Chapter 8

Neurophysiology and traumatic brain injury

Emilie Szymkowicz[1,2]; Paolo Cardone[1,2]; Olivia Gosseries[1,2]; Steven Laureys[1,2,3], Aurore Thibaut[1,2]

[1] Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium.

[2] Centre du Cerveau[2], University Hospital of Liège, Liège, Belgium.

[3] Joint International Research Unit on Consciousness, CERVO Brain Research Centre, Laval University, Canada.

Abstract

Neurophysiological techniques, such as electroencephalography, provide valuable information to aid the acute and chronic clinical management of traumatic brain injury. They provide complementary and additional information to neurological assessment, neuroimaging and biofluid examinations. This chapter discusses the use of neurophysiology in the assessment of post-traumatic altered cerebral activity, prognosis of recovery and monitoring of trauma-related conditions. It provides an overview of resting state electroencephalography, event-related potentials techniques, as well as magnetoencephalography. This chapter provides practical resources for clinicians involved in the management of TBI patients, with a particular emphasis on resting state quantitative EEG.

Keywords

Mild traumatic brain injury, moderate traumatic brain injury, severe traumatic brain injury, disorders of consciousness, clinical neurophysiology, neurophysiological techniques, electroencephalography, EEG, event-related potentials, ERPs, magnetoencephalography, MEG.

Abbreviations

TBI: traumatic brain injury

GCS: Glasgow Coma Scale

AOC: alteration of consciousness

LOC: loss of consciousness

PTA: post-traumatic amnesia

PPCS: persistent post-concussive symptoms

DoC: disorders of consciousness

UWS: unresponsive wakefulness syndrome

MCS: minimally conscious state

LIS: locked-in syndrome

EEG: electroencephalography

MEG: magnetoencephalography

ERPs: event-related potentials

qEEG: quantitative electroencephalography

PSG: polysomnography

BIS: bispectral (index)

BCI: brain-computer interface

REM: rapid eye movement

NREM: non-rapid eye movement

AAN: American Academy of Neurology

ACNS: American Clinical Neurophysiology Society

ECNS: Clinical Neuroscience Society

AAPB: Applied Psychophysiology and Biofeedback

SSNR: Society for the Study of Neuronal Regulation

MRI: magnetic resonance imaging

AFR: amplitude-frequency-reactivity (scale)

EAN: European Academy of Neurology

NCS: non-convulsive seizure

NCSE: non-convulsive status epilepticus

cEEG: continuous EEG

CT: computed tomography (scan)

MMN: mismatch negativity

ERN: error-related negativity

Pe: post-error positivity.

TMS: transcranial magnetic stimulation

Structure

1. Introduction
2. Generalities
3. Application
   - 3.1 Conventional EEG
     - 3.1.1 Mild TBI
     - 3.1.2 Moderate TBI
     - 3.1.3 Severe TBI
     - 3.1.4 Post-traumatic seizures
   - 3.2 Quantitative EEG
     - 3.2.1 Mild TBI
     - 3.2.2 Moderate TBI
     - 3.2.3 Severe TBI
     - 3.2.4 Discriminant classification
   - 3.3 Event-related potentials
   - 3.4 Magnetoencephalography

1. Introduction

Clinical neurophysiology offers the potential to probe the severity and underlying pathophysiology in traumatic brain injury (TBI) by investigating brain functions through the recording of bioelectrical activity. TBI-related neurophysiological changes result from structural and functional alterations of neural tissues classified into primary neural alteration (focal and/or diffuse), occurring directly after the traumatic impact, and secondary neural alteration, resulting from multiple neuropathological processes that can occur over minutes to years after the impact (1).

As discussed in Chapter 1, classification of TBI is complicated by the complexity and heterogeneity of the underlying disease process. It can be classified according to the mechanism of injury, resultant pathophysiology or specific clinical and imaging criteria. Historically, TBI has been divided into mild, moderate or severe based on clinical (e.g., Glasgow Coma Scale (GCS), alteration of consciousness (AOC) or loss of consciousness (LOC) and post-traumatic amnesia (PTA)) and imaging criteria (2). Mild TBI represents around 80% of TBI and is often defined by a GCS score of 13–15, AOC under 24 hours, LOC under 30 minutes and PTA under 24 hours (3). About 30 to 50% of patients with mild TBI develop persistent post-concussive symptoms (PPCS) lasting weeks to months after the injury (e.g., neurological, psychological or emotional complaints) (4), which represents an important socio-economic burden. However, PPCS can be caused by factors unrelated to a potential underlying structural brain injury (e.g., vestibular impairment, psychiatric diagnoses such as PTSD, extracranial injuries, legal processes and medications). Moderate TBI has been defined as a GCS

score of 9–12, AOC under 24 hours, LOC between 30 minutes and 24 hours, and PTA between 24 hours and 7 days (3). Finally, severe TBI is defined by a GCS score of 3–8, AOC above 24 hours, LOC above 24 hours and PTA above 7 days (3). Due to disruptions in neural systems regulating arousal and awareness, some patients with severe TBI remain in disorders of consciousness (DoC) including coma, unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) (5,6). See Box 8.1 for a detailed description of DoC entities. In the case of severe traumatic brainstem injury, some patients suffer from a locked-in syndrome (LIS) due to disruption of corticospinal and corticobulbar pathways. However, unlike coma and UWS, arousal and awareness remain intact in LIS (7).

>> Start of Box 8.1

Box 8.1 Clinical characteristics of DoC and related conditions

Coma is characterized by the absence of arousal (eyes continuously closed) and the presence of reflex behaviours (8). After coma, the patient will either die or recover (partially or completely) depending on the severity of the brain damage. UWS, formerly referred to as vegetative state, is characterized by the recovery of arousal (i.e., eyes opened either spontaneously or following an auditory, tactile or nociceptive stimulation) and by reflex behaviours (e.g., flexion withdrawal following a nociception stimulation) (6). MCS corresponds to severely impaired consciousness with minimal, discernible but fluctuating evidence of awareness (5). MCS minus is characterized by lower-level non-reflexive behaviours (e.g., visual pursuit and fixation, pain localization) and the absence of language-related behaviours (5). MCS plus is characterized by higher level non-reflexive behaviours (such as response to commands) and by a (partial)

preservation of language comprehension (9). Advances in neuroimaging and neurophysiology supports the detection of covert consciousness in patients with limited or absent behavioural motor response but residual brain activity through active paradigms (i.e., task-based) (10). Covert consciousness is referred to as non-behavioural MCS, MCS* or cognitive-motor dissociation (11,12). Patients emerging from MCS demonstrate reliable and consistent evidence of awareness including functional communication and/or use of objects (5). Based on temporal criteria, DoC are classified as acute under 28 days post-injury and prolonged after 28 days post-injury (13). Finally, LIS corresponds to preserved consciousness with quadriplegia and anarthria (14).

End of Box 8.1 <<

The heterogeneity of TBI pathologies and the broad spectrum of TBI severity (from concussion to coma) are not fully reflected by current clinical classification systems, which is a matter of controversy (15). A multimodal classification system integrating neurological, neuroimaging, biofluid, and neurophysiology techniques would further characterize the injury, thereby improving diagnosis and prognosis precision (15).

As a complement to neurological, neuroimaging and biofluid techniques, neurophysiological techniques applied to TBI provide valuable insights for diagnosis and prognosis (recovery and survival), but also to investigate post-traumatic epileptogenic processes, persistent symptoms in mild TBI, and (covert) awareness in patients with DoC following a severe TBI (16).

Neurophysiological techniques investigate cerebral activity through electrical potential distribution as detected by electroencephalography (EEG), and magnetic field

(produced by electrical potential arising from synchronous neuronal activation) as detected by magnetoencephalography (MEG) (17). More precisely, the neuronal afferent signal triggers a primary intracellular current associated with a magnetic field (detected by MEG) and a secondary extracellular current (detected by EEG) (17,18). Intrinsic spontaneous neuronal activity is investigated through resting-state paradigms (i.e., absence of external stimulation), and sensory-cognitive neuronal processes activation through task-related paradigms (i.e., neuronal response to repeated exogenous or endogenous stimuli) (19,20). Although both detect signals from common underlying neuronal activity, EEG and MEG have fundamental differences and provide complementary information (18,21). EEG is particularly sensitive to the localization of radial and deep cortical sources (increase of radial component in deeper cortical sources) (21). However, the electrical signal is partly distorted by the substantial difference in electrical conductivity between biological tissues and source-to-sensor distance (18,21). MEG is specifically sensitive to tangential cortical sources and deep subcortical sources with sufficient tangential orientation (21). The magnetic signal is distorted by the source-to-sensor distance, but not by the electrical conductivity of the biological tissues (considered as "transparent" to magnetic fields) (17). Neural source localization relies on a spatial resolution of 7-10 mm by electrical signal analysis, compared to 2-3 mm by magnetic signal analysis (17). The spatial and temporal resolution of EEG and MEG provides a broad range of neuropathological process information, supporting the relevance of neurophysiology in clinical settings. Although clinically recognized as non-invasive, safe, and reproducible, the application of EEG and MEG in clinical practice differs. The clinical application of MEG is limited by the expensive equipment (whereas EEG equipment is relatively inexpensive) and the

requirement of a magnetically shielded room to attenuate the external magnetic noise (while EEG is applied at bedside, thus allowing regular and repeat assessment) (18). This chapter discusses the clinical application of resting state EEG, event-related potentials (ERPs) and MEG, with a particular emphasis on quantitative EEG (qEEG), in mild to severe TBI for the diagnosis of neuronal alterations, prognosis of recovery and survival, as well as monitoring of trauma-related conditions (e.g., PPCS, post-traumatic epilepsy and DoC). The authors intended this chapter to provide a practical resource for clinicians involved in the management of TBI patients from concussion to coma and TBI-related conditions (see section 1 for the introduction) through clinical neurophysiology generalities covered in section 2 and application outlined in section 3 (in particular, conventional EEG in section 3.1, qEEG in section 3.2, ERPs in section 3.3 and MEG in section 3.4). Finally, concluding remarks on the contribution of neurophysiological techniques to the clinical practice for TBI are provided in section 4.

