clinical and translational neuroscience

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Review

Diagnostic and Therapeutic Approaches in Neurorehabilitation after Traumatic Brain Injury and Disorders of Consciousness

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Abstract: Severe traumatic brain injury (TBI) may cause disorders of consciousness (DoC) in the form of coma, unresponsive wakefulness syndrome (UWS), or minimally conscious state (MCS). Despite significant advancements made over the last two decades in detecting, predicting, and promoting the recovery of consciousness in TBI patients with DoC, the available diagnostic and treatment choices remain limited. In cases of severe TBI, the dissolution of consciousness both in the acute and post-acute phases constitutes one of the major clinical findings and challenges. In clinical settings, neurologists and neurorehabilitation specialists are called on to discern the level of consciousness in patients who are unable to communicate, and to project outcomes and recommend approaches to treatment. Standards of care are not available to guide clinical decision-making for this population, often leading to inconsistent, inaccurate, and inappropriate care. Recent studies refer to network-based mechanisms of consciousness as a more promising method to predict outcomes and functional recovery. A further goal is the modulation of neural networks underlying awareness and arousal as the main components of consciousness. This review centers on the difficulties in characterizing individuals experiencing post-traumatic DoC and on the recent advancements made in the identification and prognostication of consciousness recovery through the utilization of advanced neuroimaging and electrophysiological techniques as well as biomarkers. Moreover, we discuss new treatment approaches and summarize recent therapeutic recommendations.

Keywords: neurorehabilitation; traumatic brain injury; disorders of consciousness

Citation: Lippert, J.; Guggisberg, A.G. Diagnostic and Therapeutic Approaches in Neurorehabilitation after Traumatic Brain Injury and Disorders of Consciousness. *Clin. Transl. Neurosci.* **2023**, *7*, 21. https://doi.org/10.3390/ctn7030021

Academic Editor: Karl-Olof Lovblad

Received: 28 March 2023
Revised: 27 July 2023
Accepted: 4 August 2023
Published: 9 August 2023

1. Introduction

Compared with common neurological disorders worldwide, TBI has the highest incidence and its potential long-term consequences are of major concern for public health [1]. Due to the clinical heterogeneity and complexity of TBI, both initial treatment and rehabilitation constitute a big challenge. Special structural, organizational, and personnel resources of medical facilities are required, as well as close cooperation between participating institutions. The high frequency and extent of impairments in functioning and participation in daily life activities underline the need for neurorehabilitation efforts in TBI patients.

Despite the widespread recognition among clinicians of the importance of suitable post-acute care, only a small proportion of TBI patients receive the rehabilitation services they require [2]. Furthermore, existing evidence indicates that rehabilitation yields greater efficacy when initiated promptly and provided continuously [3]. However, despite cognitive and psychological impairments being reported by approximately one-third of TBI patients, interventions targeting these specific domains were received by only a minority of affected individuals [4].

Longitudinal studies which investigated rehabilitation outcomes spanning up to 30 years after TBI revealed that early and ongoing rehabilitation efforts can solidify the advancements achieved during the acute clinical phase. Furthermore, these interventions

demonstrated potential in reducing hospital stays and alleviating the socioeconomic burden associated with TBI [5,6].

Considerable efforts have been made to establish prognostic models capable of providing risk estimates based on a systematic analysis of empirical data, considering various patient and disease characteristics.

Most prognostic models have been developed for patients with moderate to severe TBI. Among the various models, the International Mission on Prognosis and Analysis of Clinical trials in Traumatic brain injury (IMPACT) [7] and Corticoid Randomisation After Significant Head injury (CRASH) [8] are the most widely used prognostic models and are based on the largest cohorts, consisting of 8509 and 10,008 individuals, respectively.

Despite the widespread acceptance of prognostic models in TBI research, their adoption in clinical practice remains limited. Several barriers hinder their clinical implementation, including the extensive clinical investigations required for prognostic estimates and the predominant focus of these models on predictors assessed at presentation. In contrast, clinicians often take into account the patient's clinical course and progression after admission when making decisions [1].

Currently, the Glasgow Coma Scale Extended (GOSE) is mostly used in depicting functional outcomes, but it falls short of capturing the intricacies of impairments, particularly those stemming from mild TBI. To achieve a more comprehensive assessment, global functional outcome measures should be supplemented with domain-specific instruments. Consequently, various aspects such as persisting post-concussion symptoms, health-related quality of life (HRQOL), depression, and post-traumatic stress disorder (PTSD) have been analyzed in the prognostic context, with a primary focus on patients with mild TBI [9,10].

A recent investigation utilizing data from the CENTER-TBI Core study focused on predicting health-related quality of life (HRQOL) in 2666 adult patients who completed the Quality of Life After Brain Injury-Overall Scale (QOLIBRI) questionnaires at the 6-month mark post-injury. The study revealed that medical and injury-related characteristics played a more significant role in predicting the physical component summary score, whereas patient-related characteristics had greater importance in predicting the mental component summary score and the QOLIBRI scores following TBI [9]. In mild TBI, the prognosis is largely influenced by the individual patient's pre-injury comorbidities and mental health, rather than in cases of moderate and severe TBI. This observation has been validated in the CENTER-TBI and TRACK-TBI studies, which identified pre-injury health factors (including mental health) and socio-demographic characteristics (such as education, employment, sex, race, ethnicity, and home country) as significant predictors of outcomes in mild TBI cases. However, it is essential to note that injury severity remains one of the most powerful indicators of the Glasgow Outcome Scale Extended (GOSE), indicating that the extent of injury impact on the patient is also relevant in determining global outcomes following mild TBI [11–13].

