Neurocrit Care (2023) 39:578–585
https://doi.org/10.1007/s12028-023-01795-1

NEUROCRITICAL CARE SOCIETY

COMMON DATA ELEMENTS FOR DISORDERS OF CONSCIOUSNESS

Common Data Elements for Disorders of Consciousness: Recommendations from the Electrophysiology Working Group

Elizabeth E. Carroll[1,2], Caroline Der-Nigoghossian[2], Ayham Alkhachroum[3], Brian Appavu[4,5], Emily Gilmore[6,7], Julie Kromm[8,9], Benjamin Rohaut[10], Mario Rosanova[11], Jacobo Diego Sitt[12], Jan Claassen[1,2*] and the Curing Coma Campaign and its Contributing Members

Abstract

Background: Electroencephalography (EEG) has long been recognized as an important tool in the investigation of disorders of consciousness (DoC). From inspection of the raw EEG to the implementation of quantitative EEG, and more recently in the use of perturbed EEG, it is paramount to providing accurate diagnostic and prognostic information in the care of patients with DoC. However, a nomenclature for variables that establishes a convention for naming, defining, and structuring data for clinical research variables currently is lacking. As such, the Neurocritical Care Society's Curing Coma Campaign convened nine working groups composed of experts in the field to construct common data elements (CDEs) to provide recommendations for DoC, with the main goal of facilitating data collection and standardization of reporting. This article summarizes the recommendations of the electrophysiology DoC working group.

Methods: After assessing previously published pertinent CDEs, we developed new CDEs and categorized them into "disease core," "basic," "supplemental," and "exploratory." Key EEG design elements, defined as concepts that pertained to a methodological parameter relevant to the acquisition, processing, or analysis of data, were also included but were not classified as CDEs.

Results: After identifying existing pertinent CDEs and developing novel CDEs for electrophysiology in DoC, variables were organized into a framework based on the two primary categories of resting state EEG and perturbed EEG. Using this categorical framework, two case report forms were generated by the working group.

Conclusions: Adherence to the recommendations outlined by the electrophysiology working group in the resting state EEG and perturbed EEG case report forms will facilitate data collection and sharing in DoC research on an international level. In turn, this will allow for more informed and reliable comparison of results across studies, facilitating further advancement in the realm of DoC research.

Keywords: Coma, Consciousness, Common data elements, Electrophysiology

Introduction

Hans Berger presented the first human electroencephalogram (EEG) approximately 100 years ago [1]. This initial recording suggested a link between levels of consciousness and brain electrical oscillations [2]. Since its first introduction, EEG has evolved due to widespread application and technological advancements (i.e., digital

*Correspondence: jc1439@columbia.edu
[1] Department of Neurology, Columbia University Medical Center, 177 Fort Washington Avenue, MHB 8 Center, Room 300, New York, NY 10032, USA
Full list of author information is available at the end of the article

Springer

recordings) to become one of the core means of noninvasive continuous monitoring of brain activity [3]. In addition to its use as a clinical tool, EEG has become a key technique in advancing research in the field of disorders of consciousness (DoC) [3]. The value of EEG is recognized by experts in the field, and it has been endorsed by the American Academy of Neurology and European Academy of Neurology for evaluation of patients with DoC [3–5].

Significant uncertainty exists within the realm of DoC, thus positioning it favorably as a nidus for emerging investigations. We propose a data collection framework for electrophysiology in DoC research, based on two primary categories of resting state EEG (rsEEG) and perturbed EEG (pEEG). rsEEG metrics pertain to variables collected from patients who are not confronted with an external stimulus. pEEG metrics are those collected from patients who are sequentially or repeatedly exposed to magnetic, electrical, auditory, or other stimuli. In the last 20 years, a variety of EEG measures, both relating to rsEEG and pEEG, have been proposed; however, no broad agreement on their categorization and collection to advance DoC research exists.

The common data elements (CDEs) project is a joint effort between the National Institute of Health and the National Institute of Neurological Disorders and Stroke to develop standardized naming, definitions, and data structure for clinical research variables, with the main goal of facilitating the comparison of clinical studies results in major neurological diseases. As such, the "electrophysiology working group" is a working group of the "Coma and Disorders of Consciousness-CDE Project" aimed to construct CDEs concerning the use of EEG either within or outside of the intensive care unit, with the goal of standardizing data collection and for the purpose of advancing DoC research. Herein we discuss the evidence supporting the CDEs used to develop the rsEEG and pEEG case report forms (CRFs).

rsEEG

Classification of EEG Findings

In 1965, the first classification system of EEG patterns in DoC was established and was based on EEG findings in postanoxic coma. The classification system described that deteriorating brain function was associated with progressive slowing and dampening of EEG background oscillations [6]. In 1988, this classification scheme was further systematized into five grades, with grade 1 referring to dominant reactive alpha activity and grade 5 referring to an isoelectric EEG [7]. This remained the primary classification system until 2013, when the American Clinical Neurophysiology Society published the standardized critical care EEG terminology, which standardized the description of not only EEG background activity in the awake and asleep states but also major epileptiform abnormalities [8]. These guidelines have more recently been updated in 2021 [8]. This classification system, which was ultimately validated by two independent groups [9, 10], has become the standard classification system used today.

