrary, P3b is elicited on parietal derivations and relates to context updating operations and subsequent memory storage (Polich 2007) linked with the controlled processing of rare stimuli and it possibly reflects the conscious perception of these rare stimuli (Picton 1992; Dehaene and Changeux, 2011).

The subject's own name (SON) has also been employed as a particularly salient deviant stimulus (Fischer et al., 2008; Schnakers et al., 2008). Compared with ERPs elicited by tones, SON paradigms seem capable of eliciting larger P3 (Li et al., 2015a) and can be particularly useful to investigate residual basic cognitive capacities in brain-injured patients.

To optimize the challenging differentiation between MMN, P3a and P3b and to improve the detectability in healthy conscious subjects, Bekinschtein and colleagues (2009) designed an ERP paradigm (called "local–global" paradigm) composed of two embedded levels of auditory regularity. Indeed, the test combined violations of local regularities and violations of global regularities. The former was associated with two successive electrical events: a vertex-centered MMN appeared at 130ms followed by a central positivity P3a ranging from 200 to 300 ms. The latter elicited a late P3b only when subjects were attentive and aware of the auditory rule and of its violations.

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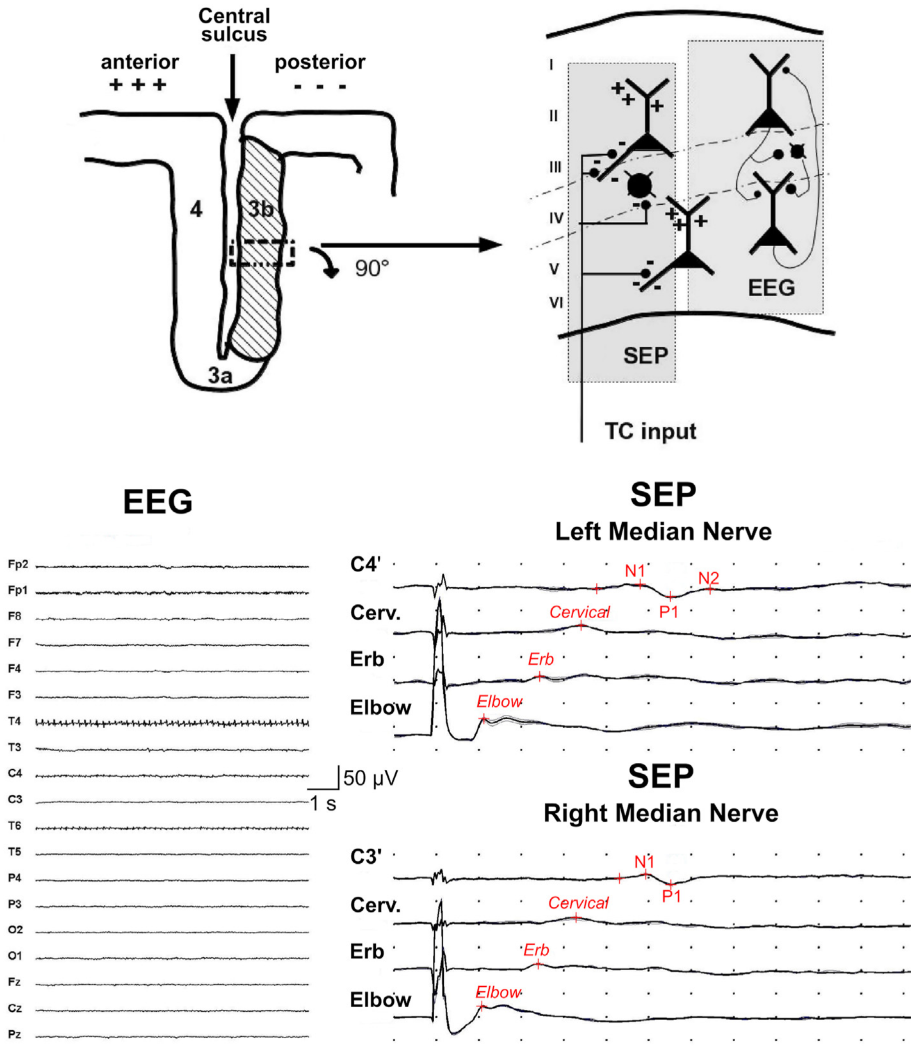

Fig. 3. The upper panel shows the location of the N20 generators in the posterior wall of the central sulcus (left) and a simple model of SEP and EEG generation according to the main thalamo-cortical (TC) input (right); in particular, SEPs reflect the thalamo-cortical "receiving mode" whereas the EEG mainly depends on pyramidal "sending" properties. The lower panel illustrates the possible coexistence of bilaterally preserved SEPs (right side) with a nearly flat EEG (left side) in a comatose patient after a severe HIE. EEG, electroencephalography; SEP, somatosensory evoked potential; TC, thalamo-cortical. Modified from (van Putten, 2012).

3.1.2. Auditory ERPs: conventional clinical approaches

The literature on MMN in comatose patients provides robust evidence of its predictive prognostic value for recovery (Kane et al., 1993; Fischer et al., 2004; Luauté et al., 2005; Naccache et al., 2005; Wijnen et al., 2007), across different etiologies and different time onsets ranging from a few days after coma (Kane et al., 1993) to weeks (Fischer et al., 2004; Naccache et al., 2005). A number of earlier studies converged on the conclusion that MMN was associated with awakening, especially in TBI with 100% PPV for recovery, which was confirmed also in a subset of sedated patients (Kane et al., 1993, 1996). Subsequently, a larger number of patients was collected by Fischer and colleagues (2004) who reported a PPV for recovery ranging from 80 to 94%, regardless of the etiology. These findings were further corroborated by Naccache and colleagues (2005) who showed that MMN could predict awakening with 93% specificity, 56% sensitivity and a PPV of 90%.

While seminal studies on the prognostic capacity of MMN were conducted in non-sedated comatose patients (Kane et al., 1993, 1996; Fischer et al., 2004), a recent study (Azabou et al., 2018) focused on deeply sedated critically ill patients. In this sample, the amplitude of MMN elicited by a classical oddball paradigm was significantly greater in patients in whom eye opening and visual contact subsequently occurred within 28 days. However, the authors acknowledged that visual analysis alone is unreliable and it is necessary to assess MMN systematically with individual level statistics.

Similar to MMN, the presence of a novelty P3 response elicited by the subject's own name in comatose patients with a passive oddball paradigm correlated with the patient's chances of recovery (P3 to subject's own name, SON, provided 85 % specificity for awakening in Fischer et al., 2008). Overall, the presence of a P3b global effect appeared to be related to better prognosis, predicting the transition from MCS to a fully conscious state (Bekinschtein et al., 2009). However, these results were partially contradicted by another study showing that P3 was not associated with a better functional outcome (Steppacher et al., 2013; Rohaut et al., 2015).

According to one of the most important meta-analyses of ERPs in comatose patients (Daltrozzo et al., 2007), MMN and P3 should be considered as significant positive but not negative early predictors in comatose patients. Hence, their presence reliably indicates a

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good chance of emerging from coma whereas their absence does not necessarily predict a poor outcome due to the low sensitivity (Daltrozzo et al., 2007).

3.1.3. Auditory ERPs: Advanced approach

Despite the high predictive power of MMN for awakening in comatose patients, there has been scant use of this paradigm in clinical routine, possibly due to the difficult appraisal of MMN at individual patient level, in the presence of brain lesions. For this reason, auditory discrimination protocols have been devised to assess brain responses through decoding algorithms, based on ML techniques, that can adapt to the variability of scalp topographies without an *a priori* definition of fixed-length time windows. This novel approach holds the promise of an operator-independent assessment of ERPs that can take into account the heterogeneity of responses in brain-injured patients (Tzovara et al., 2012a, 2012b).

Recent findings suggested that comatose patients (during the first two days of coma) can discriminate infrequent tones in a MMN paradigm largely irrespective of their outcome, suggesting that rudimental auditory processing in these patients might be preserved (Tzovara et al., 2016). However, decoding algorithms applied to auditory EPs revealed that an improvement in auditory discrimination over time was typical of those post-anoxic comatose patients who do survive. Specifically, in a large cohort of patients, auditory discrimination yielded 93% PPV for awakening with 89% specificity (when patients with epileptiform activity were excluded) (Tzovara et al., 2016). This indicates a promising role for this approach as an early quantitative marker of good outcome (recovery of consciousness) in comatose patients.

In a further validation of the auditory tests in patients treated with TTM of 36 °C, these results were confirmed suggesting that the progression of auditory discrimination over time can predict a good recovery in HIE irrespective of body temperature and across different hospital sites (Pfeiffer et al., 2017). In addition, the auditory test results have received support from the empirical observation that predicted survivors had a better functional outcome at awakening than unpredicted ones (Juan et al., 2016).

In a preliminary assessment of the automated auditory test with conventional neurophysiological markers (such as EEG and SEPs), an increase in overall prognostication (both positive and negative) was obtained (Rossetti et al., 2014) and this test appears complementary to existing neurophysiological predictors of poor outcome.

This evidence encourages the use of auditory discrimination tests in the clinical routine of ICU to optimize treatment and help refine prognostication. So far, auditory discrimination tests for comatose patient outcome prediction have been used exclusively in HIE. Future studies should assess how well these tests can be generalized to different etiologies.

3.2. EP/ERP-based assessment of prolonged and chronic DoC

3.2.1. EP/ERP-based prognosis

Few studies have addressed the role of EPs and ERPs in predicting outcome in prolonged DoC. In the case of SEPs, the recording of short latency components is recommended for long-term prognostic purposes in DoC after HIE; indeed, the presence of residual early components in VS/UWS suggests a better chance of recovery (MCS or EMCS at 24 months) (Estraneo et al., 2013).

Regarding MMN, the presence of a residual MMN component is associated with better chances of improvement at 6 months in prolonged DoC of different etiologies (Kotchoubey et al., 2005). Interestingly, an increase of MMN amplitude in VS/UWS patients may parallel a progressive recovery of consciousness (Wijnen et al., 2007).

Evidence to date is equivocal about the prognostic value of the P3 component. A recent extensive meta-analysis (Kotchoubey and Pavlov, 2018a) reported that P3 was insufficient to differentiate between poor (UWS/VS and MCS patients who remained in the same condition) and good outcome (patients who evolved toward MCS or, if MCS, regained full consciousness). This was possibly due to the strong heterogeneity of datasets (Kotchoubey et al., 2005; Hildebrandt et al., 2007; Steppacher et al., 2013, 2020; Sitt et al., 2014; Wijnen et al., 2014; Li et al., 2015b; Wang et al., 2017).