Significant progress has been made in predicting outcomes in TBI through the application of MRI, especially in cases where injuries may not be visible on CT imaging. Both the CENTER-TBI and TRACK-TBI studies reported the presence of structural traumatic abnormalities on MRI in approximately 30% of patients with mild TBI who had a normal CT scan upon presentation [14,15].

The use of advanced MRI techniques, such as diffusion tensor imaging (DTI) and susceptibility-weighted imaging, has proven to be more sensitive in detecting superficial contusions, traumatic axonal injury, and traumatic vascular injury [16,17]. These advancements in MRI technology have significantly improved our ability to identify and characterize TBI-related abnormalities, even when they may not be apparent on traditional CT scans. A recent study demonstrated associations between diffusion abnormalities and various cognitive impairments. Notably, the study revealed significant negative correlations between executive function and structural damage in specific brain regions, such as the corpus callosum, the inferior longitudinal fasciculi, and the middle cerebellar peduncle [18].

Functional MRI (fMRI) [19], MR spectroscopy [19], and electroencephalography (EEG), particularly high-density (HD)-EEG [20], hold the potential to provide supplementary methods for predicting outcomes in TBI. However, these techniques are still in the process of transitioning from research tools to clinically applicable instruments.

Among the technologies to improve the phenotyping of TBI, blood biomarkers have emerged as the most promising candidates for integration into routine clinical care. While previous research primarily concentrated on S100B, recent investigations have explored a group of new brain injury biomarkers (GFAP, NfL, UCH-L1, and tau) in various TBI studies [21].

Taken together, in recent years and due to large observational studies, there has been huge progress in the characterization of TBI, based on advanced neuroimaging and neurophysiological approaches as well as biomarkers [22]. These new diagnostic approaches will facilitate the identification of common disease mechanisms and lead to new therapeutic approaches and improvements in prognosis. However, these advances have not fully entered clinical diagnosis and care. Additional progress is needed in terms of individualized disease management in both acute and post-acute settings.

2. Epidemiology of TBI and Burden of Disease

Former epidemiological studies report a huge variance in the incidence rates of between 979 per 100,000 people in North America and 282.7 per 100,000 people per year in Europe, with considerable variation between member states [23]. Due to methodological variations confounding the comparisons of TBI epidemiology patterns between regions, countries, and continents, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has provided estimates of global TBI incidence by using a standardized approach [24]. Recent data from the GBD study estimated the TBI incidence of 369 per 100,000 people (CI 298-401) worldwide (Global Health Data Exchange (https://ghdx.healthdata.org/gbd-results-tool (accessed on 1 August 2022)).

Measures of disease burden as years of lost life (YLLs) and years lived with disability (YLDs) better capture the socioeconomic consequences of TBI, which goes beyond the incidence and fatality rate. The GBD study estimated that TBI was a cause of 8.1 million YLDs in 2016 worldwide, and data from Europe captured from 16 countries were used to estimate that each TBI death is associated with about 24 YLLs [1].

The highest frequency of hospital admissions for TBI is observed in the older population, aged 65 years and above, followed by children and adolescents [25]. This trend is associated with a rising incidence of TBI in older individuals, surpassing population growth rates in certain countries [26]. Compared to younger age groups, older adults are more prone to experiencing TBI resulting from falls, leading to more severe cognitive and functional impairments [27]. Additionally, they may face an increased risk of functional decline during the post-recovery phase [28].

The age group comprising pediatric and adolescent individuals (ranging from 0 to 19 years) demonstrates the second-highest incidence of hospital admissions due to TBI [29]. In the EU, approximately 345 children or adolescents per 100,000 are admitted to hospitals annually, with around 3 per 100,000 succumbing to TBI, leading to approximately 184 YLLs per 100,000 individuals [29]. In the USA, there are an estimated 1 to 2 million cases of mild TBI in children and adolescents each year, and those with a history of concussion have a four-fold higher risk of experiencing a recurrent concussion [30]. Furthermore, children and young people (aged 5 to 18 years) face significantly elevated risks of mental health problems, psychiatric hospitalization, and self-harm following TBI compared to orthopedic injuries [31]. Although the pediatric and adolescent age group exhibits the lowest overall TBI mortality (constituting about 5% of all TBI-related deaths), the burden of these fatalities remains substantial. In the EU, approximately 3000 TBI-related deaths annually result in nearly 200,000 YLLs [32]. These findings underscore the potential for targeted TBI prevention in this population to yield substantial improvements in quality of life and reductions in YLLs. Moreover, the Lancet Neurology Commission on TBI estimates

tremendous socioeconomic costs of around US $400 billion annually worldwide. The Commission further states, that TBI remains one of the top three causes of injury-related death and disability up to 2030.

Concerning mortality in moderate and severe TBI, the currently available data are inconsistent, varying from 12% to 44% during acute inpatient care [33]. Moreover, 45% to 87% of mortality in severe TBI is due to a withdrawal of life-sustaining therapy during the acute setting and when DoC continues [34–36].

3. Network-Based Mechanisms and Their Dysfunction on Circuitry and Cellular Levels after TBI

TBI mostly induces both localized brain damage and diffuse axonal injury (DAI). Focal injuries arise from direct impact to the head or when the brain collides with the inner surface of the skull, leading to the occurrence of skull fractures or hematomas [37]. Typically, these injuries manifest in specific regions of the brain, including the orbitofrontal, temporal polar, and occipital regions [38].

The pattern of focal brain injuries often demonstrates poor correlation with the clinical impairments observed after TBI [39]. This discrepancy seems to be explained by the presence of DAI which is a prevalent pathological finding across all TBI severities [40,41]. It is nearly ubiquitous in cases of fatal TBI and exhibits a characteristic distribution pattern throughout various brain regions. Particularly severe cases of DAI result in extensive damage, including the corpus callosum and brainstem [42].