2. Generalities

Excitatory and inhibitory postsynaptic potentials generated by cortical pyramidal neurons tend to oscillate across alpha, beta, delta, theta, or gamma frequency bands (Table 8.1) and reflect cortico-cortical and thalamocortical connections (15,22). Delta rhythm corresponds to a frequency band between 0.5 and 4 Hz, mainly distributed in fronto-central regions during deep sleep. Theta rhythm corresponds to a frequency band between 4 and 8 Hz, mainly distributed in fronto-central regions during light sleep stage. The presence of delta and theta rhythms in awake states suggests focal cerebral dysfunction. Alpha rhythm corresponds to a frequency band between 8 and 13 Hz, mainly distributed in posterior regions during wakefulness (rest). Background

alpha rhythm slowing suggests generalized cerebral dysfunction. Beta rhythm corresponds to a frequency band between 13 and 30 Hz, mainly distributed in fronto-central regions during wakefulness (mental activity). Focal, regional, or hemispheric beta rhythm attenuation suggests a cortical lesion. The gamma rhythm corresponds to a frequency band between 30 and 80 Hz, mainly distributed in the somatosensory cortex during cognitive and sensory processing. Attenuation and irregularity of gamma rhythm suggest cognitive dysfunction.

>> Table 8.1 Frequency bands description in resting state. Delta, theta, alpha, beta, and gamma frequency bands are considered according to the principal distribution, physiological and pathological significance. <<

Frequency band	**Principal distribution**	**Physiological state**	**Pathological alteration**
Delta 0.5 – 4 Hz	Fronto-central regions	Sleep – deep stage	Delta rhythm in awake states (focal cerebral dysfunction)
Theta 4 – 8 Hz	Fronto-central regions	Sleep – light stage	Theta rhythm in awake states (focal cerebral dysfunction)
Alpha 8 – 13 Hz	Posterior regions	Wakefulness – rest	Background alpha rhythm slowing (generalized cerebral dysfunction)
Beta 13 – 30 Hz	Fronto-central regions	Wakefulness – mental activity	Focal, regional, or hemispheric beta rhythm attenuation (cortical injury)
Gamma 30 – 80 Hz	Somatosensory cortex	Cognitive & motor-sensory processing	Gamma rhythm attenuation and irregularity (cognitive dysfunction)

Conventional EEG (also termed clinical EEG) refers to the standard digital recording of raw electrical signals. The interpretation of conventional EEG consists of visual inspection of waveform variations through frequency, amplitude, localization, morphology, continuity, synchrony, symmetry, and reactivity parameters (described in Table 8.2) (23,24). qEEG relies on the application of analytical algorithms to the digital recording of electrical signals. By applying multichannel measurements (EEG-based brain mapping), qEEG improves the spatial determination of preserved or altered brain areas (19). The software-assisted analysis of qEEG consists of the extraction and processing of raw signal data to derive precise and specific parameters, such as power spectrum (also referred to as power spectral density), phase synchronization, coherence, connectivity, entropy and complexity (22,24–26) (described in Table 8.2). ERPs are voltage fluctuations (i.e., potentials) generated through time-locked EEG (or MEG) averaged response to sensory (i.e., visual, auditory, or somatosensory stimuli), cognitive (i.e., mental or attention tasks) or motor events (i.e., movement execution or imagery commands) (27,28). Potentials analysis consists of visual inspection or quantitative processing of spatial and temporal components distribution (defined by positive or negative polarity, amplitude, latency and scalp distribution) (29,30) – for an overview of ERP components, see (31). In particular, event-locked analysis tracks the activation of neural sources whereas response-locked analysis provides a temporal focus on response-related neural processes (32). MEG refers to the recording of magnetic signals generated by neuronal electric activity (33). Since the principal physiological sources of MEG and EEG signals are the post-synaptic currents in the cortical pyramidal cells, magnetic signals analyses are similar to those described for

EEG, including visual inspection and software-assisted processing (except for the source estimation) – for an overview of MEG signals analysis, see (34).

>> Table 8.2 Description of conventional EEG and qEEG parameters. Conventional EEG inspection relies on frequency, amplitude, localization, morphology, continuity, synchrony, symmetry, and reactivity. qEEG analysis derives a range of parameters including power spectrum, phase, coherence, connectivity, entropy, and complexity. <<

Conventional EEG	
Parameters	**Description**
Frequency	Number of waves or complexes cycles in 1 second, in Hertz (Hz) or cycles per second (c/s).
Amplitude	Measure of signal intensity oscillations, in microvolts (mV).
Localization	Focal, diffuse, or lateralized spatial pattern.
Morphology	Monomorphic or polymorphic structural pattern.
Continuity	Rhythmic, intermittent, or continuous activity pattern.
Synchrony	Simultaneous wave patterns on distinct regions (unilateral or bilateral).
Symmetry	Equivalent distribution of wave patterns between opposite homologous areas.
Reactivity	Consistent and reproducible change in frequency and/or amplitude upon stimulation.
qEEG	
Parameters	**Description**
Power spectrum	Distribution of the frequency-specific power, represented by a spectrogram (basis of qEEG analysis).
Phase	Temporal relationships between two similar activations at different locations.
Coherence	Correlation between the spectral content of brain regions over time.
Connectivity	Measure of functional interactions between neural systems operating in each frequency band (based on functional connectivity metrics such as coherence and phase synchronization).
Entropy	Measure of disorder describing the components distribution of a stochastic signal through irregularity, complexity, or unpredictability.

Complexity	Measure of the degree of integration and differentiation over time and over space.

EEG-derived techniques, including polysomnography (PSG), Bispectral (BIS) index and brain-computer interface (BCI), provide complementary information on neural processes. PSG records sleep components (e.g., sleep time, fragmentation, and stages: rapid eye movement – REM and non-rapid eye movement – NREM stages 1, 2, 3) through the combination of long-term continuous EEG, electrooculogram, electromyogram, electrocardiogram, and pulse oximetry (35). BIS neuromonitor processes a combination of time domain, frequency domain, and high-order spectral EEG subparameters (such as the activity in the beta frequency range, synchronized fast-slow activity, bispectrum, and burst suppression) to derive a BIS index value reflecting the level of consciousness (from 0 for isoelectric EEG to 100 for conscious state) (36,37). Initially introduced to monitor the depth of the hypnotic component of sedation and anaesthesia, the BIS index guides the titration of hypnotics to the target point of reduced brain activity (36). BCI translates neural signals (e.g., sensorimotor rhythms, slow cortical potentials and P300 ERPs extracted from EEG) into messages or commands relayed by the output device (38). Typically applied in nervous system injury, the interface substitutes defective neuromuscular pathways in spinal cord injury (frequent co-occurrence with TBI), provides brain-derived communication in LIS and detects covert consciousness in DoC (39,40).

The international recommendations of the American Clinical Neurophysiology Society (ACNS) for digital EEG provide guidance regarding technical requirements (i.e., the placement, number and mounting of electrodes on the cranial surface) and digital recording (i.e., recording duration, sampling rate, impedances and filter settings)

(23,41,42) – for an overview of recommendations for clinical MEG acquisitions, see (34). Electrode placement follows by consensus the "10 to 20 system" or the "10 to 10 system" for extended combinatorial system (43) and is used for both conventional EEG and qEEG. The minimum number required for spatial resolution corresponds to 16 channels of simultaneous recording (41). Additional channels are required, especially in research, to target activity in specific regions (e.g., high-density EEG provides spatial sampling from 60 to 256 channels). The electrodes are identified by a letter (i.e., F for frontal, C for central, P for parietal, O for occipital, Z for median line) and a number according to the position on the scalp (i.e., even number for the right hemisphere and odd number for the left hemisphere). The montages provide logical and ordered arrangements of channels: bipolar montages pair the electrodes two by two (less sensitive to artefacts) and referential montages pair a single electrode called reference to all the other electrodes (more sensitive to artefacts) (44). The recording duration for conventional EEG is set to at least 20 minutes of artefact-free electrical activity, whereas the recording time for qEEG is set between 3 and 10 minutes of artefact-free electrical activity depending on the analyses performed (exponential function of the qEEG test-retest reliability according to the recording duration) (41,45). Long-term continuous recording (over a period of 24 hours or longer) is recommended to investigate the variability of electrical activity, sleep (e.g., sleep latency and stages), and epilepsy components (e.g., spikes and seizures) (46,47). The sampling rate for data acquisition is recommended to range from 250 to 500 Hz (higher sampling rates are recommended for specific applications, such as automatic detection algorithms) (42). Impedances ranging from 1 kOhm to 10 kOhms are acceptable but optimal recording requires balanced impedances (impedances < 1 kOhm indicate a shortcut between electrodes and >10 kOhms leads to distortion artefacts) (41,48). The

verification of impedances is recommended before recording as a routine procedure and during recording in case of potentially artifactual patterns. Filtering settings include notch (50 or 60 Hz line depending on the geographic location), high-pass (0.5 Hz) and low-pass (70 Hz) filters depending on the frequency bands of interest. A low-frequency filter set above 1 Hz tends to conceal slow wave activity and a high-frequency filter set below 70 Hz tends to conceal spindles and spike waves, as well as muscular artefacts (41).