Raw EEG Inspection

In the acute care setting, EEG is routinely used to detect electrographic seizures (ESzs) and electrographic status epilepticus, confirm electroclinical seizures and electroclinical status epilepticus, and monitor treatment response. Although not specific to diagnosis or prognosis of DoC, recognizing and treating acute pathology that may be contributing to a patient's level of consciousness is imperative. Electroclinical seizures are common in the population of patients with brain injury, seen in up to 30% of patients in the neurological intensive care unit with a depressed level of consciousness [11, 12]. In addition to clearly defining electrographic seizures and status epilepticus, rhythmic and periodic patterns on the ictal/interictal continuum that do not qualify as unequivocal seizures or status epilepticus are now recognized as being synonymous with possible ESz or electrographic status epilepticus and may be seen contributing to a patient's depressed level of consciousness [13]. Although the presence of certain ictal/interictal patterns is suggestive of a higher risk of ESz, equipoise regarding the clinical significance and aggressiveness of treatment remains controversial and thus an active area of research [13–15]. rsEEG characteristics have been found to correspond to preservation of cerebral pathways relating to DoC. In a study of 44 patients with severe brain injury in which continuous EEG, functional magnetic resonance imaging (fMRI), and 18-Fluoro-deoxyglucose positron emission tomography were performed, patients with evidence of covert command following on fMRI were consistently found to have a well-organized background EEG activity, with a preserved anterior posterior gradient, theta/alpha background frequencies, and an absence of marked diffuse or focal slowing [16]. This coupling of EEG and fMRI suggests that thalamocortical function is preserved in a minimally conscious state (MCS) [16]. Such EEG findings have a high specificity but low sensitivity for MCS, further supporting the use of rsEEG in diagnosis of DoC [5].

In patients with DoC, thalamocortical circuit preservation has also been explored in EEG recorded during sleep-like states. Preserved EEG sleep transients and structures, including sleep spindles and slow wave sleep, are thought to reflect intact thalamocortical circuitry. In MCS, sleep features are commonly seen in the complex transition from non-rapid eye movement to rapid eye

movement sleep stages, whereas they are rarely, if ever, observed in patients with vegetative state/unresponsive wakefulness syndrome (VS/UWS) [17]. This notion supports concepts discussed above in the resting EEG section recorded to evaluate awake-like states [3]. rsEEG has for a long time played a central role in patients with DoC following cardiac arrest to guide neuroprognostication. As a part of a multimodal protocol, rsEEG at 24 h post arrest demonstrating low voltage or suppressed (< 10 μV) background, burst suppression with or without identical bursts, generalized periodic discharges on a suppressed background, or a spontaneous discontinuous background have been considered predictors of poor outcome [18–22]. This notion has recently been challenged, with reports of late emergence from coma and good clinical outcome in patients with burst suppression with nonidentical bursts, composed of theta peak intraburst spectral power [23].

Quantitative EEG Analysis

The digitally recorded EEG signal can be transformed by applying computational analysis to investigate different EEG characteristics including frequency, amplitude, or power complexity of the signal and metrics based on information theory. Power spectrum or power spectral density (PSD) describes the power present in the signal as a function of oscillation frequency seen on raw EEG. PSD allows for quantification of slowing on raw EEG, which has been shown to negatively correlate with the Coma Recovery Scale-revised score [24–26]. PSD has been applied to study the rsEEG in patients with DoC, and it has been suggested that there is an increased prevalence of low frequency power bands (delta) seen in patients with VS/UWS, whereas higher frequency power bands (theta/alpha) are seen in MCS patients [3, 24, 27, 28]. A number of measures investigate the complexity of the EEG signal such as permutation entropy, which may be restricted to specific frequency power bands (e.g., theta permutation entropy, which correlates with states of consciousness in patients with brain injury). There are several measures that explore functional connectivity between different recording sites (e.g., weighted symbolic mutual information [wSMI]). wSMI, a marker of cerebral complexity, is yet another means by which one can correlate brain function to level of consciousness [25, 28–30]. Automatic behavioral state classification is increasingly more reliable combining a panel of these metrics, and recovery prediction may be feasible [25, 26]. In a study of 181 patients with DoC, the combination of absolute power, average complexity related metrices, and wSMI in the theta frequency band were found to be the most effective at attempting to discriminate between VS/UWS and MCS [25].

The disconnection or deafferentation within and among the cortical and subcortical structures in patients with impaired consciousness is at least partially reflected in the degree of slowing on rsEEG [31, 32]. This concept has been captured by the ABCD classification building on the anterior forebrain mesocircuit model classifying the degree of thalamocortical disconnection based on spectral EEG background changes [33]. Describing the spectral patterns of EEG background, A-type classification refers to a slow EEG with 1 Hz oscillations, whereas D-type classification refers to normal alpha/beta range oscillations. The dynamic hierarchical classification system has been suggested to represent the degree of thalamocortical integrity and has been shown to correlate with behavioral improvement in patients with severe anoxic brain injury [16, 33, 34]. A recent study conducted on 87 patients with DoC found that power in the EEG alpha band is significantly suppressed in patients with anoxic DoC, yet it does not distinguish between consciousness and unconsciousness in DoC due to other causes [35]. Conversely, a bivariate index combining EEG spectral PSD slope and anteriorization stratifies patients and identifies consciousness in nonanoxic DoC with high sensitivity [35]. This study confirms that EEG alpha power is linked more to the degree of integrity of the thalamocortical system rather than to consciousness, whereas a well-preserved EEG can be consistent with covert consciousness [16]. In cases of negative or uncertain predictions, more sensitive tools may be of interest, such as the Perturbational Complexity Index (PCI) based on the combination of Transcranial Magnetic Stimulation with EEG (TMS-EEG) measurements as described in the next section.

pEEG

Event-Related Potentials

Event-related potentials (ERPs) encompass the group of brain responses seen on EEG secondary to an external stimulus and reflect the summed activity of postsynaptic potentials produced when similarly oriented cortical neurons fire in synchrony [36, 37]. The early component of the waveform generated is considered the "exogenous" response given its dependence upon the stimulus itself, whereas the later aspect of the waveform is considered the "endogenous" response, reflecting the information processing [36].