On the other hand, the application of P3 with SON paradigms has yielded some promising results; a detectable P3 at 2–3 months after TBI was associated with an increased chance of recovery within 12 months (Cavinato et al., 2009) whereas the lack of P3 did not rule out recovery towards MCS. Notably, this finding resulted in an AAN recommendation (Giacino et al., 2018b, 2018a). Along these lines, a subsequent study in a small sample of patients of mixed etiology found that P3 elicited by SON paradigms was able to predict recovery of consciousness at 12 months (Zhang et al., 2017).

3.2.2. EP/ERP-based diagnosis

The use of SEPs for assessing consciousness in prolonged and chronic DoC is limited by an insufficient diagnostic power. In particular, the preservation of cortical SEP components is not specific of MCS patients (Fischer et al., 2010; Ragazzoni et al., 2013) since they can also be detected in up to 65% of VS/UWS patients (de Biase et al., 2014). Confirming their relevance as predictors of poor outcome in the comatose phase, the bilateral absence of cortical SEPs was confirmed as more frequent in VS/UWS patients, mainly of post-anoxic etiology (Ragazzoni et al., 2013; de Biase et al., 2014).

Also MMN, despite its good predictive value in comatose patients, has a very limited diagnostic capacity since it cannot reliably distinguish VS/UWS from MCS (Sitt et al., 2014; Wang et al., 2017). Indeed, it was reported in 65% of VS/UWS patients and in 34% of MCS patients (Kotchoubey et al., 2005). Further results on sensitivity are quite discordant ranging from 100% obtained with a local–global paradigm (Bekinschtein et al., 2009) to the very low 27% reported in previous oddball studies (Fischer et al., 2010).

Several studies have explored the potential of the P3 component as a marker of conscious processing in DoC patients. However, the single-subject sensitivity of the conscious component of the P3 is too low for detecting clinical awareness (Höller et al., 2011, 2013). In line with this, other studies using auditory deviant tones (Pokorny et al., 2013) or novel approaches with somatosensory stimuli (Gibson et al., 2016) suggest that P3 may be better suited for the detection of residual cognition in a neuroimaging-based battery of assessments, rather than for the direct detection of awareness *per se*.

A somatosensory oddball paradigm has also been tested (Gibson et al., 2016) and showed that a bottom-up effect (P3a) may be preserved in some VS/UWS and MCS patients, while a P3b could not be detected in any.

The use of SON paradigms may increase the probability of observing a P3 response in conscious brain-injured patients (Wang et al., 2017; Kempny et al., 2018). Moreover, comparing passive versus active listening (counting the occurrence of specific names), some MCS patients have shown a higher-amplitude P3 in the active condition than in the passive one (Schnakers et al., 2008). Similarly, the comparison of two kinds of active SON P3 paradigms demonstrated a higher rate of responders to the active counting of SON than to active listening for a change of pitch in SON (Hauger et al., 2015). These results suggest that active paradigms can address voluntary and therefore conscious brain activity, whereas passive paradigms may be insufficient. Other studies found significant P3 effect to SON not only in MCS but also in VS/UWS patients, albeit with delayed latencies (around 600 ms) and

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atypical localizations (Perrin et al., 2006; Sergent et al., 2017). Recent findings confirmed that SON might be particularly useful to unmask covert residual attention orientation (Crivelli et al., 2019) and to characterize fluctuations in DoC patients with a single-trial power modulation analysis (Rivera-Lillo et al., 2018).

It is worth noting, however, that a P3 SON and P3b have also been reported in presumably unconscious conditions, such as sleep (Pratt et al., 1999; Ruby et al., 2008) and even coma (Signorino et al., 1995; Fischer et al., 2008; Holeckova et al., 2008). In clinical conditions, a P3 response is typically found in about 40% of comatose patients, tested on average at 20 days after coma onset (Fischer et al., 2008). When patients are in chronic VS/UWS or MCS, the chances of detecting a P3 response are considerably less (about 25%; Fischer et al., 2010).

Much attention has been devoted to the potential diagnostic role of the P3b elicited by global violations of auditory regularities; since the detection of P3b decreases when healthy participants are distracted from the task, this may indicate that subjects are engaged in voluntarily attending to global regularities (Bekinschtein et al., 2009). Although some studies suggest that patients who can detect this type of irregularity are either in a MCS (Bekinschtein et al., 2009) or eventually regain consciousness (Faugeras et al., 2012), the diagnostic power of P3b seems very limited as this component does not discriminate between VS/UWS and MCS (Sitt et al., 2014). As shown in the comprehensive confusion matrix of P3b studies (reported in Tables 2 and 3), although this component has a high specificity (90%, with a PPV of 73%), it is absent in the majority of patients with brain damage who remain

Table 2
Studies on the diagnostic role of acoustic ERPs in DoC patients. Number of subjects (or recordings) showing a significant effect for MMN and P3 according to the clinical diagnosis is reported.

	MMN	P3b (global effect)	P3 to own name or tone
Conscious healthy controls	32/32 (100%) (Bekinschtein et al., 2009) 7/8 (88%) (Faugeras et al., 2012)	11/11 (100%; active counting) 6/11 (55%; mind-wandering) 3/10 (30%; visual interference) (Bekinschtein et al., 2009) 8/8 (100%) (Faugeras et al., 2011, 2012) 8/15 (53%) (Sergent et al., 2017) 4/11 (36%) active task ; 2/10 (20%) passive listening (Tzovara et al., 2015)	9/15 (60%) (Sergent et al., 2017) 12/12 (100%) (Schnakers et al., 2008) 10/10 (100%) (Kempny et al., 2018)
MCS patients	4/4 (100%) (Bekinschtein et al., 2009) 9/28 (32%) (Faugeras et al., 2012) 23/48 (48%) (Kotchoubey et al., 2005) 3/11 (27%) (Fischer et al., 2010) 42/65 (65%) (King et al., 2013a) 4/8 (50%) (Sergent et al., 2017) 12/14 (85%) (Rohaut et al., 2015) 5/5 (100%) (Wang et al., 2017)	3/4 (75%) (Bekinschtein et al., 2009) 4/28 (14%) (Faugeras et al., 2012) 20/65 (31%) (King et al., 2013a) 1/8 (13%) (Sergent et al., 2017) 5/14 (36%) (Rohaut et al., 2015)	6/6 (100%) (Perrin et al., 2006) 4/8 (50%) (Sergent et al., 2017) 29/35 (83%) (Steppacher et al., 2013) 4/11 (36%) (Fischer et al., 2010) 6/6 (100%) (Cavinato et al., 2011) 22/48 (46%) (Kotchoubey et al., 2005) 9/14 (64%) (Schnakers et al., 2008) 8/16 (50%) (Schnakers et al., 2015) 11/20 (55%) (Hauger et al., 2015) 3/11 (27%) (Kempny et al., 2018) 5/5 (100%) (Wang et al., 2017)
VS/UWS patients	3/4 (75%) (Bekinschtein et al., 2009) 6/24 (25%) (Faugeras et al., 2012) 26/50 (52%) (Kotchoubey et al., 2005) 2/16 (13%) (Fischer et al., 2010) 36/70 (51%) (King et al., 2013a) 1/4 (25%) (Sergent et al., 2017) 11/15 (73%) (Rohaut et al., 2015) 5/6 (83%) (Wang et al., 2017)	2/22 (9%) (Faugeras et al., 2012), same in (Faugeras et al., 2011) 0/4 (0%) (Bekinschtein et al., 2009) 10/70 (14%) (King et al., 2013a) 0/4 (0%) (Sergent et al., 2017) 0/15 (0%) (Rohaut et al., 2015)	3/5 (60%) (Perrin et al., 2006) 1/4 (25%) (Sergent et al., 2017) 33/48 (69%) (Steppacher et al., 2013) 0/8 (0%) (Schnakers et al., 2008) 1/10 (10%) (Schnakers et al., 2015) 3/16 (19%) (Fischer et al., 2010) 6/11 (54%) (Cavinato et al., 2011) 12/50 (24%) (Kotchoubey et al., 2005) 1/5 (20%) (Kempny et al., 2018) 4/6 (67%) (Wang et al., 2017)

Abbreviations: DoC, disorders of consciousness; ERP, event-related potential; MCS, minimally conscious state; MMN, mismatch negativity; UWS, unresponsive wakefulness syndrome; VS, vegetative state.

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Table 3
Confusion matrices for MMN, P3b, P3 (SON or tones) paradigms obtained from the studies reported in Table 2.

MMN	MCS (183)	VS/UWS (189)	**P3b global**	MCS (119)	VS/UWS (115)	**P3 SON/tone**	MCS (180)	VS/UWS (163)
Test + (182)	102	90	Test +(45)	33	12	Test + (162)	107	64
Test – (179)	81	99	Test – (189)	86	103	Test – (170)	73	99

Abbreviations: MCS, minimally conscious state; MMN, mismatch negativity; SON, subject's own name; UWS, unresponsive wakefulness syndrome; VS, vegetative state.

conscious, yielding a very low sensitivity (28%). Multivariate decoding of the P3b signal can improve the sensitivity of global violations in response to auditory regularities (King et al., 2013a). When this kind of analysis is applied to comatose patients, however, it is possible to find a global violation response in 40% of them and even under sedation and hypothermia (Tzovara et al., 2015).

A comprehensive review of the literature (see Tables 2 and 3 for details) on the diagnostic performance of ERPs in prolonged and chronic DoC patients confirmed the low sensitivity of ERPs (around 54% for MMN paradigms ranging from 27% to 100%; around 47% for P3 paradigms ranging from 13% to 75%) for detecting minimal signs of consciousness. This further suggests that these markers are not sufficiently sensitive for a reliable diagnostic application in clinical practice, possibly because they index cognitive functions that are not necessarily preserved in conscious brain-injured patients. Achieving a significant reduction of type-II errors (i.e. false negative) will be crucial for future investigations aimed at confirming the role of ERPs in clinical practice.

Along these lines, an interesting complementary approach could be the investigation of how visceral signals shape cognition (Azzalini et al., 2019). Several reports seem to indicate that heart-rate variability might help distinguish VS/UWS from MCS patients (Riganello et al., 2018, 2019; Tobaldini et al., 2018; Crivelli et al., 2019). Moreover, a recent paper showed a relevant interaction of acoustic ERPs with autonomic parameters. Indeed, the cardiac cycle of MCS patients can be significantly modulated by auditory global violation and heart-derived information (including the heart-EPs) may enhance the classification performance of consciousness-related EEG markers in DoC (Raimondo et al., 2017).