Clinical interpretation of recordings requires consideration of artifactual interferences as well as relevant medical conditions potentially interfering with cerebral activity, such as arousal state fluctuations and neuroactive medications (34,49). Artefacts refer to electrical noise stemming from extracerebral physiological (i.e., cardiac, respiratory, ocular, muscular and cutaneous artefacts) or non-physiological sources (i.e., equipment-related artefacts from electrodes, amplifier or cable and environment-related artefacts from respirator, electronic devices or noise exposure), which need to be discarded from both visual and quantitative analyses (50). In contrast to extracerebral electrical interferences, neuroactive medications and arousal state fluctuations directly modulate cerebral activity (51). Pharmacological agents (including sedatives, antipsychotics, antiseizure drugs, opiates, and antibiotics), generally induce molecule-dependent and dose-dependent modulations ranging from no effect, accentuation of beta activity, background slowing with decreased amplitude and/or frequency of alpha rhythm, intermixed theta and/or delta activity, decreased seizure activity, as well as lowering of seizure threshold with increased spike and wave discharges (alpha/theta coma, burst suppression, and isoelectric pattern in case of severe overdose) (51,52). Coherence and phase-lag, respectively measuring long-distance cortical communication linkages and axonal conduction velocities, appear

relatively insensitive to pharmacological modulation (no difference observed between patients on medication and patients without medication as well as between types of medication including tranquillizers, muscle relaxants, antidiuretics, antibiotics, anti-inflammatories) (51,53). A drowsy state induces a reduction in alpha band amplitude in posterior regions, and an apparition of theta rhythm in frontal lobes depending on the level of drowsiness (uncommon during the first minutes of recording) (51). Diffuse and global electrical deviations induced by pharmacological agents or drowsiness can be corrected using remounting procedures (eliminating spatially common fields and enhancing focal activity) to localize abnormal activity, notably in TBI through correlation with the traumatic impact point (51). As a fundamental process in research and clinical practice, artifactual identification and removal ensure a clinically relevant EEG recording (54). The interference of extracerebral electrical potentials, in more than 50% of the EEG recording involving more than 50% of the electrodes, affects the reliability and validity of the clinical interpretation (23).

3. Application

The application of resting state EEG, ERPs and MEG in TBI provides insights into spontaneous and stimuli-induced deviations of cortical activity from normative reference (55). Importantly, cortical activity deviations are not specific to TBI and should be interpreted according to the aetiology (56).

The clinical relevance of conventional EEG and qEEG in TBI has generated scientific disagreements among neurophysiology expert committees. Through a conservative report (published in 1997 and presently considered as a historical reference), the American Academy of Neurology (AAN) and the ACNS rejected the application of

qEEG in TBI (negative recommendation based on inconclusive, conflicting, or investigational evidence), while supporting the relevance of conventional EEG as a standard routine technique (57). As a rebuttal to the AAN and ACNS report, the Clinical Neuroscience Society (ECNS), the Association for Applied Psychophysiology and Biofeedback (AAPB), and the Society for the Study of Neuronal Regulation (SSNR) supported the relevance of qEEG in TBI through evidence-based statement reports (including references in line with positive recommendation standards) (58,59). The ECNS, AAPB and SSNR rebuttal stemmed from factual distortions and omissions in the AAN and ACNS report that hindered research development and clinical implementation of a valuable technique in the management of TBI patients (58–60). According to scientific and technical eligibility standards, conventional EEG, qEEG, ERPs and MEG are considered clinically valid and reliable techniques for the characterization of neurological pathologies such as TBI, although qEEG reaches higher test-retest reliability (34,60). As for conventional EEG, the implementation of qEEG, ERPs and MEG in clinical practice requires theoretical and practical qualification of the practitioners (including physicians and nonphysicians). Certification programs for conventional EEG, qEEG, ERPs, MEG and EEG-derived techniques such as PSG are provided, notably by committees of experts in neurophysiology. The implementation of qEEG in clinical practice is expected to expand in the coming years.

3.1 Conventional EEG

Conventional EEG was a pioneering clinical neurodiagnostic technique in TBI, demonstrating abnormal slowing of brain function after traumatic injury (61). Standard conventional recording is predominantly applied in neurocritical care for acute

monitoring of severe TBI through the inspection of qualitative electroencephalographic changes reflecting global brain state, the assessment of post-traumatic seizures, and the control of medication effects (e.g., anti-seizure medication and sedatives). The presence of pathological changes (i.e., focal or generalized slowing) on conventional EEG recording reveals a brain injury with 86% and 77% sensitivity in the presence and absence of neurological symptoms respectively (62). Generalized slowing, generalized bursts and focal abnormalities are more frequently observed in LOC lasting longer than 2 minutes (56% compared to 17% for LOC lasting less than 2 minutes) and in PTA lasting longer than 8 hours (62). As representative examples, Figure 8.1 depicts waveform patterns of alpha, theta, and delta waves (theta and delta frequency bands indicating local or general activity slowing) as well as triphasic waves (i.e., distinctive but non-specific pattern linked to consciousness alteration), focal or generalised epileptiform activity (i.e., rhythmic spike waves underlying brain lesions), alpha coma (i.e., diffuse irregular waves of 8-12 Hz), burst suppression (i.e., brief periods of bursts followed by periods of electrical silence < 10 uV) and inactivity (i.e., absence of cerebral electrical activity < 2 uV) (63).

>> Figure 8.1 Standard physiological and pathological waveform patterns in severe brain injury. Five-second recordings in a bipolar montage including right hemisphere derivations (i.e., Fp2-C4, C4-T4 and T4-02) and left hemisphere derivations (i.e., Fp1-C3, C3-T3 and T3-01).

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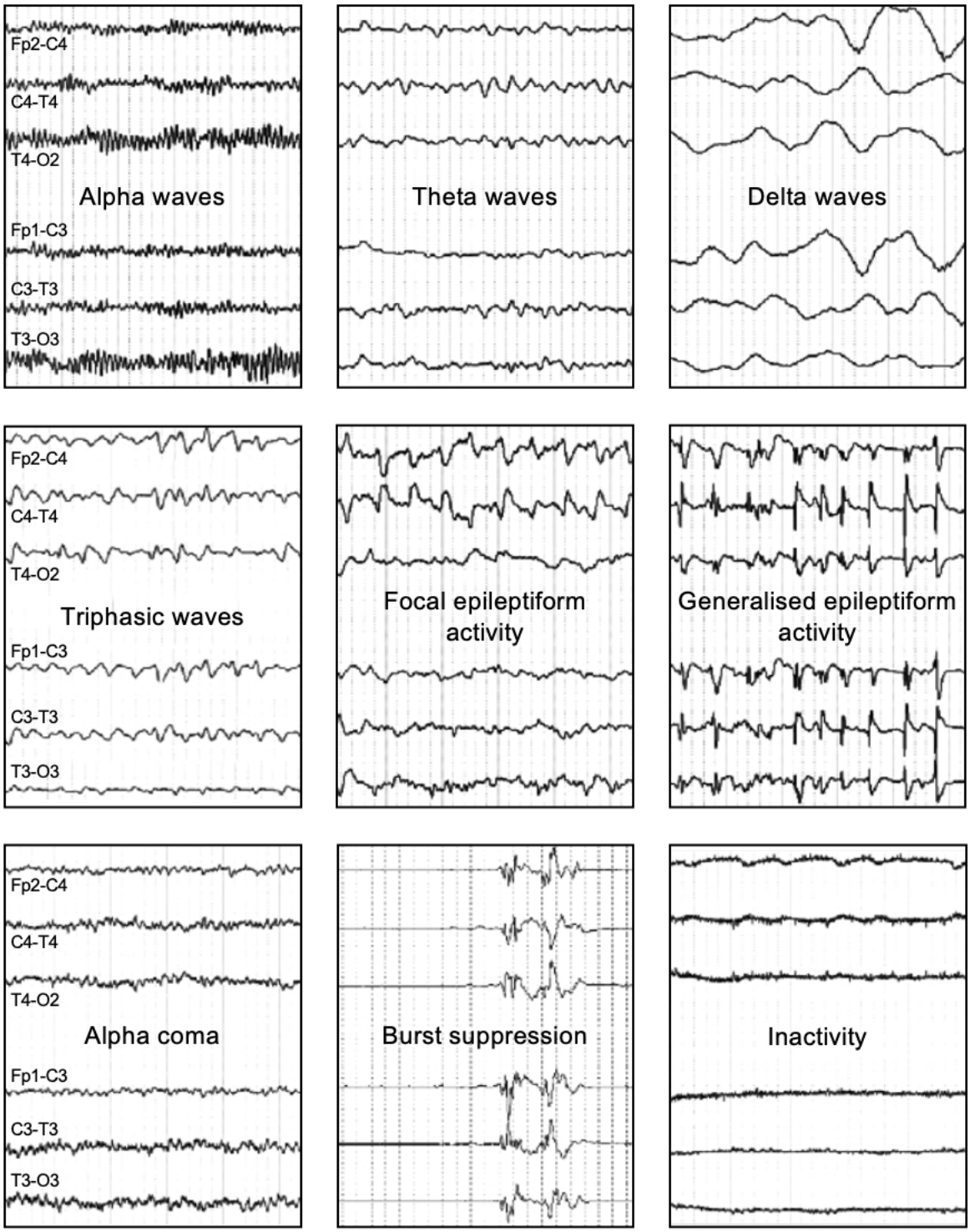

3.1.1 Mild TBI

Mild TBI conventional electroencephalographic changes consist of generalized or focal slowing (especially theta activity in temporal regions) with an attenuated posterior

alpha rhythm (64,65). Posterior focal slowing tends to evolve towards a slight alpha asymmetry before disappearing (65). Restoration of the pre-injury neural baseline, as reported by conventional EEG, is expected within one year of the trauma (66). Although relevant for the detection of acute and subacute electroencephalographic changes, conventional EEG is not recommended for chronic monitoring after mild TBI due to limited correspondence with clinical symptoms, neuroimaging results and psychometric tests (65,67). Indeed, persistent symptoms after mild TBI are frequently related to factors other than the brain injury/dysfunction (e.g., vestibular, psychiatric, personality, social, and environmental factors). Moreover, the visual inspection of raw conventional EEG patterns is associated with poor inter-rater agreement (15).