Mismatch negativity (MMN) describes an established protocol for assessing auditory processing using ERPs [38, 39]. It employs a series of repetitive tone bursts, with an oddball stimulus deviating from the standard tones, and as such eliciting the MMN [38, 40]. If the deviant exceeds the study participant's discrimination threshold and the brain can detect the auditory violation, the ERP

waveform will peak at 100–150 ms after stimulus onset, with a prominent frontocentral distribution [3, 39]. Across a wide range of acute and subacute brain pathologies, MMN is now an accepted metric in predicting neurologic recovery given its robust positive predictive value of 80–94% [41–45]. However, as with nearly all prognostic studies involved in comatose patients, these studies may be limited by positive verification bias of early withdrawal of life-sustaining treatment given the lack of clinician blinding reported in the studies. Although MMN remains a promising tool, its use in the diagnosis of DoC to differentiate VS/UWS from MCS has yet to be established.

The P300 response describes an ERP assessing a patient's attentiveness and reaction to a novel stimulus [46]. Recorded maximally in the centroparietal area approximately 300 ms after the rare stimulus, this response is further divided into the P3a and P3b components [47]. P3a denotes the automatic detection to the change in environment, whereas the P3b represents the more complex processing of the rare stimuli [48], and possibly conscious perception of the novel stimuli [49, 50]. The P3b response has been shown to have potential to assist in DoC diagnosis and prognostication when applied to a local–global paradigm (an ERP oddball auditory paradigm with two embedded levels of auditory regularity, testing one's ability to distinguish between local auditory regularities and global long-term rule violations [51]), with presence of a P3b response ("global effect") associated with covert awareness and increased likelihood of progressing toward MCS or fully conscious state [51, 52].

Somatosensory Evoked Potentials

Somatosensory evoked potentials, specifically the N20 response elicited by stimulation of the median nerve and recorded over the somatosensory cortex, have long been used as a component of the multimodal approach to neuroprognostication in DoC [53, 54]. The bilateral absence of N20 responses is considered as one of the more powerful indicators of poor outcome and is a key component of postcardiac arrest prognostication guidelines [55–58]. In a meta-analysis of 4,500 postanoxic patients, bilaterally absent N20s within the first week had a 100% specificity to predict poor outcome [59]. In a 2018 systematic review, survivors after cardiac arrest with N20 amplitudes > 4 uV at 48–72 h from return of spontaneous circulation had greater than 80% specificity and 40% sensitivity for favorable functional outcome [22]. This has led to recent recommendations for neuroprognostication in adults after cardiac arrest that the bilateral absence of the N20 wave, with preservation of responses at Erb's point and the cervical spine, on somatosensory evoked potentials, is a reliable predictor of functional outcome at 3 months or later after arrest [22]. However, presence of an N20 response does not guarantee a good prognosis [60], and the significance of SSEP findings in other brain injuries is much less certain.

Activation Paradigm

Assessments of command following are the foundation for behavioral diagnoses of patients with DoC. Motor activation or imagery paradigms allow detection of brain activation using fMRI or EEG [3] without behavioral signs of motor activity to commands a phenomenon also known as cognitive motor dissociation (CMD) or covert consciousness. Initially reported in fMRI studies [61–64], the most widely reported motor activation paradigms involve asking patients to engage in mental imagery of spatial navigation, swimming, or playing tennis. To detect CMD using EEG, repeated trials asking the study participant to move or imagine moving and then to stop moving or stop imagining to move are performed. The recorded EEG signal is then transformed applying PSD analysis at each electrode. Machine learning algorithms such as support vector machine learning then determine whether the response associated with the move command is systematically different [2, 60–62]. Used both as a diagnostic and prognostic tool, a large single center study of 104 patients with DoC identified that up to 15% of patients in coma, VS/UWS or MCS minus, and behaviorally unresponsive to commands were in fact capable of producing reliable brain activation to simple motor commands [65]. CMD predicts better long-term outcomes at 1 year after injury [65], independent of age, admission diagnosis, and admission neurological deficits [66].

TMS-EEG and Pertubational Complexity Index

Transcranial magnetic stimulation allows for the noninvasive, direct, and focal perturbation of corticothalamic circuits thought to be responsible for the emergence of consciousness [67], whose pathological alteration may bring to DoC. The EEG response to this perturbation reflects the ability of one cortical neuronal group to causally interact with other groups of neurons to produce complex dynamics, which are thought to be responsible for the emergence of consciousness [Click or tap here to enter text [67–69]. TMS-EEG allows direct assessment of cortical circuits independent of behavior and hence without relying on the integrity of neural circuits that normally support sensory, motor, or executive functions. In healthy study participants in NREM sleep or under anesthesia, or patients with coma and disruption of the thalamocortical system, TMS stimulation will result in an EEG response that is simple and local, secondary to loss of integration, or stereotypical, secondary to loss

of differentiation [3, 70–75]. The PCI has been devised to quantify the complexity of the overall EEG response to TMS. Before applying it to DoC, PCI was first calibrated in a benchmark population ($n = 150$) of healthy study participants and patients who could report about their state of consciousness. This process allowed setting an empirical cutoff (PCI = 0.31) above which consciousness is always present. This PCI cutoff was then applied to deduce the presence of consciousness in patients with DoC with VS/UWS or MCS [76–78]. PCI showed an unprecedented sensitivity (about 95%) in identifying MCS patients, whom by definition show minimal behavioral outputs [77].