3.2.3. ERPs indexing higher cognitive functions

Besides the detection of consciousness, recent lines of ERP research have focused on investigating hierarchical levels of auditory processing (auditory, perceptual and semantic) (Beukema et al., 2016; Gui et al., 2020) or multiple cognitive dimensions (including novel markers of spatial attention) (Sergent et al., 2017). This kind of study that combines multiple ERP markers within a single test may not only improve diagnostic sensitivity but also capture a patient-specific profile of residual cognitive functions. Following the same logic as a clinical evaluation using the CRS-R scale, these protocols may probe several complementary domains of cognitive processing of high and low-level complexity of potential prognostic significance. For example, rhythmic EEG responses tracking single-words, phrases and sentences were recently explored by Gui and colleagues (2020) with a novel hierarchical linguistic paradigm. Despite very promising results on outcome prediction (80% accuracy), 39% of MCS patients were still misdiagnosed as VS/UWS by this ML-based model, maybe due to the lack of repeated assessments and to fluctuations in levels of consciousness.

3.3. EPs and ERPs in DoC: technical and conceptual caveats

An interesting multicenter survey attempted to map the real extent of neurophysiological evaluations carried out in daily practice (André-Obadia et al., 2018) and found that the main limits to the use of ERPs were the poor reproducibility and lack of normative values. We outline here some suggestions that may improve the interpretation of current ERP findings in DoC patients.

1. Consider the potential impact of fluctuations on cognitive performances

Specific clinical issues in DoC patients such as fluctuation of vigilance, limited attentional capacities and impaired circadian rhythms may hamper a consistent neurophysiological assessment and particularly a full engagement in ERP paradigms. In addition, considering the low ERP retest reliability and intra-individual fluctuations of vigilance in DoC patients, a negative result from a single ERP evaluation should not be taken as proof of unconsciousness and a longitudinal assessment is needed for confirming negative results (Schorr et al., 2015). This issue should be addressed by simplifying and shortening recording protocols. For example, a 70-min spectral periodicity in the levels of EEG entropy was found to be linked to fluctuations of arousal in MCS (Piarulli et al., 2016). Similar indices may be used to identify the optimal time window to assess cognitive ERPs.

2. Account for large inter-individual variability of ERPs in brain-injured patients

Due to the presence of multiple brain lesions in DoC patients, the amplitude, latency and topography of ERP components can be significantly disrupted. To address this issue and deal with interindividual differences, automatic and more liberal analyses independent of *a priori* hypotheses about the signal, such as multivariate pattern analysis, may improve ERP detection (Tzovara et al., 2012b; King et al., 2013a).

3. Avoid confirmation bias

ERP paradigms are often evaluated by "proof-of-concept" studies based on small samples of DoC patients. Larger clinical populations with an adequate and balanced size of the diagnostic subgroups are needed (Kotchoubey, 2017). To avoid confirmation bias, outcome assessment should be performed blind of the electrophysiological results; this was recently found to be the case in only 17% of neuroimaging studies in DoC patients (Kotchoubey and Pavlov, 2018a).

4. Combine multiple markers to increase sensitivity

Since none of the reported ERP paradigms can stand as a single gold standard of prognosis in DoC patients, some studies proposed a multidimensional framework (Beukema et al., 2016; Sergent et al., 2017) to capture the performance of patients across a range of cognitive and behavioral tasks (Bayne et al., 2017). In particular, the conjunction of multiple cognitive functions showed promising results in terms of distinguishing MCS from VS/UWS (Sergent et al., 2017). However, it is important to bear in mind that this kind of approach is time-consuming (up to 1.5 h per patient) and increases the risk of discordant results.

4. Investigational applications in DoC: qEEG, TMS/EEG and active EEG paradigms

The last decade has witnessed intense research activity at the crossroads between the science of consciousness and clinical neurophysiology, raising the hope that new concepts and tools may be available at the bedside of brain-injured patients. Although their

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integration with standard tools in the clinical routine will take time, it is important to critically review emerging EEG-based techniques that may change the way we assess DoC patients. Below, we focus on three promising electrophysiological approaches that, in combination, may represent a sequential workflow for screening, stratifying and attempting interaction with DoC patients: qEEG, TMS/EEG, and active EEG paradigms.

4.1. Screening DoC patients by qEEG measures

As described in Section 2 and Box 2, an educated visual inspection of clinical EEG recordings can provide key information about the state of thalamo-cortical circuits and in some cases may suggest the presence of covert consciousness (CMD) in patients with a poor behavioral repertoire. Here, we discuss in detail advanced quantitative analysis approaches that may foster the standardization and the accuracy of EEG-based assessment.

By simply capitalizing on the notions derived from the clinical inspection of EEG (see Section 2), it is possible to derive automated EEG markers that can reflect the level of thalamo-cortical integrity/activation based on the quantification of the power of EEG oscillations. The current consensus is that θ (4–8 Hz) and α (8–13 Hz) bands are significantly lower in VS/UWS than in MCS patients, whereas δ band (<4 Hz) shows the opposite pattern (Fellinger et al., 2011; Lehembre et al., 2012; Lechinger et al., 2013). This qEEG-derived evidence that a progressive slowing of the EEG spectrum correlates negatively with the CRS-R score, confirmed the value of the clinical notion of 'EEG slowing' (Fig. B.1). Such EEG slowing can be quantified by considering the frequency of the dominant peak of the power spectral density (PSD) (Lechinger et al., 2013), or the central tendency of the whole PSD, through the median or the mean frequency (Sitt et al., 2014; Engemann et al., 2018). Another option is to assess the decay of the arrhythmic background of the PSD, by means of the spectral exponent, which showed promising results in sleep (Miskovic et al., 2019) and anesthesia (Colombo et al., 2019). By adopting more complex signal processing pipelines, it is also possible to develop EEG markers that tap more directly into electrophysiological processes that are thought to be relevant for the emergence of conscious experience. For example, indices that reflect the ability of distributed brain areas to share information can be computed on the assumption that the brain's ability to engage in integrated patterns of activity is a key correlate of consciousness. In this vein, King and colleagues (2013b) introduced a novel measure, coined weighted symbolic mutual information (wSMI), to quantify the sharing of information among cortical sites. In a large cohort of patients, wSMI was found to vary systematically with the state-of-consciousness, particularly for long-distance connections within parietal regions (Fig. 4). The notion of integration as a necessary element for consciousness was further corroborated using graph theory-based EEG measures (Chennu et al., 2014).

In parallel with measures of connectivity and integration, the quantification of the variability, or complexity, of EEG time series has yielded promising results (Gosseries et al., 2011; Sarà et al., 2011; Sitt et al., 2014; Schartner et al., 2015). Along similar lines, Fingelkurts and colleagues (2011, 2012a, 2013) quantified the dynamic repertoire, duration and oscillatory type of EEG microstates in eyes-closed resting EEG and found a positive correlation between the differentiation of microstates and the level of consciousness.

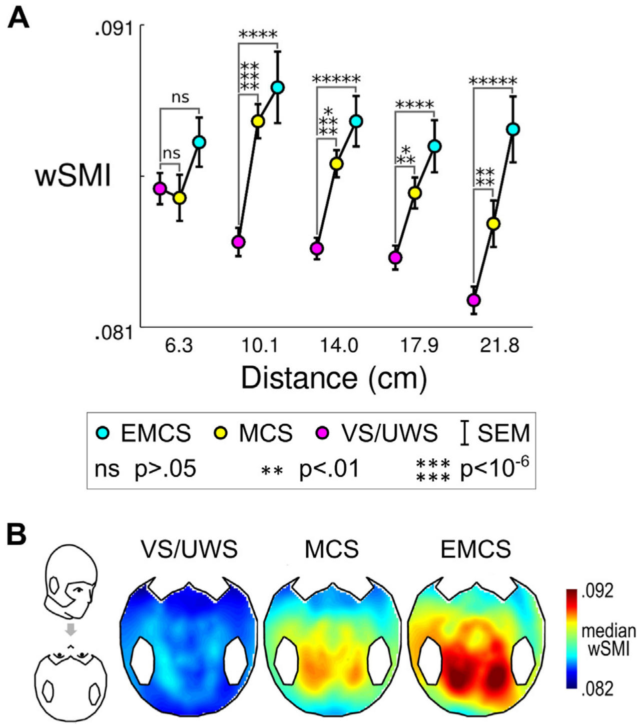

Fig. 4. In panel A, wSMI as a function of inter-channel distance. VS/UWS patients present lower information sharing compared to MCS and EMCS patients, particularly over medium and long inter-channel distances (>10 cm). In panel B, median wSMI from a given EEG channel to all other channels for each clinical state; MCS and EMCS patients show significantly higher values particularly over centro-posterior channels. EMCS, emergence from minimally conscious state; MCS, minimally conscious state; SEM, standard error mean; UWS, unresponsive wakefulness syndrome; VS, vegetative state; wSMI, weighted symbolic mutual information. Modified from (King et al., 2013b).

A broader, more systematic step in this direction was taken by a study (Sitt et al., 2014) that considered both the variability and average values of 92 different EEG-derived measures in a cohort of 181 DoC patients. Fig. 5 provides a graphical comparison of the discrimination power based on the mean or the fluctuation of each measure for MCS versus VS/UWS. Such a systematic screening provides a data driven assessment of the performance of different EEG features, by identifying:

1) markers that simply fail to separate these two groups (e.g. low γ power);

2) markers that show a significant increase in both the average value and the fluctuation over time for MCS compared to VS/UWS (i.e, power in θ, α and β bands, median spectral frequency and wSMIθ);

3) markers that exhibit a dissociation between average value and fluctuation. In particular, the presence of consciousness is associated with a high average but a low fluctuation of Kolmogorov complexity (K) and permutation entropy, indicating that a stable and lasting increase in complexity and entropy may reflect consciousness;

4) markers that are discriminative only for averages (i.e. spectral entropy) or for fluctuations across trials (i.e. phase lag index in β and α bands).

One way to make this characterization useful in clinical practice is to draw pragmatic boundaries in this multidimensional space that discriminate between the different clinical labels (i.e. VS/UWS versus MCS). This can be done by employing ML techniques (also known as decoding or multivariate pattern analysis) which are increasingly used in the context of DoC (for a specific review see Noirhomme et al., 2017). In these techniques, a classifier is trained using EEG data and diagnostic labels to learn patterns that discriminate the state of consciousness. The reliability of the classifier is then assessed based on its capacity to predict a correct diagnosis in an independent dataset.