3.1.2 Moderate TBI

Moderate TBI conventional electroencephalographic changes overlap with mild TBI and severe TBI depending on the severity of injury (68,69). Conventional EEG is not reliable and sensitive for detecting differences between moderate TBI and mild or severe TBI (70).

3.1.3 Severe TBI

Severe TBI conventional electroencephalographic changes depend on the severity of the injury and on the acute, sub-acute or chronic situation (71). The classification of coma patterns ranges from reactive diffuse theta or delta activity to isoelectric pattern according to coma severity (Table 8.3) (72,73). Reactivity, rhythmic theta activity and frontal rhythmic delta activity are associated with favourable survival prognosis after brain injury (74). Epileptiform activity, non-reactive, low-amplitude delta activity, and burst suppression patterns are associated with unfavourable survival prognosis after

brain injury (74). Complete isoelectric EEG activity is associated with increased mortality (isoelectric activity below 2 volts is a criterion of brain death) (74,75).

>> Table 8.3 Classification of EEG patterns in acute coma introduced by Synek et al. (1988) (72) and adapted by Young et al. (1997) (73). Coma patterns range from diffuse reactive theta or delta activity (grade 1) associated with favourable survival prognosis to isoelectric patterns (grade 5) associated with unfavourable survival prognosis.

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Category	**Subcategory**
I. Delta/theta >50% of record (no theta coma)	(a) Reactivity (b) No reactivity
II. Triphasic waves	
III. Burst suppression	(a) With epileptiform activity (b) Without epileptiform activity
IV. Alpha/theta/spindle coma (unreactive)	
V. Epileptiform activity (no burst-suppression pattern)	(a) Generalized (b) Focal or multifocal
VI. Suppression	(a) <20 μV but >10 μV (b) <10 μV
Guidelines: - Burst-suppression pattern should present generalized flattening at standard sensitivity for more than 1 second at least every 20 seconds. - Suppression: for this category, voltage criteria should be met for the entire recording; there should be no reactivity. - When more than one category is present, select the most critical one.	

Regarding DoC patients specifically, conventional EEG changes indicate a generalized slowing of electrogenesis (76). Background activity organization reflects the functional integrity of thalamo-cortical networks in DoC patients (77,78). The classification of DoC patterns ranges from partially preserved activity (or normal activity) to low voltage activity (Table 8.4) (77,79). Partially preserved and mildly abnormal activity detect the MCS with high specificity, whereas low voltage activity and lack of reactivity (with moderately abnormal activity or diffuse slowing) detect UWS with high sensitivity (79). Non-behavioral MCS, as objectified by covert command-following on functional magnetic resonance imaging (MRI), is also related to partially preserved and mildly abnormal activity (77). Based on visual inspection, the amplitude-frequency-reactivity scale (referred to as AFR scale) is a multiparametric system for DoC recovery prognosis (Table 8.5) (80). AFR scores of 3 and 4 are associated with an unfavourable recovery prognosis while ARF scores of 6 and 7 are associated with a favourable recovery prognosis in UWS and MCS patients (a score of 5 represents an intermediate value, with a favourable recovery prognosis trend) (80,81). Progressive improvement from delta to theta and alpha frequencies is associated with a favourable survival prognosis in traumatic DoC patients, whereas the absence of alpha rhythm is associated with increased mortality in DoC patients (82,83). Clinical improvement towards EMCS is associated with the reappearance of dominant alpha background frequency, spontaneous background variability, and reactivity (84). Considering this evidence, conventional EEG is recommended by the European Academy of Neurology (EAN) to detect patients with preserved consciousness in DoC patients, as a complement to behavioural and neuroimaging assessment (85).

>> Table 8.4 Classification of EEG patterns in DoC introduced by Forgacs et al. (2014) (77) and completed by Estraneo et al. (2016) (79). DoC patterns range from partially preserved (or normal activity) associated with MCS (grade 1) to low voltage associated with UWS (grade 5).

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Category	**Description**
I. Partially preserved (or normal activity)	Predominant posterior alpha, anterior-posterior gradient, without focal or hemispheric slowing or epileptiform abnormalities
II. Mildly abnormal activity	Predominant posterior theta, symmetric or not, with frequent posterior alpha
III. Moderately abnormal activity	Predominant posterior theta, symmetric or not, with rare or occasional alpha, poorly organized anterior-posterior gradient
IV. Diffuse slowing	Predominant diffuse theta or theta/delta, without anterior-posterior gradient
V. Low voltage	Predominant diffuse and low theta or delta (<20 μV)

>> Table 8.5 ARF scale introduced by Bagnato et al. (2015) (80). The ARF scale range from a score of 3 associated with the worst clinical outcomes (including reduced amplitude, delta frequency and absence of reactivity) to a score of 7 associated with better clinical outcomes (including normal amplitude, alpha frequency, and reactivity).

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Category	**Subcategory**	**Score**

I. Amplitude	(a) Reduced (b) Normal	1 2
II. Frequency	(a) Delta (b) Theta (c) Alpha	1 2 3
III. Reactivity	(a) Absent (b) Present	1 2
Guidelines: - Calculate the sum of the amplitude, frequency, and reactivity scores.		

3.1.4 Post-traumatic seizures

The incidence of post-traumatic seizures and epilepsy increases according to the severity of the injury. Approximately 20% of moderate to severe brain-injured patients suffer from seizures (non-convulsive seizures in 50% of cases) in neurocritical care (86). Mild and moderate TBI involve less epileptic seizure complications than severe TBI, but even mild and moderate TBI lead to an increased risk compared to the general population (87). Importantly, conventional EEG is used to detect post-traumatic electrographic seizures, including non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE). Electrographic seizures are defined as "generalized or focal repetitive spikes, sharp waves, spike-and-wave complexes, or sharp and slow waves at ≥ 3 Hz, or rhythmic, periodic, or quasi-periodic sequential waves at ≥1 Hz and an unequivocal pattern (gradual increase or decrease ≥ 1 Hz)" by the ACNS (88). Ictal-interictal continuum patterns, as distinguished from electrographic seizures, consist of periodic and rhythmic patterns occurring at a frequency of 1 to 2.5 Hz (or interictal patterns at a frequency < 1 Hz without additional features) (89). NCS and NCSE are defined by the Salzburg criteria: epileptiform patterns occurring at > 2.5 Hz, concomitant subtle clinical accompaniments, or spatiotemporal progression (at least

one of the criteria for 10 seconds in NCS and for 30 minutes in NCSE) (90). A conventional EEG recording demonstrating an absence of seizures during the first 30 minutes predicts a relatively reduced risk of subsequent seizures, but a 24-hour continuous EEG (cEEG) recording detects 95% of critical events (91,92). Synchronized video recording is recommended to identify artefacts and obtain additional information in case of seizure (93). Anti-seizure medication refractory seizures, predominantly non-convulsive, and epileptiform activity are associated with unfavourable recovery and survival prognosis (94,95).

3.2 Quantitative EEG

qEEG provides an extensive characterization of TBI-induced neural alterations through high-resolution quantitative measurements of cortical activity (time-domain resolution in milliseconds and spatial-domain resolution around 1cm) (25,45). As quantitative signal analysis provides higher clinical sensitivity, specificity and reliability in TBI than visual inspection (for non-epilepsy evaluation), qEEG is considered a valuable advance (45,51).

The power spectral density analysis (i.e., alpha, beta, delta and theta bands power spectrum) measures the modulation of the spectral dynamics across the cortex after TBI (96,97). Power spectrum changes in TBI include a reduction of power in the higher frequency bands, suggesting injury to the cortical grey matter, and an increase of power in the lower frequency bands, linearly related to the severity of white matter injury (45).

Coherence and phase-lag reflect topographic inhomogeneities (corresponding to the known features of cortical cytoarchitecture and cortico-cortical axonal fibre systems)

(53). The extent of grey and white matter lesions (particularly in the frontal and temporal regions) is linearly related to coherence and phase-lag changes, considered useful indicators of neuronal alteration and recovery prognosis in TBI (especially since coherence and phase lag are not particularly sensitive to drug effects) (45,51,60).

Entropy and complexity are analogous measures of information processing reflecting local dynamic cerebral properties (25,98). More precisely, entropy refers to signal distribution variability and complexity refers to the number of independent oscillatory signal components (99,100). Applied to TBI, entropy and complexity characterize the neuronal alteration induced by trauma and the cerebral reorganization induced by recovery (98).

Functional connectivity, considered a crucial parameter in TBI, measures the functional network disruption (reflecting structural damage) as well as network reorganization (reflecting neuronal plasticity) (101,102). Network disruption implies an increase in lower frequency bands interactions and a decrease in higher frequency bands interactions, whereas network reorganization leads to a reduction of delta band-based connections and an increase of alpha band-based connections (frontal reorganization correlated with cognitive recovery) (45). As a topological representation of spectral network connectivity, graph theory provides a framework to investigate network functional segregation, related to local information processing (i.e., connection density among subnetworks), and network functional integration, related to global information processing (i.e., joint processing of specialized information across subnetworks) (103,104). Graph metrics underlying functional connectivity analysis include clustering coefficient (related to local efficiency), path length (related to global efficiency), and degree (or strength) distribution (relative frequency of connections between nodes across the network) (99,105). Characterization of complex brain networks, through

graph theory, uncovers altered functional connectivity of cortical networks in neurological disorders, especially in the context of TBI (99,103). More specifically, traumatic brain injury impairs the ratio of local to long-distance functional connectivity (99).