In the context of the present article, which mainly aims at promoting standardization of data collection and reporting in the DoC field of research, it is important to point out that, as with other electrophysiological techniques, reliably measuring PCI requires complying with a few, key experimental procedures during TMS-EEG measurements. These procedures aim at maximizing the impact of TMS on the cortex, while minimizing both artifacts and biological confounds, as well as data preprocessing. They are eventually finalized at recording EEG responses to TMS that are reproducible and specific for the stimulation target and characterized by an optimal signal-to-noise ratio. Tools specifically designed to accurately neuronavigate TMS, to check in real-time for the signal quality, or to abolish biological confounds are today available [79–81]. Taken together, these tools and procedures can foster the routine application of TMS-EEG in patients with clinical chronic, subacute, or acute DoC when consciousness is not apparent and can be covert [77, 82, 83].

Methods

Overview

Building on this all-encompassing compilation of research involving electrophysiology and DoC, we aimed to construct CDEs focused on the use of EEG in patients with DoC, with a goal of standardizing data collection and reporting. We expect that these CDEs (version 1.0) will be adapted and redefined as additional electrophysiology discoveries continue to emerge. The various working group DoC CDEs are designed to complement one another; the electrophysiology CDEs should be used in conjunction with other relevant DoC CDEs to best depict clinical characteristics and outcomes.

CDE Development Meetings

The electrophysiology working group composed of international DoC experts was convened as a part of the Neurocritical Care Society's Curing Coma Campaign with the aim of developing electrophysiology CDEs for patients with DoC. Members of the working group performed an extensive review of existing CDEs from traumatic brain injury, epilepsy, subarachnoid hemorrhage, and other neurological diseases (https://commondataelements.ninds.nih.gov). Whenever possible, pertinent existing CDEs were used.

For development of new CDEs, a list of electrophysiology concepts related to DoC was compiled from March 2020 to June 2022. Several prospective and observational studies were reviewed to derive a comprehensive list of variables pertaining to electrophysiology and DoC that had not been described in existing CDEs. Such variables were selected based both on their use in clinical electrophysiology and established reliability and validity. The collected variables were discussed via videoconference, and a candidate list to include was finalized and approved by all working group members.

Both the selected predefined CDEs, in addition to the novel CDEs, were then classified by consensus into the previously described categories of rsEEG and pEEG. These categories were the foundation for the two CRFs ultimately produced by the working group.

Classification into Core, Basic, Supplemental, or Exploratory CDEs

Both the predefined CDEs and the novel CDEs developed by the working group, were classified as "disease core," "basic," "supplemental," or "exploratory." This classification nomenclature is consistent with that used in prior National Institute of Neurological Disorders and Stroke CDE initiatives. We assigned the "basic" designation to CDEs that are strongly recommended for all DoC studies. We assigned the "supplemental" designation to CDEs that are recommended for specific DoC studies (i.e., depending on the context and goals of the study), and the "exploratory" designation was applied to CDEs that can be considered for use in DoC electrophysiology studies but require further validation. In addition to the aforementioned CDE categories, data included in the CRFs that pertained to a methodological parameter relevant to the acquisition, processing, or analysis of electrophysiological data were termed "key design elements."

Results

Version 1.0 (see Supplementary Materials) of the proposed electrophysiology CDEs for patients with DoC were presented in the format of two CRFs: (1) rsEEG (supplemental material 1) and (2) pEEG (supplemental material 2). These CRFs underwent a two-month public feedback period from October to November 2022, advertised at the 2022 annual Neurocritical Care Society meeting and social media. The public feedback was then incorporated into the CRFs, which were finalized

following approval by all working group members. Ongoing feedback regarding modification of the CDEs is encouraged and can be submitted via email to cde.curingcoma@gmail.com. Additional feedback will be reviewed by the electrophysiology working group on an as-needed basis, following which new versions of the CRFs will be posted to the Zenodo Web site (https://zenodo.org/record/8172359).

Discussion

The primary aim of the Neurocritical Care Society's Curing Coma Campaign call for DoC CDEs was to allow for development of standardized naming, definitions, and data structure for clinical research variables that will ultimately enhance cross-study comparisons and facilitate collaborations in DoC-related research. The electrophysiology working group pulled from existing CDEs, ensuring consistency with prior reported efforts to standardize electrophysiology data acquisition [84–86]. To supplement the existing CDEs, the electrophysiology working group created novel CDEs to encourage the harmonization of data collection. The CDEs selected by the working group have been internationally disseminated in the form of a rsEEG CRF and pEEG CRF. These CRFs, and the CDEs they are composed of, are designed for ease of use to encourage broad implementation across various clinical settings.

The goal of this initiative is to encourage the advancement of electrophysiology-related DoC research, in turn developing diagnostic and prognostic tools to assist in efforts to cure coma.