Conversely, diffuse multifocal injuries commonly result from rapid acceleration and deceleration forces, causing shear, tensile, and compressive strains. These strains primarily inflict damage on long-distance connections within the white matter through DAI. Additionally, blood vessels can also be affected, leading to diffuse vascular injury [43,44]. Secondary damage can also arise from processes triggered by the initial injury, such as ischemia, elevated intracranial pressure, infection, inflammation, and neurodegeneration [45,46].

Patients with very unfavorable outcomes, such as those in a vegetative state, frequently exhibit damage to the subcortical white matter and/or the thalamic relay nuclei, while cortical damage may be minimal [47]. In contrast, patients with better outcomes show that DAI plays a significant role in determining persistent cognitive impairment, as demonstrated by recent neuroimaging studies [48].

Most studies primarily focusing on the clinical consequences of focal injuries have limited value in predicting clinical outcomes [41]. Questions pertaining to the prediction of clinical outcomes and the recovery of consciousness following severe brain injuries over long-term periods cannot be addressed by examining individual neurons in isolation. To be functionally relevant, information processed at the neuronal level often necessitates integration across various brain regions [49]. Recent research has demonstrated a growing interest in comprehending the organization of brain networks [50]. Emphasis is placed on understanding the disruption of large-scale intrinsic connectivity networks (ICNs), as interactions between these networks are crucial for higher-level cognitive functions such as memory and attention [41]. Furthermore, advancements in neuroimaging techniques have facilitated the examination of these networks in clinical populations [51,52].

ICNs consist of brain regions that exhibit temporally correlated neural activity. The functional architecture of these networks partly reflects their underlying structural connectivity, meaning that regions strongly connected by white matter tracts are likely to possess similar functional properties. This characteristic renders ICNs susceptible to the effects of TBI since DAI often damages long-range white matter tracts that connect nodes within these networks. Consequently, neuroimaging techniques, including fMRI, offer valuable tools for investigating network function in the context of TBI (see neuroimaging and neurophysiological approaches). TBI-induced network dysfunction exhibits intricate patterns and certain underlying principles are becoming evident. These principles can be exemplified by examining the impact of TBI on two well-defined ICNs: the default mode network (DMN) and the salience network (SN) [41].

The DMN comprises brain regions with high metabolic activity and highly coordinated functionality [53]. Its central nodes include the posterior cingulate cortex (PCC) and ventromedial prefrontal cortex (VMPFC). In cases of TBI, various degrees of damage can be observed within the cingulum bundle, a tract encompassing connections between the PCC and VMPFC [54]. This damage is associated with impairments in sustained attention, where patients struggle to maintain focus over time. The extent of damage to the cingulum bundle correlates with worsening attention deficits, which can be predicted by reductions in functional connectivity within the DMN [55]. This observation highlights how damage to ICN connections can disrupt the functional connectivity of the network and impact cognitive functions supported by that network.

Efficient cognitive function relies on coordinated activity between different networks, and abnormal interactions between the SN and DMN are observed following TBI [56]. The SN responds to behaviorally salient external events and appears to signal the need for decreased activity within the DMN [57]. Structural damage to a specific SN tract connecting the right anterior insula to the midline pre-supplementary motor area-dorsal anterior cingulate cortex serves as a robust and specific predictor of the failure to appropriately deactivate the DMN [58].

At the cellular level, compelling evidence indicates that TBI has the potential to initiate neurodegenerative processes, which play a significant role in determining long-term outcomes [59]. TBI can lead to the development of dementias, such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE), with both single and repetitive injuries predisposing individuals to subsequent cognitive decline [60–62]. These findings suggest a prolonged and dynamic element in the pathophysiology of TBI, with interactions among the initial injury, neurodegenerative proteins, and chronic neuroinflammation playing crucial roles [63].

Mechanisms of neurodegeneration following TBI involve the accumulation of amyloid-β plaques and hyperphosphorylated tau neurofibrillary tangles, which are characteristic features of AD [59,63]. Studies in rodents have demonstrated that aggregated tau can initiate the formation of neurofibrillary tangles and spread trans-synaptically from the initially affected brain region to distal but connected areas [64]. The organization of white matter tracts likely constrains the spread of pathogenic proteins, thereby influencing the pattern of neurodegeneration, which may reflect the structure of large-scale ICNs [65].

Neuroinflammation, characterized by the activation of microglia, plays a central role in the neuroinflammatory response to TBI and can persist for months to years after the initial injury [45,66,67]. This persistent neuroinflammation may influence the spread of abnormal proteins and potentially contribute to neurodegeneration following TBI [68]. Neuroinflammatory processes are often observed at the sites of axonal pathology but can also be detected in regions distant from focal injuries as a result of Wallerian degeneration of damaged axons [69].

The relationship between persistent inflammation and the development of neurodegeneration remains unclear, including whether persistent inflammation is a response to pathological features such as amyloid plaques and neurofibrillary tangles or whether unregulated inflammatory responses drive the progression of neurodegeneration [41].

4. Challenges in the Clinical Diagnosis of TBI Patients with DoC

In clinical and research contexts, the Glasgow Coma Scale (GCS) is mostly used to graduate the initial severity of TBI. The simplicity and rapid assessment of the scale led to its international application in the acute treatment setting and is applied both for diagnostic and prognostic applications [70]. The GCS is based on behavioral observations across three subscale scores—eye-opening (score range 1–4), verbal (score range 1–5), and motor (score range 1–6)—that are summed to provide a total score ranging from 3–15 [71]. The total score is intended to reflect the severity of the injury, with scores of 3–8 indicating a severe injury, 9–12 a moderate injury, and 13–15 a mild injury. Moreover, GCS total scores of 3–8 are often used to define coma [72].