Integrative disruption of neocortical function is predominantly induced by parietal and frontal alterations (106,107). In addition, acute focal network alterations can affect the global performance of brain networks (107,108). Figure 8.2 represents the functional connectivity patterns in alpha, theta, and delta frequency bands among a healthy control, mild TBI, moderate TBI and severe TBI patients. The electrical activity was recorded by high-density qEEG (256 electrodes) and the functional cortical connectivity was analyzed by graph theory (109). According to graph theory, the topological organization of spectral network connectivity is represented as a graph with nodes representing regions and edges representing the functional connectivity between the nodes (110). Functional connectivity strength decreases in the high-frequency alpha band but increases in low-frequency theta and delta bands according to TBI severity with an (expected) inversion of connectivity strength between alpha frequency band in the control subject and theta frequency band in the severe TBI patient.

>> Figure 8.2 Alpha, theta, and delta frequency bands connectivity networks topographs among a healthy control, mild TBI, moderate TBI and severe TBI patients (original data).

Mapping: The degrees of nodes involved in the network are represented by the colour of the arcs from green (low degree) to red (high degree). The strength of the connectivity between nodes is represented by the height of the arcs. *Demographics:*

control (28 years old, female), mild TBI (30 years old, male, sport-related TBI, 38 days post-injury), moderate TBI (41 years old, male, assault-related TBI, 89 days post-injury) and severe TBI (75 years old, male, work-related TBI, 26 days post-injury). *Results:* Mild TBI revealed a subtle decrease in alpha and theta frequency bands strength as well as a slight increase of delta frequency band density compared to control. Moderate TBI revealed a decrease in alpha frequency band strength (overlapping with mild TBI) but an increase in theta and delta frequency bands strength compared to control. Severe TBI revealed a striking decrease in alpha frequency band strength (almost no activity) accompanied by a substantial increase in theta and delta frequency bands strength compared to control, mild TBI and moderate TBI.

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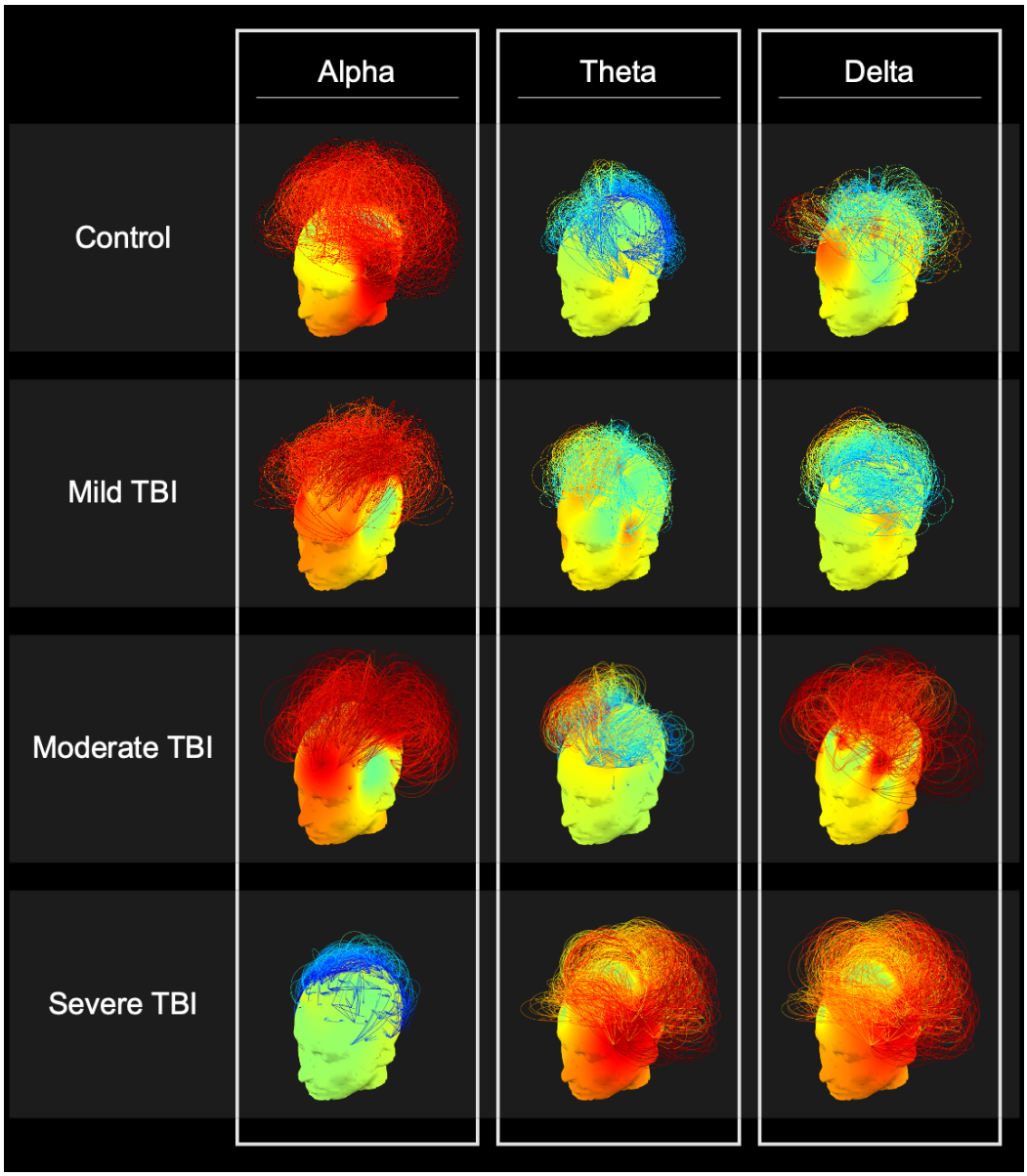

Clinical application of qEEG is therefore relevant for TBI diagnosis, discriminating classifications, prognosis, and monitoring response to therapeutic interventions (22,111). From a multimodal perspective, qEEG provides additional insight in conjunction with clinical and neuroimaging investigations (56).

3.2.1 Mild TBI

Mild TBI qEEG changes commonly involve a reduction in posterior alpha band power, anterior-posterior spectral power differences, coherence across left-right hemispheres and phase between frontal and fronto-temporal regions as well as an increase in beta, delta and theta bands power, the theta/alpha ratio, left-right hemispheres power asymmetry, and coherence across frontal and fronto-temporal regions (56,112). Electrophysiological recovery is associated with clinical symptom resolution but may extend longer than the clinical recovery, expected within weeks post-injury (65). The neural baseline recovery process, as reported by qEEG, consists of a progressive return to the initial dominant alpha frequency accompanied by intermittent dysrhythmias within 6 months post-injury (66,99). Delayed electrophysiological recovery is reported in cases of cumulative functional impairment due to recurrent mild TBI resulting in increased entropy reduction in temporal, parietal and occipital regions (113,114).

PPCS qEEG changes, reflecting residual brain impairment, involve a decrease in global relative alpha band power, in interhemispheric coherence (fronto-parietal, fronto-temporal and temporo-parietal regions) and in entropy across occipital, temporal and central regions as well as an increase in global relative theta band power (4,115,116). Persistent cognitive symptoms suggest a residual slowing in left temporal region (65,117). Severity and persistence of PPCS are predicted by slow electrophysiological recovery process (117).

According to the current literature, qEEG complements recommended assessment procedures such as computed tomography scan (CT scan – typically negative in mild TBI due to the absence of visible structural lesions) (118,119). Research involving large sample sizes demonstrate the accuracy, sensitivity, and specificity of qEEG parameters (such as coherence, phase, and amplitude difference) in discriminating

mild TBI patients from controls and severe TBI patients (as detailed previously) (15,99). Although promising for the diagnosis of mild TBI, the prediction of PPCS is still under-documented (112,113). Insufficient standardization in acquisition and analysis prevents any recommendation supporting the clinical value of qEEG in mild TBI and PPCS (113). Another consideration is the limitation of qEEG in differentiating mild TBI from other diagnoses and reliably detecting mild TBI in the presence of central nervous system medications (113). More research addressing the above considerations is required to implement qEEG in the clinical investigation of mild TBI and PPCS (112).

3.2.2 Moderate TBI

Moderate TBI qEEG changes refer to intermediate values (between mild and severe TBI) among raw and relative power, coherence, phase, and amplitude asymmetry (70). Decreasing changes relate to alpha and beta bands power (decrease of high-frequency oscillations in occipital areas) (69,120,121). Increasing changes relate to theta, delta and beta bands power (increase of low-frequency oscillations in frontal areas and high-frequency oscillations in central areas), entropy, signal complexity but also rhythm variability (i.e., spatial and temporal dynamics of rhythmic variations) (69,120,121). Reported changes in beta-band power depend on experimental settings, severity of injury, acute or chronic conditions, rehabilitation efficacy, and trauma-related complications (120). Decrease in beta-band power indicates advanced moderate TBI (especially in the acute stage) and cognitive impairment, whereas increase in beta-band power, entropy, and complexity reflect compensatory neural activity (120). Low relative alpha power, mean amplitude and spectral edge frequency 90% (i.e., frequency below which 90% of the power resides) were associated with

unfavourable recovery and survival prognosis after moderate TBI (also applies to severe TBI described hereafter) (121). Residual daytime sleepiness and fatigue after moderate TBI recovery correlate with higher delta- and theta-band power (120). Although promising for the detection of acute and residual electroencephalographic changes as well as for the prediction of neurological recovery (to a lesser extent), qEEG is not formally recommended in moderate TBI. The current standard to determine the severity of moderate TBI consists of CT scan and MRI (122). However, limited resources in clinical settings result in delayed access to neuroimaging and repeated radiation exposure to reassess TBI also raises concerns (69). qEEG is proposed as a potential alternative for early screening and identification of moderate TBI, especially in the emergency department and intensive care unit, yet the application of the technique for this purpose is constrained by a notable scarcity of studies (69).

