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Original Article

Characterization of responders to transcranial direct current stimulation in disorders of consciousness: A retrospective study of 8 clinical trials

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ABSTRACT

The treatment for patients with disorders of consciousness challenges researchers and clinicians. The stimulation of the left dorsolateral prefrontal cortex with transcranial direct current stimulation (tDCS) may enhance behavioral responsiveness of a subset of patients in a minimally conscious state, while having limited effects in unresponsive patients. However, heterogeneity in responses raises questions about the effectiveness of tDCS. Our objective was to explore the characteristics of responders to tDCS based on previously published RCTs and investigate the heterogeneity of treatment effect to better direct future tDCS studies towards patient profiles that appear to be more responsive to the treatment. We explored clinical and demographical differences between responders (i.e., recovery of a new sign of consciousness after active stimulation) and non-responder and the predictors of treatment response with a LASSO logistic regression. We included 131 patients (44 women, 61 traumatic brain injury, 90 minimally conscious, mean age 46.13 years [SD = 16], median time since injury 12.84 months [IQR: 5.25–35.10]) of which 33 responded to tDCS. While 32 % of minimally conscious patients responded to tDCS (95%CI 0.24, 0.43), 10 % (95%CI 0.04, 0.25) of those unresponsive responded. The regression model, using diagnosis at baseline, Coma Recovery Scale-Revised Index at baseline, age, sex and time since injury correctly discriminated between tDCS responders and non-responders (area under the curve of 0.77). Our findings suggest that patients in minimally conscious state, with a better cognitive profile and longer TSI respond better to tDCS, making them better candidates for the treatment.

Introduction

Although research on patients with severe brain injuries and disorders of consciousness (DoC) has dramatically increased in the last decade, their treatment still presents many challenges for clinicians, as well as for researchers. Despite the diagnostic advancements, the high variability of treatment efficacy still challenges the investigation of potential treatments for patients with DoC [1]. Patients who have recovered from a coma caused by a severe brain injury are diagnosed with an unresponsive wakefulness syndrome (UWS) [2] if they present eye-opening (spontaneous or induced) and reflex behaviors only (e.g., non-oriented movements, oromotor and visual reflexes). If patients present reproducible signs of consciousness such as response to commands, localization of nociceptive stimulation, or visual pursuit, they are considered to be in a minimally conscious state (MCS) [3]. If patients recover the ability to functionally communicate and/or use objects they are considered to have emerged from the minimally conscious state (eMCS) [4] and are no longer diagnosed as having a DoC.

Research on patients with DoC has shown growing evidence for the possibility of recovery months and even years after the injury [5,6].

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However, to date, patients with DoC still have access to a limited array of treatment options to improve their condition, thus highlighting the need for new therapeutic options. While some treatments aim at improving patients' comfort (e.g., pain, spasticity), curative treatment aims at enhancing recovery and increasing behavioral responsiveness. For instance, past clinical trials have highlighted the effectiveness of some pharmacological treatments [7,8].

Transcranial direct current stimulation (tDCS) is among the treatments that have been successfully tested for patients with DoC. It is a safe, inexpensive technique of non-invasive neuromodulation that can modify the activity of the brain by delivering a weak electrical current through electrodes placed on the scalp. It has been shown that tDCS can modulate the excitability of neuronal membrane according to the type and direction of the current [9]. The technique allows for a reliable placebo control condition referred to as *sham*. The first randomized controlled trial (RCT) using tDCS as a treatment for DoC, published by Thibaut and colleagues [10], showed that stimulating the left dorsolateral prefrontal cortex (DLPFC), compared to sham, enhanced behavioral responsiveness of patients with DoC. Since then, studies have explored the effects of different montages, brain targets, and protocols of tDCS as a therapeutic tool for DoC [11–20]. tDCS is currently the most explored non-invasive treatment technique for DoC [21] and has shown positive effects in up to 43 % of patients in MCS [10].