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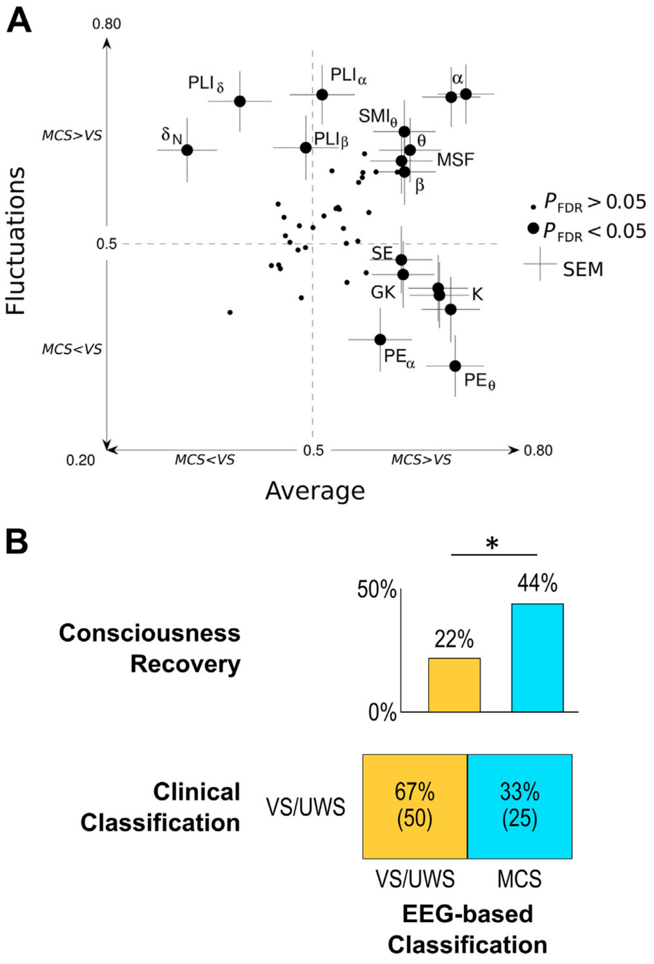

Fig. 5. In panel A, a summary of qEEG-derived measures discriminating VS/UWS and MCS patients. Each measure is plotted in a two-dimensional graph. The x-axis indicates discriminatory power for each measure's average across trials, whereas the y-axis indicates discriminatory power for their respective fluctuations across trials. For instance, the K measure appears in the bottom right quadrant, suggesting that its average value is significantly higher in MCS than in VS/UWS, whereas its standard deviation is higher in VS/UWS than in MCS. Large circles indicate significant measures (PFDR < 0.05). In panel B, a comparison of EEG-based classification with clinical diagnosis and patients' outcome. Seventy-five patients clinically classified in VS/UWS were evaluated using the EEG-based classification. While in 50 of these recordings the two classifications matched, in 25 the EEG-based system classified the VS/UWS patients as in MCS. The bar charts show the clinical outcome of these subgroups of VS/UWS patients. The probability of recovery was higher (* p = 0.02) for patients classified into a higher state of consciousness than for patients predicted to be actual VS/UWS. α, alpha; β, beta; δ, delta; γ, gamma; θ, theta; EEG, electroencephalography; FDR, false discovery rate; K, Kolmogorov complexity; MCS, minimally conscious state; MSF, median spectral frequency; PE, permutation entropy; PLI, phase lag index; SE, spectral entropy; SEM, standard error mean; SMI, symbolic mutual information; UWS, unresponsive wakefulness syndrome; VS, vegetative state. Modified from (Sitt et al., 2014).

Using such an approach, Sitt and colleagues (2014) examined whether different EEG-based measures could be combined to enhance the discrimination performance between the different labels.

The best measures to discriminate MCS from VS/UWS were absolute α power, average complexity-related metrices (Permutation Entropy and K) and functional connectivity in the θ frequency band (wSMIθ). Individually these measures yielded a maximal area under the receiver operating curve (AUC) of 71 ± 4% (Fig. 5). Yet, by combining all 92 EEG markers the AUC increased to 78 ± 4%, suggesting that complementary EEG markers may carry partially independent information and that their combination offers an advantage in detecting recovery of consciousness following brain injury.

In most cases, the EEG-based classification with multiple markers was consistent with the clinical label, nevertheless, in some cases the two diagnoses disagreed. In MCS patients, the classifier achieved a sensitivity of 76% when using the combination of markers and of 71% when using, for example, functional connectivity (wSMIθ). Hence, as recognized by the authors, the number of false-negative cases (24% of clinically MCS patients not identified) was still too high for a reliable single-subject diagnosis without a complementary behavioral evaluation.

Interestingly, however, VS/UWS patients, classified as MCS based on their EEG activity, had a significantly higher chance of recovery of 44% versus 22% (Fig. 5). Thus, in these cases, the occasional finding of disagreement may represent an error of the classifier, but it may also indicate EEG-based information not accessible through behavioral examination alone. This possibility was confirmed by a single case study of a conscious patient who was left completely sensory-disconnected and paralyzed following a series of concurrent brain injuries (Rohaut et al., 2015).

To pave the way for its widespread clinical application, the quantitative analysis proposed by Sitt and colleagues (2014) has been translated to a web-based automated solution to provide an EEG-based clinical diagnostic of state-of-consciousness. The goal of this system is to estimate, in each recording, the probability that the patient belongs to either the VS/UWS or MCS clinical groups. It consists of a flexible and scalable data analysis workflow that automates the processing of EEG recordings, the extraction of EEG measures and the communication of results.

The proposed solution is based on an open source software, is scalable on multiple levels, and it can run on the cloud (see demo.doc-eeg.net) (Engemann et al., 2015, 2018). Recently, the robustness of this approach was verified across different clinical centers and different EEG configurations and protocols (Engemann et al., 2018). Importantly, the classification performance was only marginally affected by different recording conditions, e.g. varied length of the recording and number of EEG sensors (8–256). Another example of systematic qEEG-based approach has been proposed by Chennu and colleagues (2017). In this work, graph theory was employed to quantify the spectral connectivity estimated from EEG signal. Specifically, in the brain rhythms in δ, θ and α bands organized into different levels of complexity (e.g. mean relative power over all channels, median connectivity over all channel pairs, clustering coefficient, characteristic path length, modularity, participation coefficient and modular span) were quantified. This qEEG analysis, leading to a total of 21 metrics, correlated with the level of consciousness in patients, with their brain metabolic rates assessed with FDG-PET and with their clinical outcomes. In particular, a positive correlation was found between the α network, behavioral diagnosis and preserved metabolism, whereas the EEG δ network centrality predicted outcome.

Overall, multivariate qEEG data and ML approaches hold the promise of an automated standardized bedside assessment of DoC. Though the sensitivity of these techniques alone might not afford a straightforward and univocal discrimination between MCS and VS/UWS at the single-subject level, they proved to be highly relevant to complement standard behavioral evaluation. In addition, these tools are also optimally suited for large-scale, broadly available, first screening. At the same time, the data-driven identification of EEG markers that best discriminate between states of consciousness can provide valuable mechanistic insight. In this respect, the EEG features that most contributed to the correct discrimination were α-band power, time-series complexity and large-scale θ connectivity. These findings, together with converging evidence from fMRI studies (Demertzi et al.,

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2019; Luppi et al., 2019) support the idea that the coexistence of functional integration (e.g. connectivity) and functional differentiation (e.g. complexity) within thalamo-cortical networks may be key mechanisms enabling the emergence of consciousness (Tononi and Edelman, 1998; Seth et al., 2011; Koch et al., 2016). Notably, these indices of the internal state of thalamo-cortical circuits showed better accuracy than measures relying on cognitive processing of sensory stimuli, such as ERPs (Sitt et al., 2014).

4.2. Stratifying DoC patients by TMS/EEG measures of complexity

A direct approach to gauge the joint presence of functional integration and functional differentiation within thalamo-cortical circuits involves measuring the complexity of brain responses to perturbations. The underlying principle is that one can apply direct cortical stimulations and then record the ensuing EEG response to assess, from a causal perspective, to what extent different groups of neurons interact as a whole (integration) to produce complex dynamics (differentiation) (Massimini et al., 2009). Practically, this paradigm can be applied to the brain by employing a combination of TMS and high-density EEG (TMS/EEG), a technique that allows stimulating directly a subset of cortical neurons and measuring, with good spatial–temporal resolution, the effects produced by this initial activation on the rest of the brain (Ilmoniemi et al., 1997). Compared to spontaneous EEG, this perturb-and-measure technique allows to probe the complexity of neuronal interactions unconfounded by common drivers (spurious integration), random noise or independent processes (spurious differentiation). According to this proposal, a signature of consciousness is when the brain responds to TMS with complex, rapidly changing activity patterns (functional differentiation) that affect a distributed set of cortical areas (functional integration) (Tononi and Edelman, 1998; Tononi, 2004). Conversely, during loss of consciousness the thalamo-cortical system will react to perturbations with a response that is local (loss of integration) and/or stereotypical (loss of differentiation).

A preliminary validation of these predictions was obtained in a series of studies performed during wakefulness (Rosanova et al., 2009), NREM sleep (Massimini et al., 2005, 2007), REM sleep (Massimini et al., 2010) midazolam (Ferrarelli et al., 2010), propofol and xenon (Sarasso et al., 2015) anesthesia. Importantly, a similar relationship between TMS-evoked potentials (TEPs) and the state of consciousness was confirmed by two independent investigations (Rosanova et al., 2012; Ragazzoni et al., 2013) on small populations of DoC patients.

Building up on these encouraging results and in view of clinical applications, a synthetic index - the Perturbational Complexity Index (PCI) - was subsequently developed (Casali et al., 2013) to quantify, in a single score, the amount of information (differentiation) that can be generated by engaging large-scale causal interactions (integration) within the thalamo-cortical system. In essence, the PCI works by quantifying the complexity (i.e. algorithmic compressibility) of the overall EEG response to a direct cortical perturbation with TMS.