However, the GCS total score does not accurately reflect different levels of consciousness and functional outcome at the individual patient level 7.

Previous studies found that GCS subscale scores are more relevant concerning diagnosis [73] and prognosis [74] than the total score. Moreover, different combinations of subscales that sum to the same total score are associated with variable mortality rates [75]. The implication of these findings spans across clinical and research settings where GCS scores are often further collapsed into three broad categories of mild, moderate, and severe TBI. This coarse classification may mischaracterize individual patient prognosis, as evidenced by some "severe" patients having a favorable outcome [76] and some "mild" patients having an unfavorable outcome. In a previously published sub-analysis of the TRACK-TBI study, 53% of 1453 patients classified as mild TBI (GCS score 13–15) reported functional limitations after 12 months [77].

Taken together, global functional outcome measures such as GCS do not precisely characterize the heterogeneous impairments found after TBI. Thus, there is a need for multi-dimensional outcome assessments, which will both better capture the nature of TBI recovery and increase the sensitivity of outcome variables such as residual disability [78].

The recognition that up to 15–20% of patients who appear unresponsive may be covertly conscious [79,80] (i.e., cognitive motor dissociation [81]) has led to a reappraisal of behavioral outcome measures in clinical trials and a search for both clinical assessments for prognostication and new electrophysiologic and imaging biomarkers [82,83].

For the clinical assessment of patients with DoC, standardized neurobehavioral assessments and qualitative bedside examinations should be applied. In an evidence-based review of neurobehavioral rating scales designed specifically for patients with DoC, six scales were identified that seem to be sensitive for detecting conscious awareness [82]. The Coma Recovery Scale-Revised (CRS-R) [84] received the strongest recommendation of those reviewed, on the basis of psychometric properties for clinical assessment [85].

The CRS-R examines all major categories of consciousness in all six domains (Figure 1). These categories are evaluated in a standardized examination protocol. In a clinical setting, the examination should be repeated at regular intervals at least once a week. The individual categories are summed up to a maximum of 23 points.

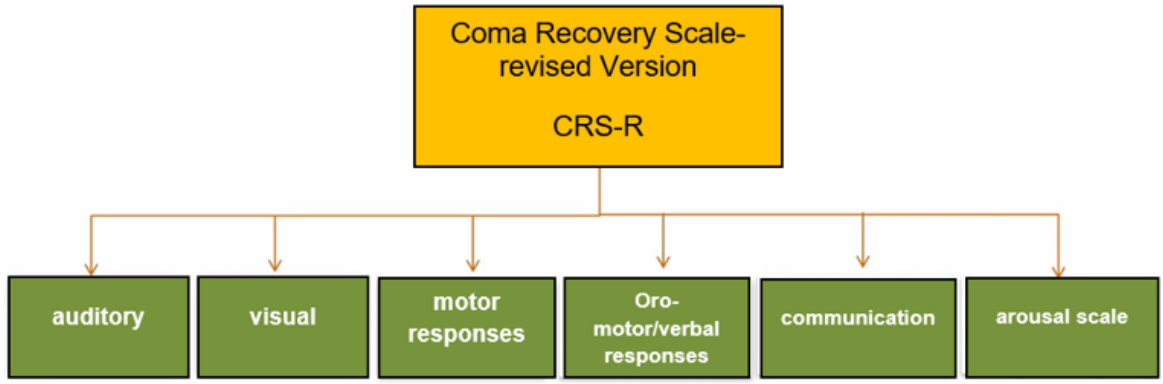

Figure 1. The CRS-R improves assessment of minimal cognitive competencies of patients with severe DoC. The scale uses modality-specific items (auditory, visual, motor, oromotor, and communicative responses) and items related to the patient's activation level. Due to the good item operationalization, the high reliability, validity, and sensitivity compared to the Glasgow Coma Scale (GCS), the CRS-R scale is widely used and internationally recognized.

Prospective studies revealed that an initial score of more than six points on the CRS-R at the beginning of early rehabilitation is a fairly strong predictor of a good outcome [86].

Cognitive motor dissociation represents a relatively new and currently still dynamically changing diagnostic category (Cognitive-Motor-Dissociation, CMD) [81]. Patients with CMD were not able and do not show any intention to communicate despite the most

careful clinical examination. So far, there is no generally accepted terminology for this patient group and apart from CMD, the term "non-behavioral MCS" is proposed [87].

However, the combination of detailed clinical examination and assessment with modern techniques such as fMRI, FDG-PET, and HD-EEG supports the diagnostic procedure of a preserved cognitive and processing ability.

5. Neuroimaging and Neurophysiological Approaches to Improve Diagnosis of Different States of Consciousness

While behavioral assessments of DoC such as the CRS-R remain the gold standard at bedside evaluation, neuroimaging permits objective evaluation of structural CNS damage after TBI. Structural imaging provides additional information concerning diagnosis and prognosis, and can serve as surrogate markers for novel therapeutic interventions. While in the acute setting, CT scanning is preferred because of its accessibility, speed of acquisition, and sensitivity to acute hemorrhage of lesion requiring immediate treatment, it is in general limited in detecting neuronal damage compared to standard MRI imaging.

Previous studies have shown the possible prognostic value of 'classic' structural MRI sequences to predict DoC outcomes; for example, the presence of corpus callosum and dorsolateral brainstem lesions correlates with a lack of recovery at the group level [88].

Moreover, elaborated techniques such as DTI permit the assessment of structural white matter damage. Studies evaluated the DTI-MRI techniques to predict 1-year functional outcomes in patients with TBI [89] or anoxic [90] injury. Thus, these techniques offer an opportunity to quantify the structural integrity of the white matter on an individual patient level and quantify the primary and secondary axonal damage encountered in DoC [91].