All DoC electrophysiology CDEs are now publicly available at (see Supplementary Materials).

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s12028-023-01795-1.

Author details
[1] Department of Neurology, Columbia University Medical Center, 177 Fort Washington Avenue, MHB 8 Center, Room 300, New York, NY 10032, USA. [2] NewYork-Presbyterian Hospital, New York, NY, USA. [3] Department of Neurology, University of Miami, Miami, FL, USA. [4] Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ, USA. [5] University of Arizona College of Medicine – Phoenix, Phoenix, AZ, USA. [6] Divisions of Neurocritical Care and Emergency Neurology and Epilepsy, Department of Neurology, Yale University School of Medicine, New Haven, CT, USA. [7] Yale New Haven Hospital, New Haven, CT, USA. [8] Departments of Critical Care Medicine and Clinical Neurosciences, University of Calgary, Calgary, AB, Canada. [9] Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada. [10] Sorbonne Université, Institut du Cerveau - Paris Brain Institute - ICM, Inserm, Centre national de la recherche scientifique, Assistance Publique–Hôpitaux de Paris, Neurosciences, Hôpital de La Pitié Salpêtrière, Paris, France. [11] Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy. [12] Paris Brain Institute (ICM), Centre national de la recherche scientifique, Paris, France.

Acknowledgements
The Curing Coma Campaign Collaborators are listed in the Supplementary Appendix.

Author Contributions
EC and JC wrote the initial draft of the manuscript. CD, AA, BA, EG, JK, BR, MR, and JDS, edited the manuscript and approved the final content. All co-authors contributed equally to the case report forms released with the article.

Source of Support
Included National Institute of Neurological Disorders and Stroke (NINDS) (R01NS106014, R03NS112760, R21NS128326) and James S. McDonnell Foundation (J.C.); Institutional KL2 Career Development Award from the Miami Clinical and Translational Science Institute (CTSI), National Center for Advancing Translational Sciences (NCATS), UL1TR002736 and by the NINDS (K23NS126577, R21NS128326) (AA); United States Department of Defense (W81XWH19-1–0514), American Heart Association (19CDA34760291) and Innovators for Neuroscience in Kids Foundation (BA); NINDS (R01NS117904, UG3NS123307), Yale New Haven Health System (YNHHS), Innovations (EG); European Research Area (ERA), PerMed JTC2019 (project PerBrain) and JTC2021 (project ModelDXConsciousness) (JDS); Calgary Health Foundation Grant for Neurocritical Care Expansion Project, Office of Health & Medical Education Scholarship Grant, Canadian Institute of Health Research Grant (BR); European Union's Horizon2020 Framework Program for Research and Innovation under the Specific Grant Agreement No.945539 (Human Brain Project SGA3) and by the Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Project PerBrain, call ERAPERMED2019-101,GA779282 (MR).

Conflict of interest
Minority shareholder in iCE Neurosystems (J.C.), Minority shareholder of Intrinsic Powers Inc., a spin-off of the University of Milan, Milan, Italy (MR). The remaining authors have no conflicts of interest.

Ethical Approval/Informed Consent
New data were not acquired or analyzed for this article, and therefore there was no need for informed consent or approval from an institutional review board.

Publisher's Note

Received: 20 June 2023 Accepted: 22 June 2023
Published: 22 August 2023

References

1. Loomis AL, Harvey EN, Hobart G. Potential rhythms of the cerebral cortex during sleep. Science. 1935;81(2111):597–8. https://doi.org/10.1126/science.81.2111.597.
2. Schomer DL, da Silva FHL. Niedermeyer's electroencephalography: basic principles, clinical applications, and related fields: sixth edition. In: Schomer DL, Lopes da Silva FH (eds) Wolters Kluver/Lippincott Williams & Wilkins. 2011. https://doi.org/10.1111/j.1468-1331.2011.03406.x
3. Comanducci A, Boly M, Claassen J, et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. Clin Neurophysiol. 2020;131(11):2736–65. https://doi.org/10.1016/j.clinph.2020.07.015.
4. Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? Prog Brain Res. 2009;177:33–48. https://doi.org/10.1016/S0079-6123(09)17704-X.