After calibration in a large benchmark population of healthy subjects and conscious brain-injured patients where the presence or absence of conscious experience was confirmable through immediate (during wakefulness) or delayed reports (upon awakenings from states of disconnected consciousness), the PCI was computed from TEPs obtained in a large population of non-communicating patients including 38 MCS and 43 VS/UWS patients (Fig. 6). These measurements showed a very high sensitivity (94%) in detecting MCS patients and could stratify VS/UWS patients based on three different electrophysiological patterns of responsiveness to TMS. When directly perturbed at multiple locations, the brain of VS/UWS patients may: 1) fail to show any significant response (no response patients); 2) show a low-complexity response similar to that observed in NREM sleep and anesthesia unconsciousness (low-complexity patients); 3) engage in complex spatiotemporal dynamics similar to those observed in conscious awake or dreaming subjects (high-complexity patients) (Casarotto et al., 2016).

The no-response subgroup was mostly composed of post-anoxic patients who showed diffuse cortical necrosis and a severely abnormal, voltage-suppressed EEG. Although structural connectivity, as assessed by global fractional anisotropy, could explain up to 74% of the PCI variance across patients and healthy subjects (Bodart et al., 2018), low- and high-complexity VS/UWS patients, showed a similar lesion load. This finding suggests that the PCI captures complex neuronal dynamics emerging on top of residual brain structures, that are relevant for recovery of consciousness. Accordingly, high-complexity patients (about 20% of all VS/UWS) also showed higher metabolic activity (FDG-PET) (Bodart et al., 2017) and a higher rate of behavioral (CRS-R) recovery at 6 months (Casarotto et al., 2016). These VS/UWS patients, in whom PCI values lay within the range of the benchmark conscious condition should thus be considered for intensive protocol aimed at promoting communication through brain-computer interface (BCI) or active paradigms (see next section) on the assumption that they are conscious but disconnected.

Besides their accuracy in patient stratification and selection, TMS/EEG-derived measures can complement spontaneous EEG by providing useful insights into the mechanisms of loss and recovery of consciousness after brain injury. Specifically, the causal approach inherent to cortical perturbations points to a key mechanism that may explain the increase of δ power/synchrony (Schiff et al., 2014; Chennu et al., 2017), the decrease of long-range connectivity (King et al., 2013b; Rosanova et al., Brain 2012), and the loss of complexity (Gosseries et al., 2011; Sitt et al., 2014; Schartner et al., 2015; Casarotto et al., 2016) commonly observed in unconscious patients. Convergent studies employing both TMS (Rosanova et al., 2018) and intracranial electrical stimulation (Pigorini et al., 2015) suggest that cortical bistability, a mechanism whereby individual neurons tend to fall into a silent hyperpolarized state (OFF-period) after an initial activation (ON-period) (Compte et al., 2003; Sanchez-Vives et al., 2017), may link and explain these three phenomena. Indeed, as shown in Fig. 7, OFF-periods, which are the neuronal underpinnings of EEG delta waves, are in a key position to interrupt the chain of causal interactions among cortical neurons and thus the emergence of patterns of activity that are long-range and complex. During physiological NREM sleep, OFF-periods and delta waves seem to be largely engendered by activity-dependent K + currents (Timofeev et al., 2001), but they can also occur in pathological conditions due to alterations of the inhibition/excitation balance and/or as a consequence of white matter injury and deafferentation (Timofeev et al., 2000). Crucially, OFF-periods disappear and brain complexity (as indexed by PCI) recovers upon awakening from sleep (Fig. 7A) as it does in patients who spontaneously recover from VS/UWS (Fig. 7B). A link between bistability, impaired connectivity/complexity and loss of consciousness is potentially interesting because OFF periods are associated with well-known neuronal and circuit mechanisms that are, at least in principle, reversible and targetable by pharmacology or brain stimulation (D'Andola et al., 2018).

4.3. Identifying covert awareness by active EEG paradigms

The capacity of a patient to follow commands is a critical diagnostic marker in DoC even though it may be compromised for many reasons, such as cognitive impairments due to brain injury or damage to the peripheral motor system. In this vein, active para-

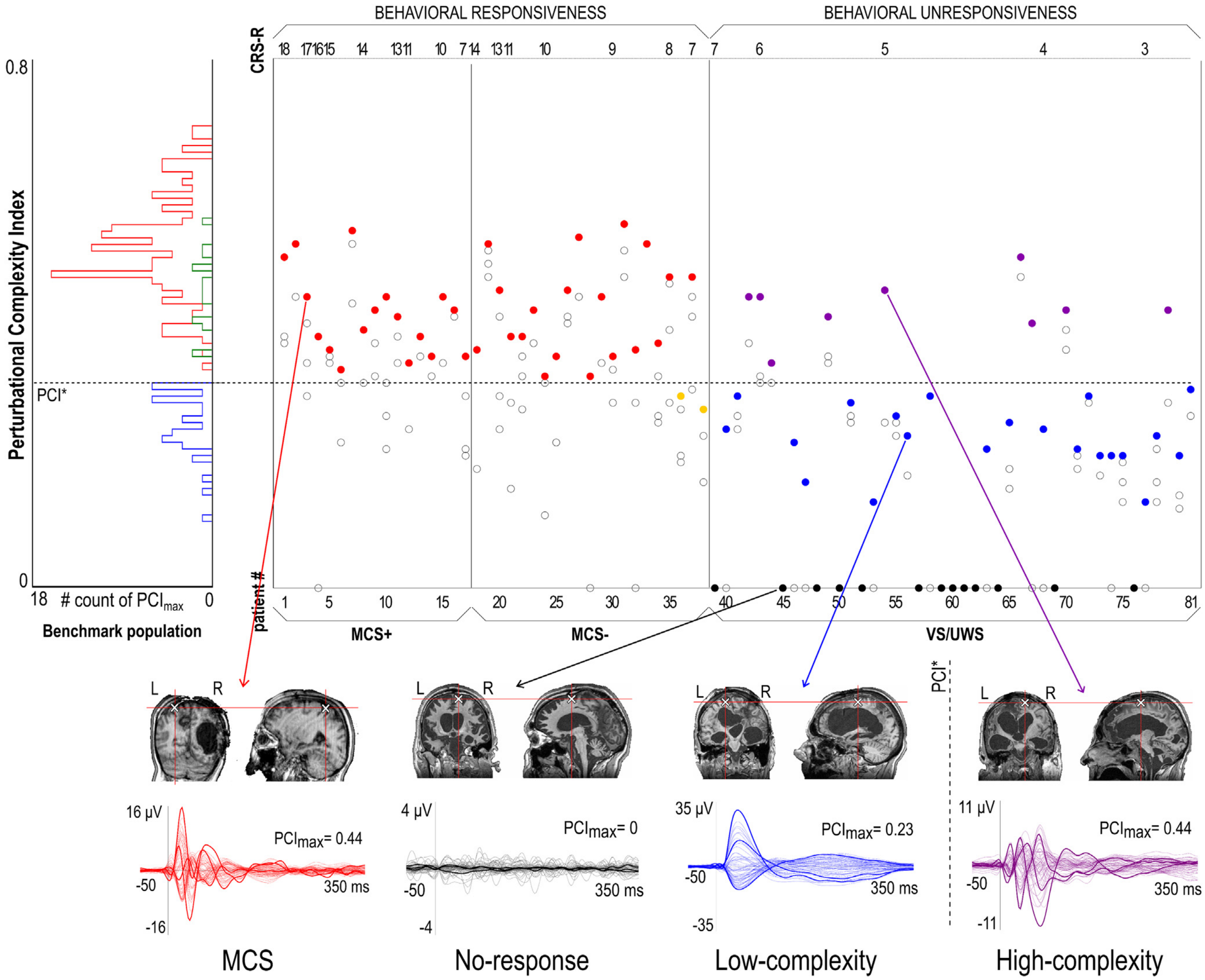

Fig. 6. The histogram on the left reports the best scores of PCI (PCImax) obtained in the benchmark population (in blue, absence of subjective reports; in green, delayed reports; in red, immediate reports). The scatter plot on the right displays PCImax values for MCS and VS/UWS patients, the dashed horizontal line highlights the optimal cutoff (PCI*) computed from receiver operating characteristic curve analysis in the benchmark population. Only 2 out of 38 MCS patients resulted in PCImax lower than PCI* yielding a sensitivity of 94% (yellow dots). Notably, VS/UWS patients could be divided into 3 subgroups according to PCImax, 9 with PCImax > PCI* (purple), 21 with PCImax < PCI* (blue), and 13 with PCImax = 0 (black). The bottom row shows individual MRIs, sites of TMS (red cross), and TEPs for one representative MCS patient (left) and 3 VS/UWS patients with PCImax equal to 0 (No response), lower than PCI* (Low-complexity) and higher than PCI* (High-complexity). CRS-R, Coma-Recovery Scale-revised; MCS, minimally conscious state; PCI, perturbational complexity index; TEP, TMS-evoked potentials; UWS, unresponsive wakefulness syndrome; VS, vegetative state. Modified from (Casarotto et al., 2016).

digms are designed to determine whether a patient who is outwardly non-responsive can modulate his or her brain activity to command (i.e. demonstrate covert command following and awareness) and avoid an inaccurate diagnosis. Among the active paradigms employed in DoC patients, one of the most widely adopted involves asking a patient to engage in mental imagery during either a fMRI (Owen et al., 2006; Bardin et al., 2011; Fernández-Espejo et al., 2011; Stender et al., 2014) or a EEG (Cruse et al., 2011; Goldfine et al., 2011; Gibson et al., 2014). In this approach, the patient's engagement in the mental task is quantified by his/her ability to generate reliable, temporally and/or spatially specific modulations of brain activity identified in validation studies (Boly et al., 2007; Naci et al., 2013; Fernández-Espejo et al., 2014). The identification of covert awareness by active EEG paradigms is of strategic importance in DoC research because it can convey diagnostic information in the prolonged/chronic phase, improve sample fidelity when comparing covariates against diagnostic categories and provide prognostic clues in the acute phase.