3.2.3 Severe TBI

Severe TBI qEEG changes commonly involve an increase in theta and delta frequency bands power spectrum, a deregulation of coherence and phase synchronization between regions, and a reduction in alpha frequency band power spectrum (45,51). qEEG deviations (from normative references) correlate with the severity of traumatic neuronal alterations and with clinical impairments (51). Dynamic spectral characteristics underlie the identification of dysfunctional brain structures, and the determination of local cortical injury area and the general path of traumatic injury development (123). Spectrum features are considered predictors of consciousness level in severe TBI patients with DoC (123–125). The spectral power and variability predict clinical outcomes within the first year post-TBI (126,127). Alpha power, fast

theta power variability, and alpha power variability are associated with favourable outcomes, whereas loss of alpha power variability is indicative of unfavourable outcomes (alpha coma) (128). Thalamic and basal ganglia lesions as well as diffuse oedema are associated with reduced alpha power variability (126). The clinical relevance of qEEG application in severe TBI resides in the quantification of trauma-induced neural deviations, whereas conventional EEG is restricted to the detection of cortical activity deviations (22). The quantification of neuronal alterations provides extensive information on the characterization of severe TBI, considering the wide heterogeneity of traumatic injuries compared to anoxic injuries for example (129). (93,128). Also, qEEG computer technology provides artefact rejection algorithms (in contrast to conventional EEG), which is of particular interest regarding the various artefact sources present in intensive care environments (required for the acute management of severe TBI) (93,128).

Considering the extensive and heterogeneous literature in DoC, qEEG changes induced by severe brain injury indicate local and global electrogenesis downregulation affecting the level of consciousness (130) – for an overview of qEEG changes in DoC, see (131). DoC-related qEEG changes consist of a decrease in alpha spectral power, entropy, phase-lag, complexity, network connectivity, and fast-alpha microstates as well as an increase in delta spectral power, power ratio index and delta, theta and slow-alpha microstates in UWS compared to MCS (63,132–137). Interestingly, spectral and connectivity analysis holds particular relevance for complementing an ambiguous clinical diagnosis by revealing covert consciousness through alpha activity preservation (132). Regarding recovery and survival prognosis, alpha and fast-theta spectral power as well as increased entropy, coherence and functional connectivity are associated with favourable outcomes, whereas delta and slow-theta spectral power,

theta and delta microstates (depending on duration and frequency) as well as decreased entropy, coherence and functional connectivity are associated with unfavourable outcomes (109,131). As described above, the clinical interest of qEEG in DoC relates to the differential diagnosis of UWS and MCS (including covert consciousness detection) as well as in the prognosis of consciousness recovery and survival. In particular, high-density qEEG is supported by the EAN to differentiate UWS and MCS as a complement to behavioural assessment in patients without command-following at the bedside (85). The pathophysiological mechanism underlying DoC in severe brain injury, as proposed through the mesocircuit hypothesis, relies on widespread neuronal deafferentation (i.e., disruption or disconnection of afferent neuronal inputs) across the thalamo-cortical system (138,139). As complete or near-complete neuronal deafferentation is commonly found in severe anoxic injury, most trauma-induced DoC arise with partially preserved thalamo-cortical connections (76). Neuronal reafferentation (i.e., restoration of afferent neuronal inputs) during recovery from DoC systematically involves the anterior forebrain microcircuitry and the frontoparietal network (progressive reemergence of connectivity hubs in frontal and parietal regions consistent with neuroimaging evidence) (139). The spectral-based classification of thalamo-cortical deafferentation patterns in DoC, referred to as the "ABCD model", provides a framework to investigate thalamic and neocortical functional integrity from channel-level EEG dynamics (78,140). As schematically illustrated in figure 8.3, the "ABCD model" infers complete neuronal deafferentation (A-type, spectral power concentration < 1 Hz), severe neuronal deafferentation (B-type, spectral power concentration between 5 - 9 Hz), moderate neuronal deafferentation (C-type, coexisting spectral power concentrations between 5 - 9 Hz and 20 - 35 Hz) and normal neuronal profile (D-type, coexisting spectral power concentrations between

8 - 13 Hz and 20 - 35 Hz) (78,139). The expected central thalamic and neocortical activity consists of thalamic neurons quiescence with slab-like neocortical dynamics in complete deafferentation or with intrinsic oscillations in severe deafferentation, thalamic activity bursting with high-frequency neocortical activity (driven by thalamic bursting) in moderate deafferentation, and thalamic activity toning with specific neocortical cell types depolarization (e.g., fast rhythmic bursting) (78,139). Behavioural correlates associate complete deafferentation with coma and UWS, severe deafferentation with UWS and MCS, moderate deafferentation with MCS and confusional state, and normal neuronal profile with confusional and healthy states (139,141). Recovery from UWS or MCS to higher levels of recuperation (including confusional and healthy states) is typically associated with normal neuronal profile restoration (139,142).

>> Figure 8.3 Spectral-based thalamo-cortical deafferentation patterns in DoC (“ABCD model”) proposed by Schiff (2016) (78,143). The A-type indicates neocortical neuron membrane hyperpolarization marked by delta frequency oscillations restricted to 1 Hz, reflecting complete (or nearly complete) thalamocortical deafferentiation. The B-type indicates neocortical neuron membrane depolarization marked by theta frequency oscillations from 5 to 9 Hz, reflecting severe thalamocortical deafferentiation. The C-type indicates a partial restoration of neocortical membrane potentials along with deafferented thalamic neurons firing (i.e., thalamocortical dysrhythmia) marked by co-existing theta frequency oscillations from 5 to 9 Hz and beta frequency oscillations from 20 to 35 Hz, reflecting moderate (or partial) thalamocortical deafferentation. The D-type indicates normal neocortical neuronal firing pattern marked by alpha frequency

band oscillations from 8 to 12 Hz with peaks in higher frequencies, reflecting recovery of functional interactions between the thalamus and the cortex).

Adapted from Presse Médicale, 52(2), Schiff ND, Mesocircuit mechanisms in the diagnosis and treatment of disorders of consciousness, Copyright (2023), with permission from Elsevier.

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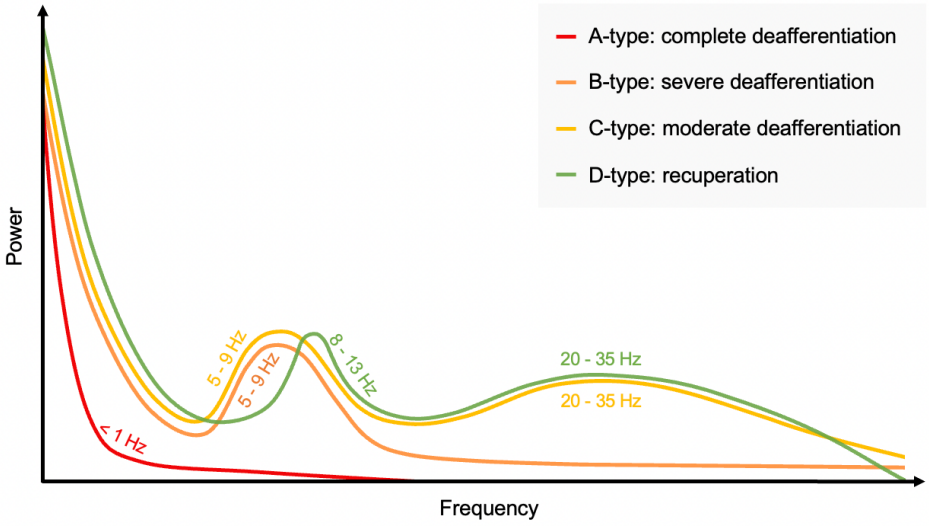

3.2.4 Discriminant classification

Multiparametric discriminant indexes, including the EEG severity index, the brain function index and the Seville Independence Index, support the classification of TBI severity based on the aggregation of the above-mentioned qEEG parameters – for an overview of qEEG discriminant functions, see (99). The EEG severity index (based on relative power, total power, coherence, phase, and amplitude asymmetry) discriminates between controls and mild TBI with an accuracy of 95% as well as between mild and severe TBI with an accuracy of 96%, sensitivity of 95%, and specificity of 97% (higher multivariate contribution of coherence, phase, and amplitude) (53,70). The discrimination of moderate TBI, based on the linear severity hypothesis, relies on intermediate index between mild and severe TBI (70). The brain function index (based on coherence, phase synchrony, power ratios, complexity, and changes

in alpha power activity) correlates with the severity of functional impairment in mild TBI/concussion population (144). The Seville Independence Index (based on coherence, phase-lag, absolute amplitude and absolute asymmetry) discriminates the level of functional dependence with an accuracy of 100% from independence to complete dependence, respectively correlated to mild TBI and severe TBI (99,145). The discrimination of the functional dependence level is clinically valuable to predict the required level of care during rehabilitation (99).

3.3 Event-related potentials

ERPs complement resting state EEG by investigating (with a high temporal resolution) sensory, cognitive, and motor information-processing pathways, typically impaired in TBI due to neuronal resource depletion (30,146). In particular, stimulus- and response-locked potentials provide temporal insight into disruption of activation- and response-related neural processes (30,146). Short-latency components (elicited within 50 ms of the stimulus) reflect brainstem and subcortical processing integrity whereas long-latency components (elicited over 50 ms after the stimulus) reflect subcortical and cortical processing integrity (147,148).