5. Kondziella D, Bender A, Diserens K, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur J Neurol. 2020;27(5):741–56. https://doi.org/10.1111/ene.14151.
6. Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab RS. Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. Electroencephalogr Clin Neurophysiol. 1965;18(6):575–86. https://doi.org/10.1016/0013-4694(65)90075-1.
7. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. J Clin Neurophysiol. 1988;5(2):161–74. https://doi.org/10.1097/00004691-198804000-00003.
8. Hirsch LJ, Fong MWK, Leitinger M, et al. American clinical neurophysiology society's standardized critical care EEG terminology: 2021 version. J Clin Neurophysiol. 2021;38(1):1–29. https://doi.org/10.1097/WNP.0000000000000806.
9. Gaspard N, Hirsch LJ, LaRoche SM, Hahn CD, Brandon M. Interrater agreement for critical care EEG terminology. Epilepsia. 2014;55(9):1366–73. https://doi.org/10.1111/epi.12653.
10. Westhall E, Rosén I, Rossetti AO, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol. 2015;126(12):2397–404. https://doi.org/10.1016/j.clinph.2015.03.017.
11. Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8. https://doi.org/10.1212/01.WNL.0000125184.88797.62.
12. Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: An investigation of variables associated with mortality. Neurology. 1996;47(1):83–9. https://doi.org/10.1212/WNL.47.1.83.
13. Rodríguez V, Rodden MF, LaRoche SM. Ictal-interictal continuum: a proposed treatment algorithm. Clin Neurophysiol. 2016;127(4):2056–64. https://doi.org/10.1016/j.clinph.2016.02.003.
14. Claassen J. How i treat patients with EEG patterns on the ictal-interictal continuum in the neuro ICU. Neurocrit Care. 2009;11(3):437–44. https://doi.org/10.1007/s12028-009-9295-8.
15. Westhall E, Rosén I, Rundgren M, et al. Time to epileptiform activity and EEG background recovery are independent predictors after cardiac arrest. Clin Neurophysiol. 2018;129(8):1660–8. https://doi.org/10.1016/j.clinph.2018.05.016.
16. Forgacs PB, Conte MM, Fridman EA, Voss PhD HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol. 2014;76(6):869–79. https://doi.org/10.1002/ana.24283.
17. Landsness E, Bruno MA, Noirhomme Q, et al. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain. 2011;134(8):2222–32. https://doi.org/10.1093/brain/awr152.
18. Cloostermans MC, Van Meulen FB, Eertman CJ, Hom HW, Van Putten MJAM. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med. 2012;40(10):2867–75. https://doi.org/10.1097/CCM.0b013e31825b94f0.
19. Sivaraju A, Gilmore EJ, Wira CR, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med. 2015;41(7):1264–72. https://doi.org/10.1007/s00134-015-3834-x.
20. Hofmeijer J, Tjepkema-Cloostermans MC, van Putten MJAM. Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma. Clin Neurophysiol. 2014;125(5):947–54. https://doi.org/10.1016/j.clinph.2013.10.017.
21. Rossetti AO, Carrera E, Oddo M. Early EEG correlates of neuronal injury after brain anoxia. Neurology. 2012;78(11):796–802. https://doi.org/10.1212/WNL.0b013e318249f6bb.
22. Sandroni C, D'Arrigo S, Nolan JP. Prognostication after cardiac arrest. Crit Care. 2018;22(1):150. https://doi.org/10.1186/s13054-018-2060-7.
23. Forgacs PB, Devinsky O, Schiff ND. Independent functional outcomes after prolonged coma following cardiac arrest: a mechanistic hypothesis. Ann Neurol. 2020;87(4):618–32. https://doi.org/10.1002/ana.25690.
24. Lechinger J, Bothe K, Pichler G, et al. CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest. J Neurol. 2013;260(9):2348–56. https://doi.org/10.1007/s00415-013-6982-3.
25. Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain. 2014;137(8):2258–70. https://doi.org/10.1093/brain/awu141.
26. Engemann DA, Raimondo F, King JR, et al. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain. 2018;141(11):3179–92. https://doi.org/10.1093/brain/awy251.
27. Fellinger R, Klimesch W, Schnakers C, et al. Cognitive processes in disorders of consciousness as revealed by EEG time-frequency analyses. Clin Neurophysiol. 2011;122(11):2177–84. https://doi.org/10.1016/j.clinph.2011.03.004.
28. Gosseries O, Schnakers C, Ledoux D, et al. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. Funct Neurol. 2011;26(1):25.
29. Schartner M, Seth A, Noirhomme Q, et al. Complexity of multi-dimensional spontaneous EEG decreases during propofol induced general anaesthesia. PLoS ONE. 2015;10(8):e0133532. https://doi.org/10.1371/journal.pone.0133532.
30. King JR, Sitt JD, Faugeras F, et al. Information sharing in the brain indexes consciousness in noncommunicative patients. Curr Biol. 2013;23(19):1914–9. https://doi.org/10.1016/j.cub.2013.07.075.
31. Schiff ND, Nauvel T, Victor JD. Large-scale brain dynamics in disorders of consciousness. Curr Opin Neurobiol. 2014;25:7–14. https://doi.org/10.1016/j.conb.2013.10.007.
32. Schiff ND. Mesocircuit mechanisms underlying recovery of consciousness following severe brain injuries: Model and predictions. In: Brain function and responsiveness in disorders of consciousness. 2016. https://doi.org/10.1007/978-3-319-21425-2_15.
33. Forgacs PB, Frey HP, Velazquez A, et al. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest. Ann Clin Transl Neurol. 2017;4(2):119–29. https://doi.org/10.1002/acn3.385.
34. Frohlich J, Crone JS, Johnson MA, et al. Neural oscillations track recovery of consciousness in acute traumatic brain injury patients. Hum Brain Mapp. 2022;43(6):1804–20. https://doi.org/10.1002/hbm.25725.
35. Colombo MA, Comanducci A, Casarotto S, et al. Beyond alpha power: EEG spatial and spectral gradients robustly stratify disorders of consciousness. Cereb Cortex. 2023;33(11):7193–210. https://doi.org/10.1093/cercor/bhad031.
36. Sur S, Sinha V. Event-related potential: an overview. Ind Psychiatry J. 2009;18(1):70. https://doi.org/10.4103/0972-6748.57865.
37. Peterson NN, Schroeder CE, Arezzo JC. Neural generators of early cortical somatosensory evoked potentials in the awake monkey. Electroencephalogr Clin Neurophysiol. 1995;96(3):248–60. https://doi.org/10.1016/0168-5597(95)00006-E.
38. Näätänen R, Gaillard AWK, Mäntysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst). 1978;42(4):313–29. https://doi.org/10.1016/0001-6918(78)90006-9.
39. Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: A review of underlying mechanisms. Clin Neurophysiol. 2009;120(3):453–63. https://doi.org/10.1016/j.clinph.2008.11.029.
40. Morlet D, Fischer C. MMN and novelty P3 in coma and other altered states of consciousness: a review. Brain Topogr. 2014;27(4):467–79. https://doi.org/10.1007/s10548-013-0335-5.
41. Kane NM, Curry SH, Butler SR, Cummins BH. Electrophysiological indicator of awakening from coma. The Lancet. 1993;341(8846):688. https://doi.org/10.1016/0140-6736(93)90453-N.
42. Fischer C, Luauté J, Adeleine P, Morlet D. Predictive value of sensory and cognitive evoked potentials for awakening from coma. Neurology. 2004;63(4):669–73. https://doi.org/10.1212/01.WNL.0000134670.10384.E2.
43. Luauté J, Fischer C, Adeleine P, Morlet D, Tell L, Boisson D. Late auditory and event-related potentials can be useful to predict good functional outcome after coma. Arch Phys Med Rehabil. 2005;86(5):917–23. https://doi.org/10.1016/j.apmr.2004.08.011.
44. Naccache L, Puybasset L, Gaillard R, Serve E, Willer JC. Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure [1]. Clin Neurophysiol. 2005;116(4):988–9. https://doi.org/10.1016/j.clinph.2004.10.009.
45. Wijnen VJM, van Boxtel GJM, Eilander HJ, de Gelder B. Mismatch negativity predicts recovery from the vegetative state. Clin Neurophysiol. 2007;118(3):597–605. https://doi.org/10.1016/j.clinph.2006.11.020.