Several active paradigms have been used to detect awareness after severe brain injury. In an initial approach, Cruse and colleagues (2011) developed a technique based on a ML method for detecting mental imagery in the EEG. After showing that the method could detect responses in 9 out of 12 healthy controls, they found that 3 of 16 VS/UWS patients repeatedly and reliably generated appropriate EEG responses to commands, despite their lack of overt behavior. In a subsequent study with the same motor imagery task, consistent and robust responses to command were observed in 22% of MCS (Cruse et al., 2012a). Since the statistical model in the original work may have produced false positive results (Goldfine et al., 2013) due to the peculiar nature of EEG artifacts in patients, alternative methods were developed to circumvent this issue (please see Recommendation 3 in the next section for further methodological considerations). Hence, Cruse and colleagues (2012b) in a follow-up study, employed a simpler and more clinically viable paradigm in which participants were asked to try to move their hands. Unlike the two previous investigations,

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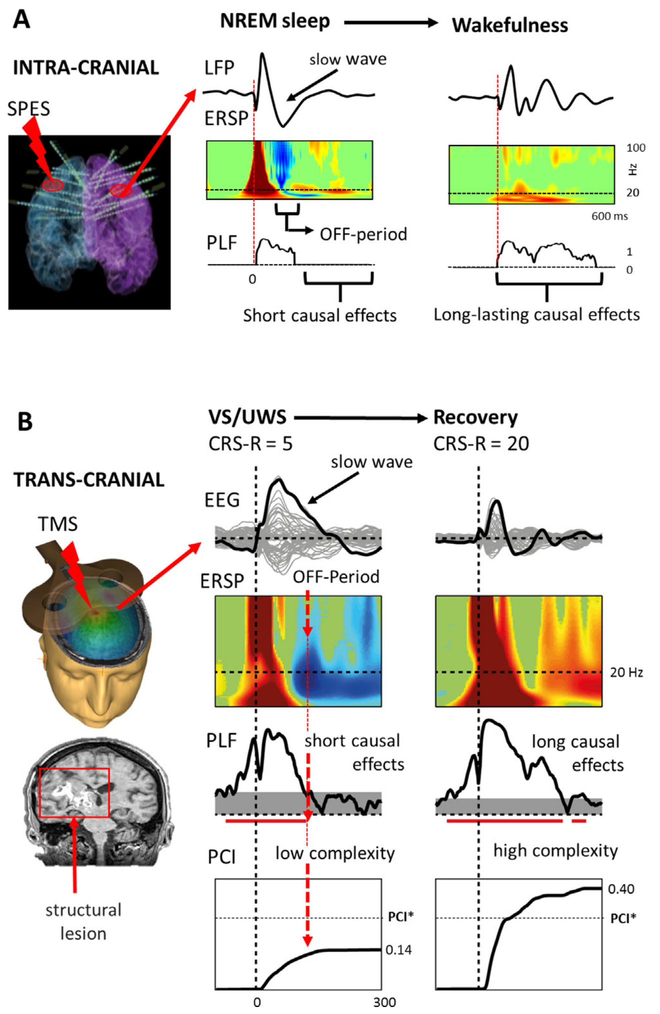

Fig. 7. In panel A, intracortical single pulse electrical stimulation (SPES) and local field potential (LFP) recorded in humans during wakefulness and NREM sleep. For each condition, the average LFP response to SPES is shown, together with the corresponding event-related spectral perturbation (ERSP) and the time course of the phase-locking factor (PLF). During wakefulness, SPES triggers a complex LFP response associated with long-lasting causal effects (PLF in distant cortical targets ~ 500 ms). During NREM, the same input induces a slow wave associated with a cortical OFF-period (suppression of power > 20 Hz in the ERSP, reflecting a period of neuronal silence) which shortens the causal effects (short-lasting PLF). In panel B, two subsequent (30 days apart) TEPs in one patient who recovered consciousness from VS/UWS. MRI shows the site of TMS and the structural lesion. The evolution during recovery of TEP, ERSP, PLF, and PCI is shown. Similar to what shown in (A) during sleep, in VS/UWS condition TMS triggers an EEG slow wave associated with an OFF-period, which results in a short-lasting PLF. Crucially, the timing of the OFF-period (red, dashed arrow) corresponds to the time at which complexity stops building up (the plateau of the PCI time course). Upon recovery of consciousness, the OFF-period disappears, causal interactions are long-lasting and PCI can grow above PCI*. CRS-R, Coma-Recovery Scale-revised; EEG, electroencephalography; ERSP, event-related spectral perturbation; LFP, local field potential; MCS, minimally conscious state; NREM, non-rapid eye movement; PCI, perturbational complexity index; PLF, phase-locking factor; SPES, single pulse electrical stimulation; TEP, TMS-evoked potentials; TMS, transcranial magnetic stimulation; UWS, unresponsive wakefulness syndrome; VS, vegetative state. Modified from (Pigorini et al., 2015) and from (Rosanova et al., 2018).

all healthy volunteers showed reliable EEG responses to the commands to attempt to move. Moreover, one patient who had been repeatedly diagnosed as VS/UWS for 12 years exhibited reliable modulations of his brain activity in response to the attempted movement commands, at the single-trial level (Cruse et al., 2012b).

Gibson and colleagues (2014) demonstrated that multiple active paradigms based on both EEG and fMRI responses to mental imagery may further improve the detection of covert awareness after severe brain injury, as shown in Fig. 8. Multimodal assessments may provide patients with the best opportunity to demonstrate residual cognitive abilities, perhaps owing to individual differences in mental imagery strategies or time-variant fluctuations in fatigue and arousal.

Active paradigms may also be employed to establish a communication channel that enables patients to answer questions with either 'yes' or 'no' (Ortner et al., 2017). Along these lines, a promising motor imagery paradigm was proposed (Coyle et al., 2015). DoC patients were asked to imagine movements of their hand or toes with simultaneous visual and auditory cues and were able to produce significant, appropriate, and consistent responses across multiple assessments. These preliminary findings in a small sample suggest that DoC patients can engage in device control using the EEG correlates of motor imagery and that a true two-way communication and environmental control may eventually be restored (Coyle et al., 2015). In addition to motor imagery, also somatosensory or auditory stimuli are assessable with a P3-based paradigm. A vibrotactile P3-based BCI has been proposed (Annen et al., 2018; Spataro et al., 2018) to investigate somatosensory discrimination and probe "covert command-following" with an interesting correlation with subsequent recovery (Spataro et al., 2018) and the brain metabolism profile (Annen et al., 2018). More interestingly, this kind of approach has been successfully used to calibrate a BCI able to assess yes/no communication abilities in VS/UWS patients (Guger et al., 2018).

The current feasibility of commercially available EEG-based BCI systems was also tested and discussed (Chatelle et al., 2018) by comparing auditory oddball, vibrotactile and motor imagery paradigms in the same cohort of patients with DoC or LIS. These commercial systems are feasible to deploy in a clinical setting and may have a role to assess consciousness but they still need technical improvements such as paradigm optimization, shorter protocol duration, and a more accurate statistical threshold assessment.

An active EEG paradigm may also have a prognostic role in helping clinicians to identify patients with an overall greater functional cerebral integrity. In this vein, a prospective study (Edlow et al., 2017) combined active EEG and fMRI paradigms in patients with TBI during the first 2 weeks of ICU. This approach was strategic in providing evidences of intact language comprehension or cortical processing in patients without behavioral signs of language function and showed that all patients with CMD recovered beyond a confusional state within 6 months. The authors introduced the new term, "higher-order cortex motor dissociation" (HMD) (see Table 1), to label patients able to show contingent brain responses to stimuli without any evidence of language output (Edlow et al., 2017; Schiff 2017). A recently published paper (Claassen et al., 2019) extended the application of a simplified motor active EEG paradigm in ICU to 104 patients who were in a condition of coma, VS/UWS or MCS minus. This work showed that up to 15% of patients, even if behaviorally unresponsive to commands, may show a brain activation to simple motor commands and that these CMDs are associated with better long-term outcome at 12 months. The prognostic relevance of active paradigms in a subacute phase was further corroborated by Pan and colleagues (2020) who recently showed that CMDs identified with a hybrid P3 and steady-state visual BCI have a better 3-months outcome, irrespectively of being VS/UWS or MCS at the evaluation time.

4.4. Investigational approaches in DoC: technical and conceptual caveats

Although the three investigational approaches reviewed above are not yet available for use in clinical practice, it may be of interest to briefly outline, based on our direct experience, their potential

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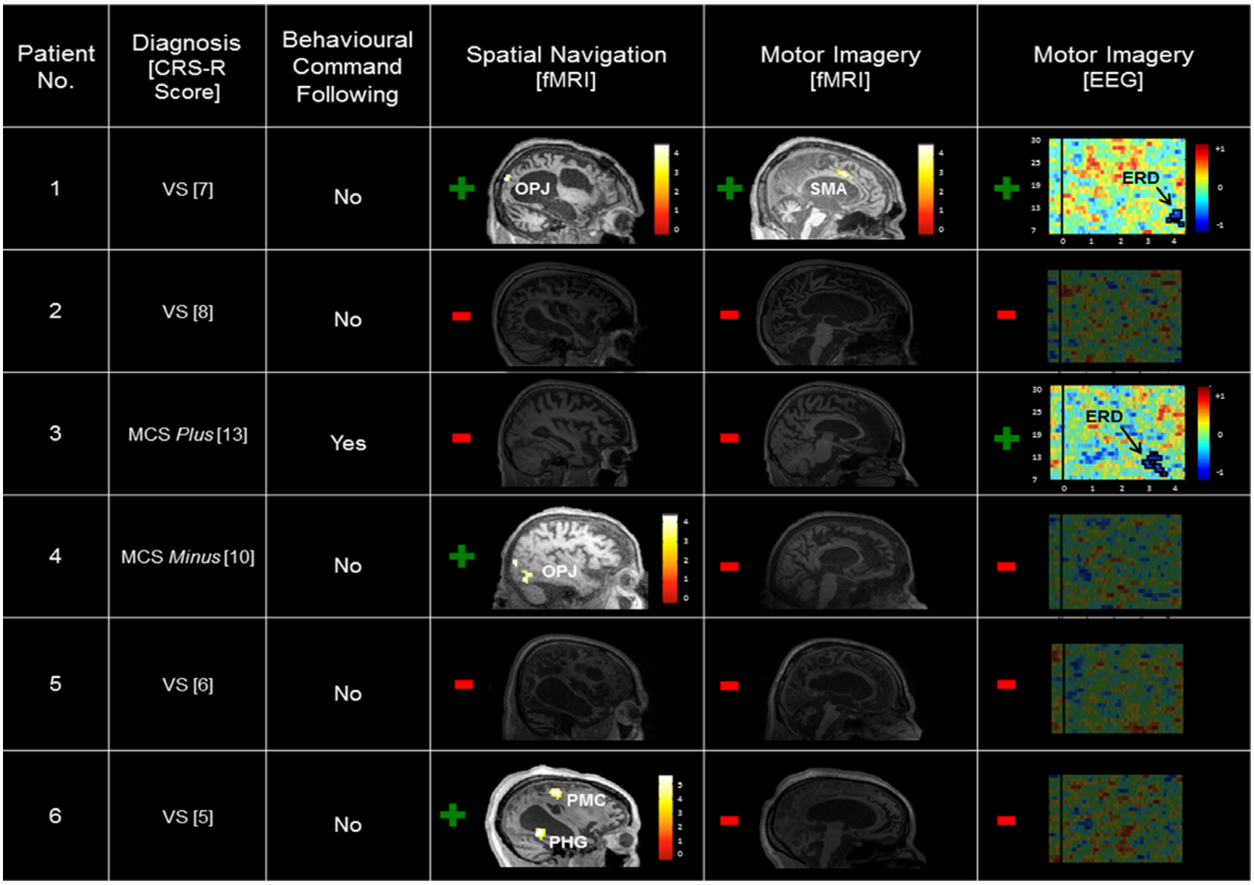