5.1. Electrophysiology

In DoC, a standard 10–20 low-density EEG (LD-EEG) is routinely used for diagnostic purposes in the acute setting. Visual analysis of the LD-EEG can identify epileptiform activity, guide treatment, and help establish prognosis, especially in anoxic cases [92,93]. However, visual analysis of standard LD-EEG showing a global slowing of brain activity fails to differentiate between different stages of DoC, such as UWS or MCS. Therefore, HD-EEG which utilizes a higher spatial sampling of scalp electrodes and a higher spatial resolution is a more accurate diagnostic tool to predict recovery in a clinical setting. Currently, using HD-EEG in a clinical routine is impeded by cost, setup and interpretation time, and lack of specific or sufficient procedural billing codes.

Recent clinical studies investigated the sensitivity and accuracy of quantitative EEG (qEEG) and EEG-based functional connectivity to predict clinical outcomes in DoC patients [94,95]. These studies revealed that patients with reactive EEG signals to external stimuli, larger EEG amplitudes, and stronger activity in the higher-frequency bands (i.e., alpha 7–13 Hz and beta 14–25 Hz) are more likely to have a positive outcome after 3–6 months [96,97]. Elaborating techniques such as the use of machine learning approaches integrating EEG biomarkers, HD-EEG-based functional connectivity and clinical outcome parameters advance the accuracy of outcome prediction and may help to classify DoC patients in terms of rehabilitative potentials and functional recovery.

5.2. FDG-PET

Previous studies investigating brain metabolism in DoC patients used FDG-PET imaging techniques. DoC was mostly associated with hypometabolic areas in the lateral and medial frontoparietal associative cortices [98] and functional recovery was characterized by regained activity in the frontoparietal awareness network [99]. Further studies applied elaborated techniques with automated classifiers to analyze FDG-PET data to evaluate outcome parameters and to distinguish between MCS and UWS [100]. Interestingly, FDG-PET studies could not reliably distinguish between MCS and UWS, but group studies revealed that CRS-R total score correlated with metabolic activity in frontoparietal cortex areas [101].

5.3. Functional MRI

Numerous studies performed fMRI measurements based on spontaneous fluctuations of blood oxygen level-dependent effects (BOLD) during a 'resting state' condition and identified various functional networks associated with conscious cognitive activity [102,103]. One of the best-classified networks is the DMN (see network-based mechanisms and their dysfunction after traumatic brain injury) encompassing the posterior and anterior cortical midline structures which are involved in stimulus-independent thought and self-consciousness [104]. The DMN was shown to be absent in brain death [105] but still partially preserved in UWS [106,107], probably reflecting residual structural connectivity [102].

Further fMRI studies investigated the activation of various brain areas after using auditory, tactile, or visual stimuli both in MCS and UWS patients. Though some patients in UWS who exhibited high-level activation in fMRI showed clinical signs of recovery at a long-term follow-up [108,109], the prognostic and diagnostic value of activation patterns in fMRI studies in DoC patients remains controversial. In this respect, further studies which integrate different diagnostic modalities and combine electrophysiological and neuroimaging techniques might help to better understand the neural correlates of consciousness.

5.4. Fluid Biomarkers

Besides neuroimaging parameters, biomarkers have demonstrated their ability to prognosticate late outcomes in TBI patients [110,111]. The CENTER-TBI study identified UCH-L1, S100B, NfL, and total tau as having the greatest incremental value in predicting mortality or unfavorable outcomes [112]. However, it is worth noting that compared to more severe cases of TBI, biomarkers showed reduced predictive capabilities for outcomes in mild TBI cases and for overall incomplete recovery [1].

Biomarkers perform well in predicting CT and MRI positivity compared to clinical decision rules. The combination of GFAP and UCH-L1 has obtained FDA clearance for assisting in the identification of CT-detectable brain lesions within 12 h of mild TBI [113,114]. Moreover, GFAP has shown remarkable predictive capabilities for CT positivity [111,115] and MRI positivity in individuals with normal CT findings [15].

Initial expectations that patterns of biomarker elevation might differentiate focal from diffuse injury [116,117] have not been confirmed, and some data suggest that biomarkers are more correlated with the overall burden of injury rather than with specific pathoanatomical types of TBI [118].

In the context of predicting mortality or unfavorable outcomes, the CENTER-TBI study reported the highest incremental value for UCH-L1, S100B, NfL, and total tau [112]. However, when compared with more severe TBI cases, biomarkers showed reduced predictive abilities for outcomes in mild TBI cases and for overall incomplete recovery [119].

6. Neurorehabilitation of TBI Patients—Established Treatment Options and New Approaches

Despite broad recognition among clinicians of the need for appropriate neurorehabilitation, only a small percentage of TBI patients receive post-acute care. The CENTER-TBI study reported on 1206 TBI patients who suffered from moderate to severe disability 6 months after the incident and approximately 90% of patients had rehabilitation needs. However, only 30% received in-patient rehabilitation, and only 15% received out-patient rehabilitation [6]. Especially in individuals with mild to moderate TBI, the need for post-discharge rehabilitation is often neglected and both TBI patients and their families suffer from a deficiency of both information and post-acute care. In this regard, the CENTER-TBI showed that 90% of centers do not routinely schedule follow-up visits for patients discharged home from the emergency department. Moreover, only 26% of TBI patients received written information or educational material, and only 6% had a follow-up appointment in hospital. Both the CENTER-TBI and TRACK-TBI study revealed that 30% of patients discharged from the emergency department did not attain full recovery after 6 months [120].

Taken together, access to neurorehabilitation and structured follow-up care following TBI remains suboptimal; at the same time, post-acute diagnostic and treatment options for TBI patients, especially those with DoC, are currently limited. Thus, there is a need for increased knowledge about new diagnostic, prognostic, and evidence-based therapeutic approaches and interventions.