46. Sutton S, Braren M, Zubin J, John ER. Evoked-potential correlates of stimulus uncertainty. Science (1979). 1965;150(3700):1187–8. https://doi.org/10.1126/science.150.3700.1187.
47. Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. Electroencephalogr Clin Neurophysiol. 1975;38(4):387–401. https://doi.org/10.1016/0013-4694(75)90263-1.
48. Polich J. Updating P300: an integrative theory of P3a and P3b. Clin Neurophysiol. 2007;118(10):2128–48. https://doi.org/10.1016/j.clinph.2007.04.019.
49. Picton TW. The P300 wave of the human event-related potential. J Clin Neurophysiol. 1992;9(4):456. https://doi.org/10.1097/00004691-199210000-00002.
50. Dehaene S, Changeux JP. Experimental and Theoretical approaches to conscious processing. Neuron. 2011;70(2):200–27. https://doi.org/10.1016/j.neuron.2011.03.018.
51. Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L. Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci. 2009;106:1672–7.
52. Perez P, Valente M, Hermann B, et al. Auditory event-related "global effect" predicts recovery of overt consciousness. Front Neurol. 2021;11:588233. https://doi.org/10.3389/fneur.2020.588233.
53. Goldie WD, Chiappa KH, Young RR, Brooks EB. Brainstem auditory and short-latency somatosensory evoked responses in brain death. Neurology. 1981;31(3):248. https://doi.org/10.1212/wnl.31.3.248.
54. Zandbergen EGJ, Koelman JHTM, De Haan RJ, Hijdra A. SSEPs and prognosis in postanoxic coma: only short or also long latency responses? Neurology. 2006;67(4):583–6. https://doi.org/10.1212/01.wnl.0000230162.35249.7f.
55. Rothstein TL, Thomas EM, Sumi SM. Predicting outcome in hypoxic-ischemic coma. A prospective clinical and electrophysiologic study. Electroencephalogr Clin Neurophysiol. 1991;79(2):101–7. https://doi.org/10.1016/0013-4694(91)90046-7.
56. Madl C, Kramer L, Domanovits H, et al. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. Crit Care Med. 2000;28(3):721–6. https://doi.org/10.1097/00003246-200003000-00020.
57. Sherman AL, Tirschwell DL, Micklesen PJ, Longstreth WT, Robinson LR. Somatosensory potentials, CSF creatine kinase BB activity, and awakening after cardiac arrest. Neurology. 2000;54(4):889–94. https://doi.org/10.1212/WNL.54.4.889.
58. Logi F, Fischer C, Murri L, Mauguière F. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol. 2003;114(9):1615–27. https://doi.org/10.1016/S1388-2457(03)00086-5.
59. Zandbergen EGJ, de Haan RJ, Stoutenbeek CP, Koelman JHTM, Hijdra A. Systematic review of early prediction of poor outcome in anoxic- ischaemic coma. Lancet. 1998;352(9143):1808–12. https://doi.org/10.1016/S0140-6736(98)04076-8.
60. Amorim E, Ghassemi MM, Lee JW, et al. Estimating the false positive rate of absent somatosensory evoked potentials in cardiac arrest prognostication. Crit Care Med. 2018;46(12):e1213–21. https://doi.org/10.1097/CCM.0000000000003436.
61. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science (1979). 2006;313(5792):1402. https://doi.org/10.1126/science.1130197.
62. Bardin JC, Fins JJ, Katz DI, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain. 2011;134(3):769–82. https://doi.org/10.1093/brain/awr005.
63. Fernández-Espejo D, Bekinschtein T, Monti MM, et al. Diffusion weighted imaging distinguishes the vegetative state from the minimally conscious state. Neuroimage. 2011;54(1):103–12. https://doi.org/10.1016/j.neuroimage.2010.08.035.
64. Stender J, Gosseries O, Bruno MA, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: A clinical validation study. The Lancet. 2014;384(9942):514–22. https://doi.org/10.1016/S0140-6736(14)60042-8.
65. Claassen J, Doyle K, Matory A, et al. Detection of brain activation in unresponsive patients with acute brain injury. N Engl J Med. 2019;380(26):2497–505. https://doi.org/10.1056/nejmoa1812757.
66. Egbebike J, Shen Q, Doyle K, et al. Cognitive-motor dissociation and time to functional recovery in patients with acute brain injury in the USA: a prospective observational cohort study. Lancet Neurol. 2022;21(8):704–13. https://doi.org/10.1016/S1474-4422(22)00212-5.
67. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: progress and problems. Nat Rev Neurosci. 2016;17(5):307–21. https://doi.org/10.1038/nrn.2016.22.
68. Massimini M, Boly M, Casali A, Rosanova M, Tononi G. A perturbational approach for evaluating the brain's capacity for consciousness. Prog Brain Res. 2009;177(C):25. https://doi.org/10.1016/S0079-6123(09)17714-2.
69. Ilmoniemi RJ, Virtanen J, Ruohonen J, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. NeuroReport. 1997;8(16):3537–40. https://doi.org/10.1097/00001756-199711100-00024.
70. Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M. Natural frequencies of human corticothalamic circuits. J Neurosci. 2009;29(24):7679–85. https://doi.org/10.1523/JNEUROSCI.0445-09.2009.
71. Massimini M, Ferrarelli F, Huber R, Esser SK, Singh H, Tononi G. Breakdown of cortical effective connectivity during sleep. Science. 2005;309(5744):2228–32.
72. Massimini M, Ferrarelli F, Esser SK, et al. Triggering sleep slow waves by transcranial magnetic stimulation. Proc Natl Acad Sci USA. 2007;104(20):8496–501. https://doi.org/10.1073/pnas.0702495104.
73. Sarasso S, Boly M, Napolitani M, et al. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Curr Biol. 2015;25(23):3099–105. https://doi.org/10.1016/j.cub.2015.10.014.
74. Rosanova M, Gosseries O, Casarotto S, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain. 2012;135(4):1308–20. https://doi.org/10.1093/brain/awr340.
75. Ragazzoni A, Pirulli C, Veniero D, et al. Vegetative versus minimally conscious states: a study using TMS-EEG, sensory and event-related potentials. PLoS ONE. 2013;8(2):e57069. https://doi.org/10.1371/journal.pone.0057069.
76. Bodart O, Gosseries O, Wannez S, et al. Measures of metabolism and complexity in the brain of patients with disorders of consciousness. Neuroimage Clin. 2017;14:354–62. https://doi.org/10.1016/j.nicl.2017.02.002.
77. Casarotto S, Comanducci A, Rosanova M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol. 2016;80(5):718–29. https://doi.org/10.1002/ana.24779.
78. Sinitsyn DO, Poydasheva AG, Bakulin IS, et al. Detecting the potential for consciousness in unresponsive patients using the perturbational complexity index. Brain Sci. 2020;10(12):917. https://doi.org/10.3390/brainsci10120917.
79. Casarotto S, Fecchio M, Rosanova M, et al. The rt-TEP tool: real-time visualization of TMS-evoked potentials to maximize cortical activation and minimize artifacts. J Neurosci Methods. 2022;370:109486. https://doi.org/10.1016/j.jneumeth.2022.109486.
80. Russo S, Sarasso S, Puglisi GE, et al. TAAC-TMS adaptable auditory control: a universal tool to mask TMS clicks. J Neurosci Methods. 2022;370:109491. https://doi.org/10.1016/j.jneumeth.2022.109491.
81. Lioumis P, Rosanova M. The role of neuronavigation in TMS-EEG studies: current applications and future perspectives. J Neurosci Methods. 2022;380:109677. https://doi.org/10.1016/j.jneumeth.2022.109677.
82. Comanducci A, Casarotto S, Rosanova M, et al. Unconsciousness or unresponsiveness in akinetic mutism? Insights from a multimodal longitudinal exploration. Eur J Neurosci. 2023. https://doi.org/10.1111/ejn.15994.
83. Edlow BL, Fecchio M, Bodien YG, et al. Measuring consciousness in the intensive care unit. Neurocrit Care. 2023;38(3):584–90. https://doi.org/10.1007/s12028-023-01706-4.
84. Suarez JI, Sheikh MK, Macdonald RL, et al. Common data elements for unruptured intracranial aneurysms and subarachnoid hemorrhage clinical research: a National Institute for Neurological Disorders and Stroke and National Library of Medicine Project. Neurocrit Care. 2019;30:4–19. https://doi.org/10.1007/s12028-019-00723-6.
85. S. T, C. F, S. K, et al. National institute of neurological disorders and stroke (NINDS), national institutes of health (NIH), Common Data Element (CDE) project: Epilepsy CDE update. Epilepsia. 2009;50.
86. Loring DW, Lowenstein DH, Barbaro NM, et al. Common data elements in epilepsy research: Development and implementation of the NINDS epilepsy CDE project. Epilepsia. 2011;52(6):1186–91. https://doi.org/10.1111/j.1528-1167.2011.03018.x.