Patient No.	Diagnosis [CRS-R Score]	Behavioural Command Following	Spatial Navigation [fMRI]	Motor Imagery [fMRI]	Motor Imagery [EEG]
1	VS [7]	No	+	+	+
2	VS [8]	No	−	−	−
3	MCS *Plus* [13]	Yes	−	−	+
4	MCS *Minus* [10]	No	+	−	−
5	VS [6]	No	−	−	−
6	VS [5]	No	+	−	−

Fig. 8. Summary of the results of six DoC patients on behavioral, fMRI, and EEG-based assessments of command following. Significant blood-oxygen level-dependent responses for the fMRI mental imagery tasks are indicated by region on each patient's T1 image. Significant sensorimotor rhythm modulations from the EEG motor imagery task are enclosed with a black outline on each spectrogram. Note that both patients with statistically significant sensorimotor rhythm modulations generated responses over contralateral motor cortex from 7 to 13 Hz. CRS-R, Coma-Recovery Scale-revised; EEG, electroencephalography; ERD, event-related desynchronization; fMRI, functional magnetic resonance imaging; MCS, minimally conscious state; OPJ, occipito-parietal junction; PHG, parahippocampal gyrus; PMC, premotor cortex; SMA, supplementary motor area; VS, vegetative state. Reproduced from (Gibson et al., 2014).

advantages and pitfalls as well as their possibilities for a complementary use in synergy with other tools.

1. Consider the problem of training datasets in ML approaches

A potential pitfall of current ML-based approaches is that the classifier is initially trained to differentiate VS/UWS from MCS patients, based on behavioral labels. However, behavior-based clinical diagnosis may fail to recognize brain-injured patients who are conscious but disconnected and unresponsive. Hence, the true state-of-affairs (i.e. conscious versus unconscious subjects) necessary for a correct training remains unknown, engendering a circularity problem with potential impact on the accuracy and interpretability of the results (Harrison and Connolly, 2013; Peterson et al., 2015). Interestingly, a recent study has shown that ML-techniques, if trained with a sufficient amount of data, are robust to a mislabeling of up to 20% of the patients (Engemann et al., 2018). More generally, the problem of circularity can be addressed by refining the diagnostic labels by means of additional paraclinical markers. Another potential disadvantage of ML-based approaches to multivariate data is that, given their black-box nature, they do not necessarily provide direct mechanistic insights into the underlying neuronal processes. Yet, it is interesting to note that, in current implementations, α band power, connectivity or signal complexity were found to be among the strongest contributors to the discrimination between VS/UWS and MCS patients.

2. Consider the current feasibility of TMS/EEG measurements

Measures derived from TMS/EEG data are validated on a benchmark population of subjects that could confirm their state of consciousness (thus mitigating the problem of circularity), show high accuracy and point directly to mechanisms that are interpretable in terms of neuronal events. However, TMS/EEG has for the moment practical drawbacks that limit its widespread clinical application. These measurements currently require a complex set-up and operators with research-level expertise to acquire TEPs that are free from artifacts and confounders (Belardinelli et al., 2019; Conde et al., 2019). Streamlining and standardizing TMS/EEG measurements to become a routine bedside tool will require not only the introduction of simpler algorithms to extract the relevant indices (Comolatti et al., 2019) but also the development of novel hardware solutions and visualization tools to assist the operator during the measurement (Belardinelli et al., 2019). Thus, in their current formulation, TMS/EEG measurements may be better suited for providing (i) a second-level assessment for patients in whom the EEG screening gave inconclusive results and (ii) a direct read-out of the pathophysiological state of cortical circuits to plan and guide treatments.

3. Consider methodology and statistical assumptions when using active EEG paradigms

The nature of EEG artifacts in patients might be quite different from those in healthy subjects, both in magnitude and their correlation structure. Considering this discrepancy is crucial when choosing the statistical model for active EEG paradigms, as exemplified by a recent debate. In the spirit of open scientific inquiry, Cruse and colleagues shared data from their original 2011 investigation with Goldfine and colleagues (2013). In their reanalysis, Goldfine and colleagues employed two independent tests which, in their opinion and that of the peer reviewers, and commentators of the published reanalysis (but not shared by co-authors of the present review AMO and RG), demonstrated that the statistical assumptions employed were not valid for the dataset and further highlighted the potential problems of blocked mental imagery tasks. Specifically, block designs circumvent the potential for so-called 'automatic' responses due to task instructions (Owen and Coleman, 2007), but they can also introduce violations of certain statistical assumptions that may lead to high rates of false positives (Cruse et al., 2013; Goldfine et al., 2013). However, as discussed elsewhere (Cruse et al., 2014; Peterson et al., 2015), applications intended to inform the diagnosis of DoC require a case-by-case trade-off between an acceptable rate of false alarms (i.e. evidence of command following when the patient lacks awareness) and misses (i.e. no evidence of command following when the patient is aware). In this vein, novel models and methods have been developed that should be considered for future active EEG paradigms studies in patients (Cruse et al., 2012b; Curley et al., 2018; Edlow et al., 2017; Gibson et al., 2014).

4. Exploit the synergy of investigational approaches in hierarchical sequence

Although significant improvement in their performance are certainly possible (Curley et al., 2018), EEG active paradigms retain a low sensitivity as they rely on the patient's motivation as well as on sensory and cognitive abilities (such as language comprehension/production, aphasia) that may be compromised by brain injury (Formisano et al., 2019). In this perspective, the possibility of combining the three investigational methods described in this section in a hierarchical approach encompassing initial screening and patient stratification seems interesting. For example, once qEEG and TMS/EEG have demonstrated a high probability/capacity for consciousness (e.g. high connectivity, high complexity), patients who are otherwise unresponsive should undergo EEG active paradigms to obtain diagnostic confirmation and identify a suitable sensory modality/channel for communication.

5. Conclusions and future perspectives

In this extensive overview, we have described the state-of-the-art of consolidated and new emerging EEG-based techniques, highlighting their actual and potential contribution to the diagnostic and prognostic definition of DoC. In Section 2, we reappraised the key role of conventional EEG assessment as an effective measure of the global brain state, which provides information that is relevant for the monitoring and prognosis of comatose patients as well as for determining the thalamo-cortical integrity in prolonged and chronic DoC. In Section 3, we critically reviewed the role of ERPs, confirming their utility for early prognostication, pointing out their limitations as diagnostic markers of consciousness and suggesting their potential for probing residual cognitive functions in patients who have already regained awareness. Finally, in Section 4 we provided an overview of emerging investigational approaches and we suggested how they might be combined according to a hierarchical sequence of goals, from ML-based screening for residual consciousness probability to an accurate pathophysiological patient stratification with TMS/EEG up to the identification of covert awareness and restoration of command-following.

5.1. Towards a unifying pathophysiological framework

Whenever possible, we have tried to anchor fundamental EEG-related findings in patients to the underlying neuronal and network processes. We are convinced that the strong biological grounding of the EEG signal provides the rationale and motivation for developing further its role in the diagnosis and prognosis of DoC as well as a valid reference for interpreting a complex and rapidly growing literature. In this vein, we believe that future efforts should focus on the possibility of interpreting current electrophysiological findings in DoC patients within a systematic pathophysiological framework. Along these lines, in Box 2 we described the putative relationships between scalp EEG patterns and basic neuronal and network processes occurring as a consequence of brain damage. Here, we have highlighted that the slowing of spontaneous EEG rhythms observed in patients may result from critical levels of thalamo-cortical and/or cortico-cortical deafferentation (Schiff et al., 2014; Forgacs et al., 2017). Consistent with this observation, the TMS/EEG measurements described in Section 4.2 show that the cerebral cortex of most VS/UWS patients remains in an electrophysiological state of sleep-like reactivity even during behavioral wakefulness. Such widespread pathological engagement of sleep-like neuronal dynamics after brain injury may represent an extreme form of diaschisis, as originally defined by von Monakow (von Monakow, 1914; Pearce, 1994). Indeed, the pathological slow waves occurring in VS/UWS patients, just as the ones occurring during sleep, are associated with period of silence (OFF-period) in cortical circuits, which further disrupt long-range causal interactions and the emergence of complex dynamics (Rosanova et al., 2018). Hence, slow waves and the associated functional disconnection adding on top of structural damage may explain the evidence, provided by qEEG, that loss of connectivity and loss of dynamical complexity are among the distinctive features of VS/UWS patients (Sarà et al., 2011; Fingelkurts et al., 2013; Gosseries et al., 2014b; Sitt et al., 2014). Conversely, when slow waves give way to progressively faster rhythms, such as α, and connectivity and complexity resume within thalamo-cortical networks, one should suspect recovery of consciousness, even though the patient remains behaviorally unresponsive. In these cases, ERP and active EEG paradigms provide optimal tools to assess the chances of improvement, evaluate residual cognitive functions (CMD) and to restore basic forms of communication.

Far from being an exclusive interpretation of the current findings, this digression offers an example of how a pathophysiological common thread may help connect seemingly disparate notions, from the classic observation of EEG slowing after brain injury to the large-scale network alterations revealed by advanced analyses. Alternative and additional factors such as, for example, neuronal assembly characteristics (Fingelkurts et al., 2012b, 2014) have not been considered here, but may represent an important part of the picture.