Concerning TBI patients with severe DoC, there are neither national nor international evidence-based guidelines for therapeutic interventions available yet. Only in the UK and in the US do current practice recommendations or guidelines exist that include general recommendations for these patients. Those from the American Academy of Neurology (AAN), the American Congress of Rehabilitation Medicine (ACRM), and the National Institute of Disability, Independent Living, and Rehabilitation Research (NIDILRR) include "Practice Guidelines" that emphasize the importance of inpatient multidisciplinary rehabilitation. Moreover, these guidelines emphasize the need for the prevention of secondary complications through early recognition and treatment of medical problems as well as the early detection of available resources. The importance of the diagnosis of the different stages of consciousness applying standardized diagnostic procedures is particularly emphasized, but also the instruction of family members concerning prognosis and evidence-based therapies. The only precise therapeutic recommendation encompasses the usage of amantadin as a pharmacological activation in TBI patients with DoC [121].

6.1. Pharmacologic Therapies

The treatment amantadin was investigated in a placebo-controlled, randomized, double-blind trial in 184 patients 1–4 months after severe TBI [122].

The trial showed a significantly higher rate of behavioral recovery among patients taking amantadine compared to the placebo group.

Besides amantadine, further pharmacologic agents have been used in randomized trials to promote recovery of consciousness in patients with DoC. Dopaminergic drugs have received particular attention because of the widespread expression of dopaminergic receptors in the CNS, including the anterior forebrain mesocircuit, which appears to be essential in the alteration and recovery of consciousness [123,124] (Figure 2).

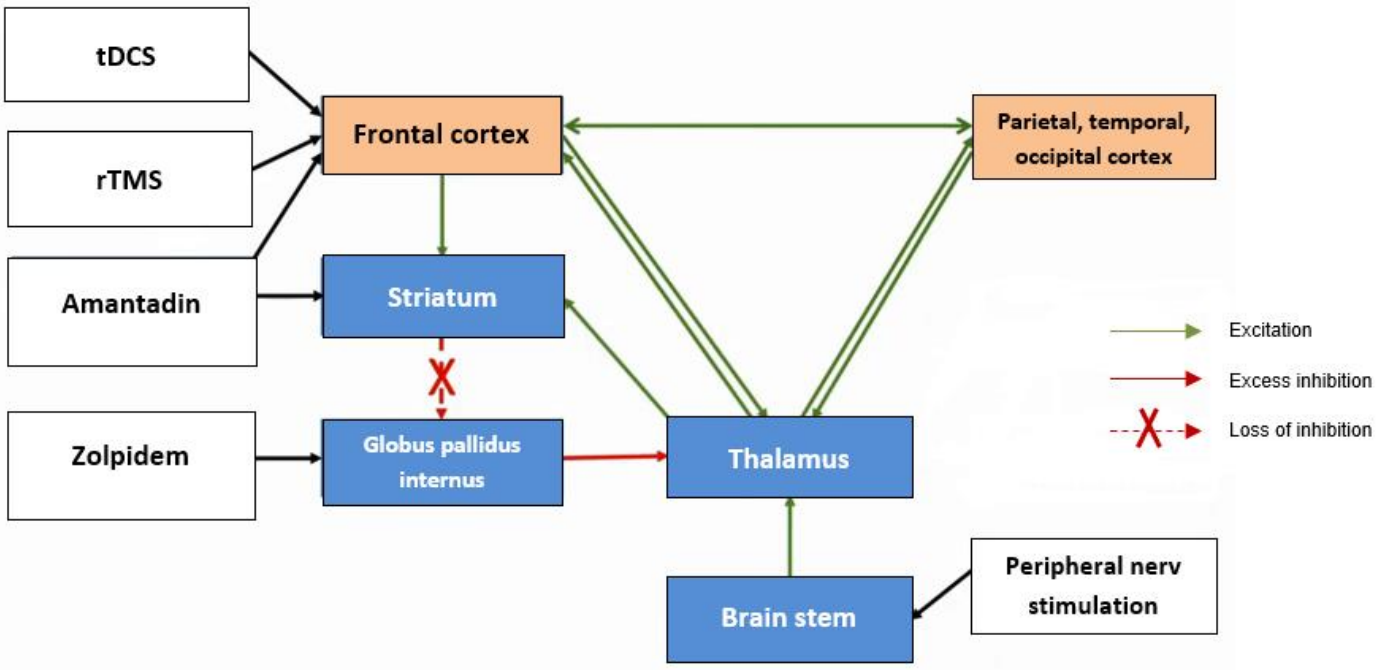

Figure 2. Scheme of the mesocircuit model adapted by Giacino, 2014. The model represents the key anatomical structures for stimulating therapies in severe DoC. The mesocircuit model integrates

neural components that maintain consciousness. The thalamus plays a central role and is activated via a cortico-thalamic loop, in particular via frontal cortex areas, and is inhibited and modulated by inhibitory signals e.g., from the globus pallidus internus. The thalamus activates other cortex areas via feedback loops. In structural brain damage, particularly when neurons in the central thalamus are damaged and afferent input to striatal neurons is lost, inhibitory signals from the striatum to the globus pallidus are inhibited, resulting in an overstimulated pallido-thalamic inhibition which decreases thalamic activity. GABAA α-1 subunit is typically abundantly expressed within the globus pallidus internus. The administration of zolpidem may inhibit the latter, thereby replacing its inhibitory role originating from the striatum. Consequently, this process could lead to an increase in thalamic excitatory modulation on prefrontal cortices.

In patients with prolonged DoC, the administration of dopaminergic agents leads to behavioral and neuroimaging responses, which have been investigated in small studies [125,126]. Nevertheless, large randomized and placebo-controlled studies are still lacking to provide definitive conclusions regarding efficacy.