The traumatic impairment of neural resources allocated to information-processing, as evidenced by reduced amplitudes and/or delayed latencies, is predominantly documented through N100, mismatch negativity (MMN), N2b, P3a, P3b, error-related negativity (ERN), and post-error positivity (Pe) components (30). Figure 8.4 provides a spatio-temporal representation of relevant ERP components in TBI. N100 reflects sensory and attention processing (negative deflection peaking in fronto-central regions between 90 and 200 ms after stimulus onset) (27,30). MMN (or N2a) reflects the

automatic process involved in deviant stimuli detection within a sequence (negative deflection peaking in frontal and temporal regions between 150 and 250 ms after stimulus onset) (27,149). N2b reflects stimulus orienting, stimulus relevance recognition, and deviance conscious detection (negative deflection peaking in fronto-central regions approximately 200 ms after stimulus onset) (27,30). P3a and P3b reflect attention and memory processing (positive deflections peaking in frontal regions between 250-300 ms after stimulus onset for P3a and in temporo-parietal regions approximately 300 ms after stimulus onset for P3b) (27,30). ERN reflect error- and conflict-related processing (negative deflection peaking in fronto-central regions approximately 100 ms after incorrect response to attentional task) (30). Pe (subsequent to ERN component) reflects conscious error recognition and post-error adjustments (positive deflection peaking in centro-parietal regions between 100 and 400 ms after incorrect response) (30,150).

>> Figure 8.4 Relevant ERPs components in TBI. The two-dimensional plot considers components latency on the x-axis and components amplitude polarity on the y-axis: stimulus onset triggers the plot including N100, MMN (or N2a), N2b, P3a and P3b components whereas incorrect response to the attentional task triggers specifically the plot including ERN and Pe components. The topographs indicate the prominent regional distribution of components. *ERPs:* event-related potentials, *MMN:* mismatch negativity, *ERN:* error-related negativity, *Pe:* post-error positivity.

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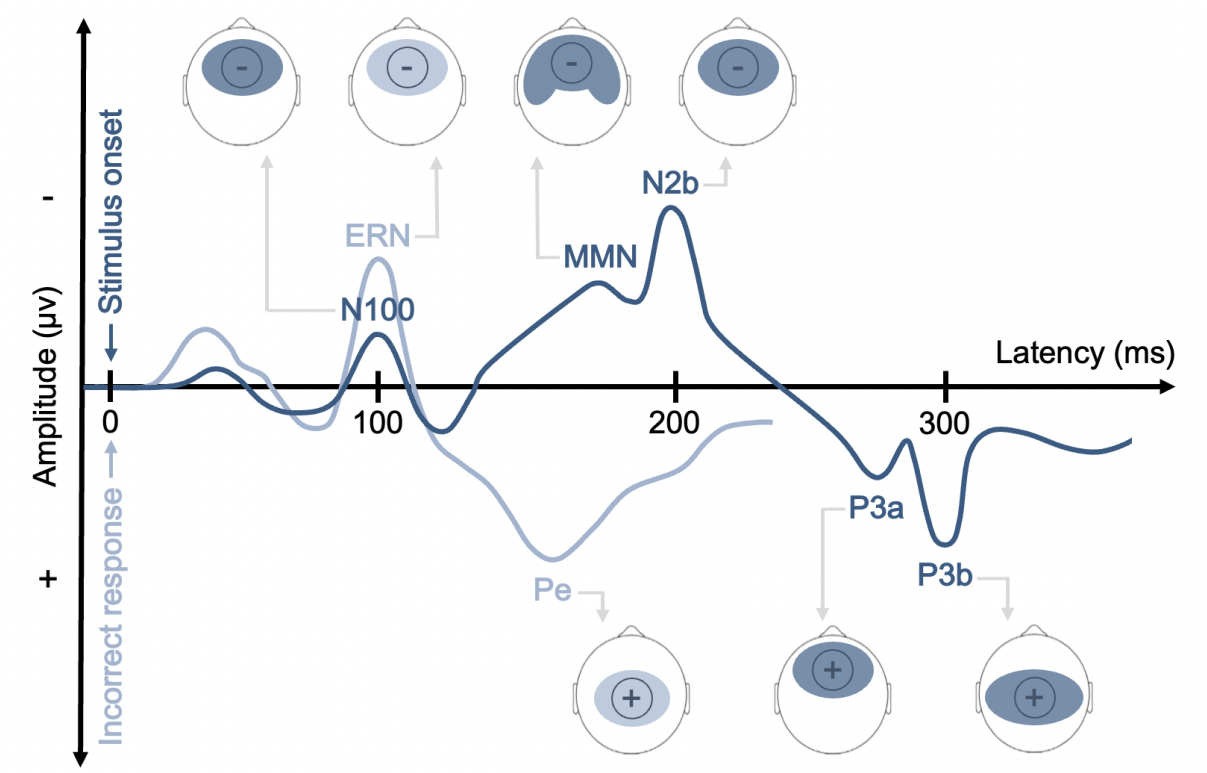

Multi-modality ERPs, including short-latency and long-latency ERPs, are recommended in TBI to enhance diagnostic and prognostic accuracy considering the heterogeneity of traumatic injury (especially in severe TBI) (147,149). Long-latency ERPs should be applied routinely in TBI (including in mild TBI) as reflecting the extent and severity of cerebral dysfunction (more than short-latency ERPs) (149). Considering the particular sensitivity of auditory processing in TBI due to the vulnerability of temporal structures to trauma, auditory ERPs should also be applied (148). The prognostic value of ERPs is supported by N100, MMN, P3a and P3b components (higher prognostic value of ERPs in trauma than in anoxia) (30,149). Bilateral absence of ERPs and short-latency ERPs alterations (as typically induced by severe brainstem injury) are associated with unfavourable recovery prognosis, whereas the presence of cognitive ERPs in a comatose state is associated with consciousness recovery and covert consciousness (30,147). As a complement to

neuroimaging techniques (i.e., CT scan and MRI), ERPs contribute to define the locus and extent of injury by identifying component sources (i.e., source reconstruction) (30,148). In particular, auditory cortex or auditory association cortex injury results in reduced amplitude (i.e., auditory P3a, N100 and, N200) and delayed latency (i.e., auditory N200 and, P3b) of auditory components (148,151), whereas visual cortex or visual association cortex injury induces reduced amplitude (i.e., visual N200 and P3b) and delayed latency (i.e., visual P3b) of visual components (30,148).

Transcranial magnetic stimulation (TMS) combined with high-density EEG (TMS-EEG) provides insight into cortical and cortico-spinal excitability and connectivity by eliciting TMS-related potentials (152). The magnetic perturbation (as induced by single or paired TMS pulse) triggers depolarization of neurons in the targeted cortex and subsequent transsynaptic propagation of the generated potentials along cortical and corticospinal neural pathways (e.g., TMS targeting primary motor cortex generates contralateral muscle contraction in response to the depolarization of corticospinal tract neurons) (153). TMS-induced potentials provide an extensive characterization of information-processing pathways by revealing cortical interactions related to sensory, cognitive and motor processing (in conjunction with sensory, cognitive and motor ERPs) (152). Applied to TBI, TMS-EEG provides valuable information on the extent of cortical and cortico-spinal axonal damage as well as on functional recovery (presumed to relate to cortical excitability normalization and cortico-spinal connectivity restoration) (154,155). Particularly relevant for patients with DoC, the investigation of brain response complexity to TMS perturbation provides insight into thalamo-cortical integration and differentiation (16). Complex and rapidly changing activity patterns (i.e., functional differentiation) involving a distributed set of cortical areas (i.e., functional integration) in response to TMS underlie consciousness preservation, whereas local

(i.e., loss of integration) and/or stereotyped (i.e., loss of differentiation) response to TMS underlie consciousness alteration (16,156). Considering the theoretical risk of TMS-induced seizures in TBI, even if estimated to 1 application out of 1000, post-traumatic epilepsy represents a relative contraindication and a frequent exclusion criterion in experimental protocols (154,157).

Although considered clinically relevant for diagnosis and prognosis, the application of ERPs in TBI still requires technical standardization and results replication to qualify as a standard clinical practice due to substantial intra-individual variability across TBI patients as well as notable inconsistencies in paradigms and results across studies (30,147,148). The clinical application of ERPs is therefore not specifically addressed here for mild, moderate, and severe TBI due to current limitations in the literature.

3.4 Magnetoencephalography

As an emerging technique in TBI, MEG provides insights into mild TBI diagnosis (mild TBI detection rate of 87% based on the amount of 1-4-Hz activity) and treatment response monitoring (i.e., rehabilitation and specific therapeutic interventions) through resting state MEG rhythm (abnormal low-frequency neuronal activity among specific regions) and functional connectivity (altered connectivity between regions), as well as task-related (e.g., language-related or spatial task) reaction time (delayed) and activation sequences of regions (disorganised) (15,34,158) – for an overview of MEG changes in TBI, see (158). Resting state and task-related MEG appears particularly sensitive for detecting subtle neuronal injury (more sensitive than CT-scan, structural MRI and single photon emission computed tomography) (158).

TBI-related conditions are also investigated through MEG, including PPCS to detect residual functional alterations potentially explaining post-concussive symptoms (post-concussion symptom scores are positively correlated with the extent of cortical regions generating abnormal MEG slow-waves and in particular, slow-wave generation in prefrontal areas are correlated with personality change, concentration deficit, affective lability, and depression symptoms), post-traumatic epilepsy to localize cortical sources and propagation of epileptiform spikes, and DoC to analyse the dynamic properties of source activations notably during sensory processing (slow evoked magnetic fields and gamma band activity, indicating partially preserved but delayed and incomplete dynamic cerebral activity in UWS) (4,34,159–161). Importantly, abnormal slow-frequency/delta neuronal activity is not specific to head injury and is also present in neurological/psychiatric disorders including infarcts, epilepsy, cerebral tumours, Alzheimer's disease and schizophrenia (161). Although predominantly applied in TBI research, MEG holds the potential to translate into clinical practice for TBI provided that the limitations of current research are overcome (158,162).