Another important open issue is the role of α oscillations; indeed, the presence of a dominant posterior α background in the conventional clinical EEG is a specific feature of MCS (Forgacs et al., 2014; Estraneo et al., 2016) and absolute α power stands as the most discriminative qEEG feature, showing a performance comparable to that of the multivariate classifier (Engemann et al., 2018). On the other hand, α oscillations are dampened in conscious subjects during dreaming and hallucinations (Rodin and Luby, 1966; Boyce et al., 2016). Hence, it will be important to understand whether posterior α oscillations are just an epiphenomenon of adequate levels of cortical excitability or whether they have a causal role in recovery of consciousness.

Finally, we here interpret delta rhythms mainly as the EEG correlate of neuronal sleep-like oscillations between ON- and OFF-periods (Sanchez-Vives et al., 2017). However, other rhythms in the δ range both faster and slower than typical sleep slow oscillations may imply other mechanisms and other relationships with the presence/absence of consciousness (Northoff, 2017).

5.2. Towards an integration of consolidated and new research techniques

From the vantage point of the unifying framework outlined in the previous sections, we would like to conclude by drawing up a provisional workflow in which conventional clinical and advanced neurophysiological techniques (assuming that they will all be available in routine clinical practice) may be logically aligned along the natural history of DoC. The aim of this scheme is not to propose specific recommendations but rather to offer a provisional taxonomy in a complex field in rapid evolution. In doing so, we follow the AAN guidelines (Giacino et al., 2018b, 2018a) in going beyond the classical dichotomy between acute and chronic DoC to specifically focus on the prolonged phase, which represents a key window during which a synergy among different approaches may make the difference. In the critical, but still poorly defined, phase of transition from ICU to rehabilitation, a prolonged DoC is not yet a stabilized condition and the underlying state of thalamo-cortical circuits is likely to evolve over time. Within this time frame (28 days from injury up to 3 or 12 months according to whether the etiology is non-traumatic or a traumatic), an operational stepwise workflow, such as outlined in Fig. 9, might help direct behaviorally unresponsive patients towards different lines of evaluation based on objective markers of thalamo-cortical integrity.

As a first step, a conventional neurophysiological assessment based on EEG and SEPs is useful to individually tailor rehabilitation according to the expectations of recovery. A favorable pattern is indicated by a normal/mildly abnormal EEG background (Forgacs et al., 2014; Estraneo et al., 2016). An unfavorable pattern is suggested by bilateral absence of SEPs (Fischer et al., 2010; Estraneo et al., 2013; Ragazzoni et al., 2013) and/or a low-voltage pattern (Estraneo et al., 2016). A third and frequent scenario is an indeterminate pattern in which EEG background is unclear for prognostic significance.

In unresponsive patients showing a favorable neurophysiological profile, a VS/UWS condition may be ruled out (Kondziella et al., 2020) and ERPs can be used, as a 2nd step, to characterize residual sensory functions and cognitive abilities still inaccessible to neurobehavioral assessment. Considering the viability of specific sensory channels, these patients should be promptly selected for communication protocols based also on active EEG paradigms or BCI. In VS/UWS patients showing an unfavorable profile, further demanding neurophysiological tools should be discouraged in favor of a longitudinal behavioral observation up to the chronic phase.

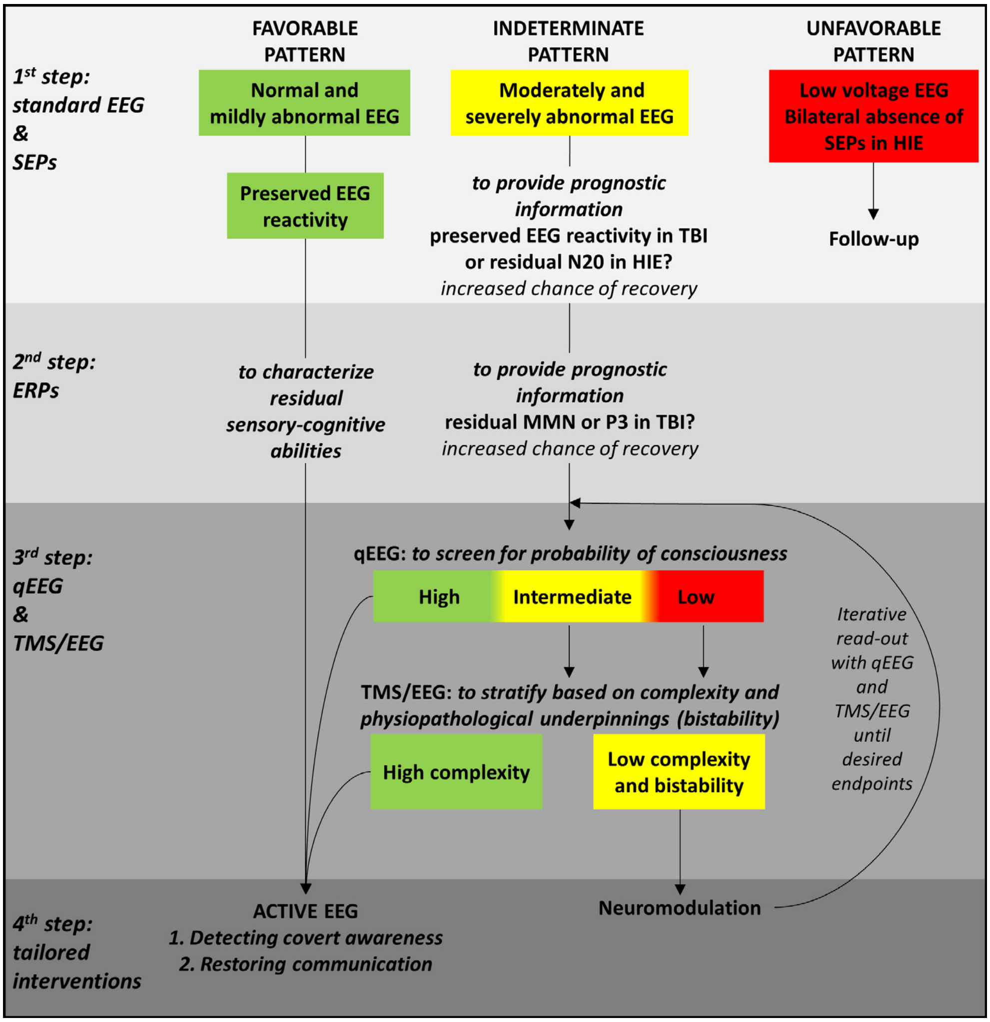

Fig. 9. Multimodal graded neurophysiological assessment in patients with prolonged DoC. The operational stepwise workflow include multiple steps of instrumental evaluation with increasing complexity starting from conventional neurophysiologic measures (standard EEG and SEPs) to ERPs and finally advanced approaches (qEEG analysis, TMS/EEG and active EEG paradigms). This general scheme might help direct behaviorally unresponsive patients towards different lines of evaluation based on objective markers of thalamo-cortical integrity. EEG, electroencephalography; ERP, event-related potential; HIE, hypoxic-ischemic encephalopathy; MMN, mismatch negativity; qEEG, quantitative EEG; SEP, somatosensory evoked potential; TBI, traumatic brain injury; TMS, transcranial magnetic stimulation; TMS/EEG, TMS combined with EEG.

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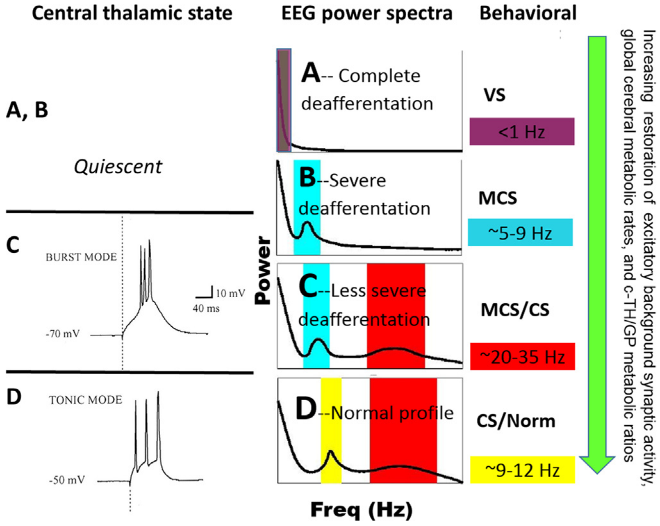

Fig. B1. Relationship of the dominant background EEG rhythm in DoC with behavioral level and functional state of the thalamo-cortical system. A general correlation is expected between the overall degree of deafferentation of the thalamo-cortical system in DoC patients, EEG classification (represented here by the expected average power spectrum) and the most likely behavioral level. CS, conscious state; EEG, electroencephalography; MCS, minimally conscious state; VS, vegetative state. Modified from (Schiff, 2016).

In the large group of unresponsive patients with an indeterminate pattern based on EEG background evaluation, additional features such as EEG reactivity (Bagnato et al., 2015, 2017; Estraneo et al., 2016) and the preservation of SEPs in HIE (Estraneo et al., 2013) may still offer valuable prognostic information for recovery and further clues can be obtained by the detection of residual ERP components (Giacino et al., 2018b, 2018a). Crucially, this is the large grey area where advanced approaches, such as qEEG, TMS/EEG and active paradigms, may help stratify patients. Individuals who, at first screening with qEEG, show a very high probability of being MCS, may be directly selected for intensive rehabilitation protocols aimed at restoring communication. Patients with intermediate or low probability of being MCS at the qEEG screening, should be assessed by a perturbational (TMS/EEG) protocol to probe the thalamo-cortical complexity. The rationale for this is that TMS/EEG measures can detect high-complexity and a capacity for consciousness with high sensitivity even in the presence of ambiguous spontaneous EEG pattern (Casarotto et al., 2016). Patients that show high levels of complexity (PCI), in the range of the conscious benchmark, can be directly selected for intensive protocols to promote a basic environmental interaction through active EEG paradigms or BCI. Conversely, patients in whom TMS/EEG detects low-complexity responses and bistable dynamics (OFF-periods) should be considered for treatments aimed at restoring the thalamo-cortical function, such as pharmacological therapy or neuromodulation (Thibaut et al., 2019, for a complete review of therapeutic interventions in patients with prolonged DoC).

In these cases, both qEEG and TMS/EEG can be employed as a dynamic read-out to longitudinally track the evolution of the state of thalamo-cortical circuits towards a desired endpoint, such as increasing probability of a MCS classification (qEEG) and a reduction of bistability associated with increasing complexity (TMS/EEG).

In more stabilized clinical conditions, such as chronic DoC, when diagnostic needs are prevalent, a similar multimodal stepwise assessment can offer a neurophysiological profile of the VS/UWS or the MCS condition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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