Interestingly, various studies revealed the stimulating effects of the sedative agent zolpidem in patients with DoC [127,128]. It is assumed that the modulation of GABAA receptors in the globus pallidus interna induces behavioral improvements through inhibition of the mesocircuit [129] (Figure 2). In a double-blinded, placebo-controlled crossover study, 5% out of 84 participants with DoC were identified as definite responders [130]. A further study revealed behavioral improvements in 20% of 84 patients with DoC after administration of zolpidem [131].

Current research focuses on exploring the therapeutic potential of neurotrophins in the management of TBI. Numerous studies have demonstrated that neurotrophins play crucial roles as modulators of neuroinflammation, apoptosis, blood-brain barrier permeability, memory capacity, and neurite regeneration. The expression of neurotrophins following TBI is influenced by factors such as the severity of the injury, genetic polymorphism, and various post-traumatic time points [132].

During the processes of post-traumatic brain remodeling, altered signaling of growth factors, synaptogenesis, angiogenesis, neuronal cell proliferation, gliogenesis, and structural changes in cells contribute to the reorganization and improved functional recovery [133–135].

Studies on neuroprotective agents demonstrate their potential to reduce inflammation, free radical production, and cytoskeleton damage, while early production of excitatory amino acids and inflammatory cytokines in the secondary injury cascade disrupts intracellular calcium homeostasis [136].

Interestingly, exogenous administration of neuropeptides, including neurotrophins, into the cerebrospinal fluid (CSF) enhances protective effects and promotes neuronal repair, regeneration, and synaptic sprouting. Several CSF peptides, such as GDNF, PACAP, VEGF, IGF, FGF2, NGF, and BDNF, have exhibited significantly improved neurogenic capacity that is diminished in TBI [137–139].

Both human and murine studies have indicated significant upregulation of proneurotrophins following brain injuries or degenerative diseases. The binding of these proteins to p75NTR receptors may regulate programmed neuronal cell death in injured or degenerative conditions [140,141].

Additionally, neurotrophins have exhibited potential as sensitive biomarkers for clinical outcomes in patients with TBI [142,143].

Cerebrolysin, a neurotrophin that has been utilized in psychiatry and neurology for over five decades, has shown promise as a therapeutic agent for TBI. It is a non-lipid mixture consisting of free L-amino acids and neuropeptides with low molecular weight, capable of crossing the blood-brain barrier. Through its ability to stimulate natural neuroprotective and neuroregeneration processes, Cerebrolysin can effectively mitigate the short- and long-term consequences of TBI, offering a safe complementary treatment option [144].

In a double-blind trial, a group of 44 individuals between the ages of 19 and 60, with GCS scores ranging from 4 to 11, were assessed for the severity of their injuries

using the Clinical Global Impression (CGI). Cognitive function was evaluated using the Syndrom Kurztest (SKT). Over a period of 21 consecutive days, half of the patients received intravenous administration of Cerebrolysin at a dosage of 50 mL, while the other half received a placebo of equal volume intravenously. Assessments were conducted at the start of the study and subsequently on the 7th, 14th, 21st, 42nd, and 63rd days. The clearest improvements in cognitive functions and GCS were observed in patients receiving Cerebrolysin during the second week of treatment [145].

Findings from another study indicate that Cerebrolysin enhances cognitive function, particularly in long-term memory and drawing abilities in patients three months after TBI, as assessed using the Cognitive Abilities Screening Instrument (CASI) [146]. Furthermore, the results of a large retrospective study confirmed the safety profile of Cerebrolysin and demonstrate its beneficial effects in treating patients following brain trauma [147].

6.2. Transcranial Electrical Stimulation

Within the last decade, some smaller clinical trials have studied the ability of transcranial electrical stimulation (tES) to ameliorate symptoms of improved functions in patients with poststroke motor or language deficits, psychiatric disorders, chronic pain [148], or DoC [149]. tES uses weak electrical current (1–2 mA) applied transcranially to modulate cortical excitability. It comprises transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). tDCS is thought to increase focal cortical excitability under the stimulating electrodes, whereas tACS entrains neural oscillation to a specific frequency [150,151].

In randomized controlled clinical trials including patients with DoC, tDCS targeted the dorsolateral prefrontal cortex. Only a small percentage of patients demonstrated alternation of consciousness following prefrontal stimulation [151–153], and other stimulation targets such as the motor cortex and posterior parietal region yielded smaller effect sizes. To summarize, tES is a safe technique with very few adverse effects reported. The main limitation of its application is currently its moderate and transient clinical effects. Larger randomized controlled trials with dose and duration findings are needed to further evaluate its therapeutic efficacy.

6.3. Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) consists of an oscillating current, creating a fluctuating magnetic field at the surface of the skull which induces an electric current of the brain cortex. While the efficacy of repetitive TMS (rTMS) has been shown in various disorders including depression, posttraumatic stress disorders, stroke, and neglect [148,154], the effect of rTMS in patients with DoC was not significant [155,156]. These studies on patients with DoC used a 20 Hz stimulation over the motor cortex, but other stimulation sites, including the prefrontal cortex and angular gyrus, have not been tested yet [157]. A more promising approach is the usage of TMS in conjunction with EEG as a diagnostic tool to measure network connectivity [158]. This approach has the potential of a new neurophysiologic biomarker of treatment effects in patients with DoC [159,160].

6.4. Vagus Nerve Stimulation

The approach of stimulating peripheral nerves follows the hypothesis that, through multiple synaptic connections, stimulation of primary sensory neurons can induce neuroplasticity within somatosensory networks and thus modulate network responsiveness [161,162]. Two approaches are followed to promote recovery in patients with DoC: median nerve stimulation (MNS) and vagus nerve stimulation (VNS). Initially, small pilot studies of MNS revealed improvement in the level of consciousness and long-term outcomes [163,164]. These studies were followed by a larger study including 437 patients with severe TBI, which also showed better recovery at 6 months in the group receiving 2 weeks of MNS compared to the control group [165].