4. Concluding remarks

The overview of resting state EEG and ERPs in mild to severe TBI provided through this chapter outlines the neurophysiological contribution to the diagnosis of neuronal alterations as well as to the prognosis of recovery and survival (Table 8.6), as well as to the monitoring of trauma-related conditions (including PPCS, post-traumatic epilepsy and DoC), and control of therapeutic interventions. Conventional EEG is relevant for diagnosis and prognosis of severe (acute) TBI, detection of preserved consciousness in DoC and investigation of post-traumatic seizures (including seizure

onset and duration, as well as location and type of epileptic activity). qEEG provides a valuable characterisation of TBI-induced neural alterations for diagnosis of mild, moderate, and severe TBI, prognosis of moderate and severe TBI as well as identification of residual alterations in PPCS (i.e., potential neural signatures of persistent symptoms such as migraines or attentional disorders), differentiation of UWS versus MCS in DoC, and classification of TBI severity (discriminating controls, mild and severe TBI). Multi-modality ERPs, integrating short- and long-latency ERPs, may complement resting state EEG to enhance TBI diagnostic and prognostic accuracy. MEG presents a particular value for the diagnosis and prognosis of mild TBI, the identification of specific neural patterns associated with PPCS, and the investigation of post-traumatic seizures (particularly for source localization of epileptic activity as a complement to EEG) through the detection of subtle neural alterations.

>> Table 8.6 Relevant neurophysiological techniques for TBI diagnosis and prognosis. The level of evidence provided by the literature (covered in sections 3.1, 3.2, 3.3 and 3.4) is defined as follows: no supporting data (-), heterogeneous data (+/-), supporting data (+) and highly supporting data (++). EEG: electroencephalography, qEEG: quantitative EEG, ERPs: event-related potentials, MEG: magnetoencephalography.
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	Diagnosis evidence			*Prognosis evidence*		
	Mild TBI	*Moderate TBI*	*Severe TBI*	*Mild TBI*	*Moderate TBI*	*Severe TBI*
Conventional EEG	+/-	-	+	-	-	+
qEEG	+	+	++	-	+	++

ERPs	+	+	+	+	+	+
MEG	+	+/-	+/-	+	-	-

Multimodal application of neurophysiological techniques including conventional EEG, qEEG, ERPs, and potentially MEG, holds the potential to improve individualized assessment and treatment planning in TBI. Figure 8.5 suggests a stepwise multimodal approach to neurophysiological techniques application in prolonged DoC related to TBI, integrating objective markers of thalamocortical integrity and adapted therapeutic interventions. The prolonged phase of DoC, corresponding to the clinical transition from intensive care to rehabilitation (28 days from injury up to 12 months for traumatic aetiology), represents a critical timeframe for synergistic combination of neurophysiological techniques (16). From the suggested procedure, unresponsive patients are oriented from conventional EEG to ERPs, qEEG, TMS/EEG and then BCI or neuromodulation interventions. This multimodal perspective underlines the interest of such neurophysiological recording techniques in the context of precision medicine.

>> *Figure 8.5* Multimodal procedure for neurophysiological techniques in prolonged DoC following TBI. Conventional EEG (first-line technique) classifies EEG background as “normal or mildly abnormal with preserved EEG reactivity” (favourable pattern - *represented in green*), “moderately or severely abnormal” (indeterminate pattern - *represented in yellow*) and “low voltage” (unfavourable pattern - *represented in red*). An indeterminate pattern presents an unclear prognostic significance, but preserved EEG reactivity suggests an increased recovery potential. An unfavourable pattern orients the follow-up towards longitudinal neurobehavioral assessment (until the chronic phase). ERPs (second-line technique) characterize residual sensory and

cognitive abilities (inaccessible to neurobehavioral assessment) in favourable pattern and indicate preservation of residual MNN or P3, suggesting an increased recovery potential, in indeterminate pattern. qEEG (third line technique) provides consciousness probability screening: high probability of consciousness promotes intensive rehabilitation to restore communication (notably through BCI technique) whereas intermediate and low probability of consciousness redirects to perturbational technique. TMS-EEG (fourth-line technique) provides a complexity-based stratification: high complexity promotes intensive rehabilitation to restore communication whereas low complexity redirects to neuromodulation interventions (along with longitudinal follow-up until a targeted endpoint, such as increased probability of MCS classification through qEEG and increased complexity through TMS-EEG). *EEG:* electroencephalography, *ERPs:* event-related potentials, qEEG: quantitative EEG, *MMN:* mismatch negativity, P3: positive deflection with a latency around 300 ms, *TMS-EEG:* transcranial magnetic stimulation combined with EEG, *BCI:* brain-computer interface.

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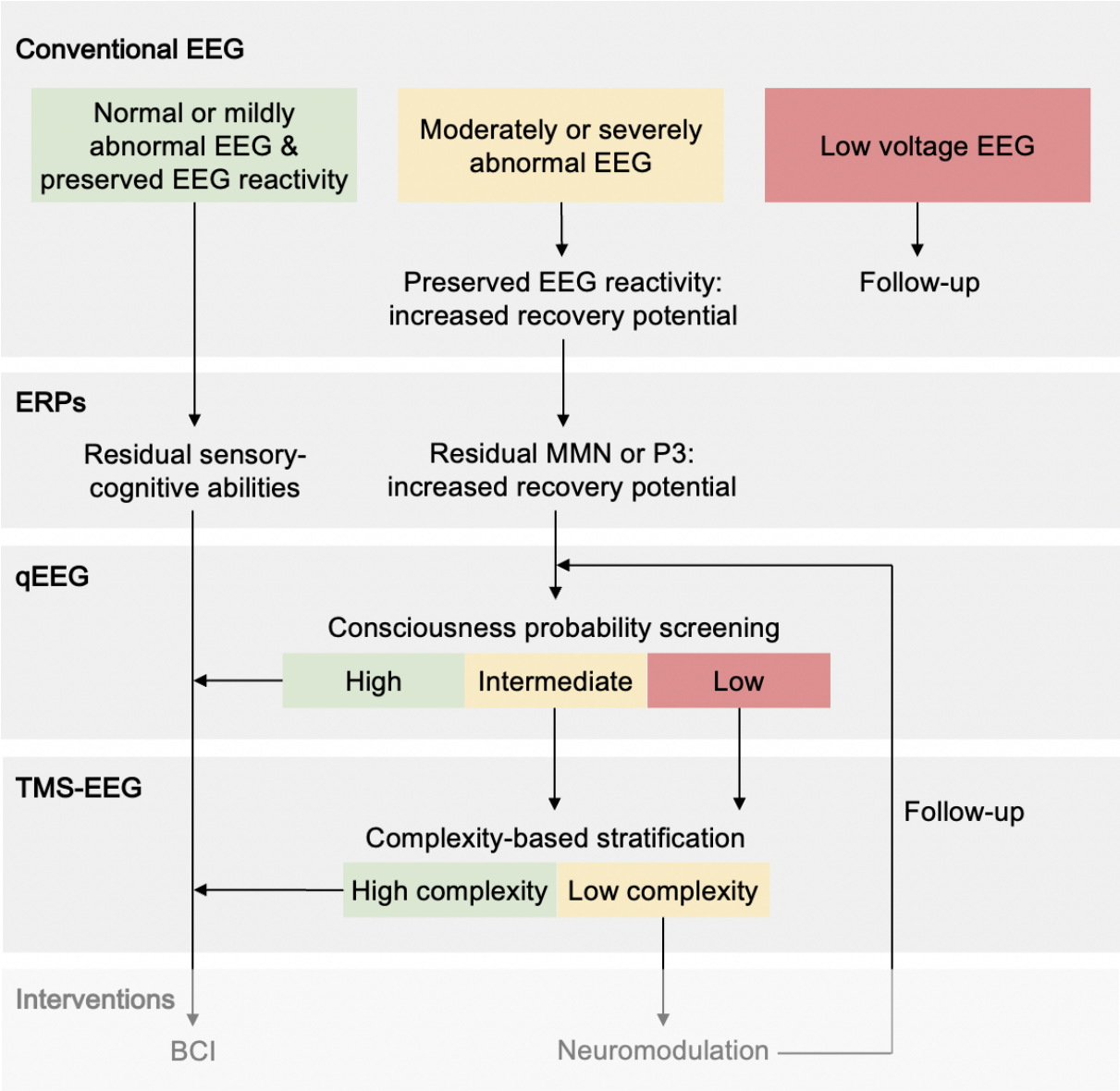

Limitations of neurophysiological techniques in TBI reside in potential confounding factors, including neurological and psychiatric conditions (e,g., post-traumatic stress disorder, depression or anxiety related to TBI), medication (i.e., anaesthetic, analgesic, or anti-epileptic administered as part of TBI management), toxic substances (i.e., alcohol or toxins potentially causing TBI event) and skull defect (i.e., cranioplasty and burr holes inducing breach rhythm) (22,163). Breach rhythm consists of unfiltered high-voltage physiological waveforms (i.e., benign EEG pattern) similar to epileptiform

abnormalities, thus leading to misinterpretation as pathologic epileptiform activity (163).

In conclusion, resting state EEG (i.e., conventional EEG and qEEG), ERPs and MEG represent a clinical cornerstone for diagnosis, prognosis and monitoring of TBI as well as trauma-related conditions that are complementary to neurological assessment, neuroimaging and biofluid techniques. Although the relevance of neurophysiological techniques is undeniable in TBI, further research is required to provide consensus and recommendations for the clinical application of such valuable techniques.

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