VNS is conducted in two different ways: invasive VNS, which is mostly used to treat refractory epilepsy, and noninvasive VNS, which is applied transcutaneously to the auricular branch of the vagus nerve. In both modalities, it is hypothesized that VNS stimulates brainstem, thalamic and cortical activity in a bottom-up manner [166].

Invasive VNS was recently shown to induce recovery of consciousness in a patient with prolonged DoC [167]. For noninvasive VNS, a small case series reported heterogeneous and less clinically apparent treatment effects [168,169]. In analogy to tDCS and TMS treatment approaches, further randomized controlled trials are needed to evaluate the effect of peripheral nerve stimulation on recovery of consciousness.

6.5. Sensory Therapies

Sensory stimulation encompassing tactile and auditory has been administered to patients with DoC for decades [170]. It is postulated that sensory stimulation may enhance neural processes and support neuroplasticity resulting in a re-emergence of consciousness. Music therapy is the most established form of sensory therapy, preferably performed by a music therapist to activate neural networks that mediate attention, emotion, auditory processing, and self-awareness [171,172]. A recently published study that applied fMRI imaging showed that the exposition of different auditory stimulation evoked both in the healthy control group and in the UWS patient group modulation of the auditory network. This study proves that auditory stimulation has the potential to modulate brain activity in patients with DoC [173].

Moreover, a recent meta-analysis gave hints that music therapy may improve functional outcomes in patients with DoC [174].

6.6. Motor Therapy

Growing evidence suggests that early mobilization and namely verticalization using a tilt-table increases vigilance, improves pulmonary gas exchange by reducing atelectasis, and prevents orthostatic hypotension as well as osteoporosis. A small randomized controlled trial revealed that early verticalization during the acute phase improves both short- and long-term functional and neurological outcomes in patients with severe TBI [175].

6.7. Psychoeducational Therapeutic Approaches in Post-TBI Fatigue

Besides DoC, long-lasting physical symptoms including fatigue headaches, impairments of visual perception, and seizures are common and limit the functional recovery among individuals not only with severe but also with mild to moderate TBI. Post-TBI fatigue (PTBIF) is a ubiquitous sequela of TBI, with an estimated prevalence ranging from 21% to 70% [176], irrespective of severity [177].

A recent systematic review describes methylphenidate and melatonin as the only pharmacological agents found to reduce fatigue in randomized controlled trials. Besides pharmacological interventions, walking and water aerobics were effective exercise interventions tested also in randomized controlled studies [178].

Apart from pharmacological and exercise interventions, an interesting new approach based on a mindfulness-based stress reduction (MBSR) program has been described in a randomized, controlled crossover study. Eighteen participants with stroke and eleven patients with TBI were included and treated with MBSR. The study revealed significant improvements were achieved both in mental fatigue as well as in neuropsychological tests [179]. Thus, the study provides evidence that neuroeducation-based approaches might be a promising non-pharmacological treatment option for mental fatigue after TBI.

7. Practice Guidelines in Neurorehabilitation

Numerous systematic reviews summarize evidence-based treatment options for TBI patients with DoC [180–182], but these conclusions have not found their way into clinical routine and practice recommendations yet.

The German neurorehabilitation society (DGNR) joined by several national medical societies recently published a guideline (S3 guideline) for the neurological rehabilitation of adults with coma and DoC [183].

The most important and relevant recommendations are based on the guidelines for the diagnosis of coma and other DoC, which were developed by a European expert group commissioned by the European Academy of Neurology (EAN) in 2020 [184].

The expert group decided to adopt only those recommendations that hold high clinical relevance while excluding other recommendations related to more experimental methodologies (e.g., fMRI).

The following main aspects are considered in the guidelines.

Adult patients with severe loss of consciousness due to acute brain injury:

1. should receive multi-professional neurological rehabilitation treatment (level of evidence B);
2. should receive a treatment attempt with amantadine in increasing doses up to 400 mg daily taken orally to improve the state of consciousness (level of evidence B);
3. should be verticalized on a tilt table (level of evidence B);
4. should undergo multisensory stimulation to improve their reactivity to the environment. Especially auditory stimuli with a high degree of emotional and autobiographic reference should be applied in the context of music therapy (level of evidence B);
5. should undergo a therapy attempt with tDCS over the dorsolateral prefrontal cortex (DLPFC) with a duration of 20 min/day over at least 5 days in addition to conventional therapies (level of evidence B).

8. Conclusions

Evidence from recent large observational studies suggests that early and continuous rehabilitation may improve impairments in function and participation in daily life activities and reduce disease burden. Despite broad recognition among clinicians of the need for neurorehabilitation after TBI, structured follow-up care remains still suboptimal not only in low- and middle-income countries but also in high-income countries.

Within the last few years, the pathophysiological understanding of TBI and DoC has been significantly expanded based on elaborate clinical examination models, neuroimaging and electrophysiological methods. A promising approach is the detection of network-based mechanisms for prognosis and outcome assessment as well as for the development and investigation of targeted therapies.

Electrostimulation methods such as TMS, tDCS, and peripheral nerve stimulation are becoming increasingly important as additional therapeutic approaches to established therapies encompassing physical, occupational, speech/language, and neuropsychological therapy.

In the future, new clinical assessments, advanced neuroimaging, and electrophysiological techniques should be addressed more scientifically in order to define new therapeutic approaches and standards.

Author Contributions: Conceptualization, J.L.; writing original draft, J.L.; review and editing, A.G.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

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