The improvements following the stimulation are usually captured with the Coma Recovery Scale-Revised (CRS-R), the most recommended tool to assess the neurobehavioral condition of patients with DOC. The CRS-R is a behavioral scale composed of 23 items measuring auditory, visual, motor and oromotor functions, as well as arousal and communication [22]. Its main benefit is that it allows for a differential diagnosis of DoC with high inter-rater reliability [23]. However, its score (calculated by adding the highest scores of each of its 7 subscales) can result from different permutations and is not linked to diagnosis. To address this, Annen and colleagues [24] developed a CRS-R Index, which translates each subscale score into a matrix, taking into account cognitive mediated behaviors and reflex behaviors, and provides examiners with a numerical value that can accurately distinguish between patients in UWS and patients in MCS, using a cutoff of 8.31. This index, unlike the CRS-R total score, is a continuous numerical variable that is more suited for statistical analyses such as regression models since the number corresponds to a specific functional profile and is directly related to the diagnostic level (ie., UWS vs MCS).

Even though most tDCS studies in DoC use the CRS-R to measure tDCS effects, their definition of response to tDCS is variable. Response to tDCS has been based either on an improvement in the CRS-R total score, or the observation of a new behavioral sign never observed before. The lack of a common definition of responder hindered the progress of identification of their characteristics.

Although there are many studies on the effect of tDCS across various patient groups, little is known about the clinical and demographic characteristics of responders. One recent meta-analysis [25] found that an initial diagnosis of MCS predicts a positive treatment effect of tDCS. However, many questions on response to tDCS as a treatment for DoC remain unanswered. What distinguishes patients who respond to tDCS from those who do not? Can factors like age, sex, etiology, and time since injury help identify patient profiles most likely to respond to tDCS treatment? Which stimulation site is most promising? Accordingly, a gap analysis identified the characterization of responders to non-invasive brain stimulation as a priority for precision neurotherapeutics targeting DoC [1]. Identifying patient profiles that are most likely to benefit from tDCS is a mandatory step towards advancing research on this type of treatment as it would increase observed effectiveness. To address this knowledge gap, we examined the heterogeneity of the treatment effect across participants pooled from RCTs evaluating tDCS in DoC. We aimed to explore the clinical and behavioral differences between responders to tDCS and non-responders in terms of sex, age, time since injury, etiology, initial diagnosis, CRS-R Index, and site of stimulation. Our goal was to direct future tDCS studies towards the patient profiles that appear to be more responsive.

Methods

Participants

Demographic and behavioral data were retrospectively extracted from the databases of 8 randomized double-blind placebo-controlled clinical trials conducted by the Coma Science Group of the University of Liège (Liège, Belgium) between 2014 and 2022 that investigated the effectiveness of tDCS on DoC and included the CRS-R as part of the measured variables studies [10,12,13,17–20,26]. Informed consent was obtained from the next of kin or legal representative of the participants. The protocols of the different RCTs were approved by ethics committee of the University and University Hospital of Liège (Liège, Belgium).

Participants of the 8 RCTs were included in the retrospective analysis if they had a time since injury longer than 28 days and completeness of clinical and demographical data. Note that the threshold of 28 days post-injury was selected to include only patients with prolonged DoC as defined by the AAN guidelines [27,28]. The participants' age at stimulation, sex, etiology, diagnosis at baseline, TSI (years), CSR-R, brain target of the stimulation, time of stimulation and response to tDCS was extracted for analysis. Response to the treatment was considered positive (i.e., the patient was considered as responder) if, after the active tDCS, the patient showed a new conscious behavior based on the CRS-R that was never observed before, nor before or after sham. Although this

Table 1
Group demographic and clinical information of responders and non-responders.

	Non-Responders (N = 98)	Responders (N = 33)	Total (N = 131)
Age (years)			
Median [Q1, Q3]	45.49 [31.0, 56.2]	56.06 [34.8, 64.8]	46.67 [31.5, 59.8]
Sex			
Male	65 (66.3 %)	22 (66.7 %)	87 (66.4 %)
Female	33 (33.7 %)	11 (33.3 %)	44 (33.6 %)
Time since injury (months)			
Median [Q1, Q3]	12.17 [4.5, 26.7]	15.67 [5.7, 81.2]	12.82 [5.2, 35.1]
CRS-R index at baseline			
Median [Q1, Q3]	5.88 [3.8, 28.2]	22.55 [5.5, 30.2]	13.18 [4.1, 30.2]
Etiology			
Anoxia	42 (42.9 %)	8 (24.2 %)	50 (38.2 %)
Hemorrhagic	13 (13.3 %)	7 (21.2 %)	20 (15.3 %)
TBI	43 (43.9 %)	18 (54.5 %)	61 (46.6 %)
Initial diagnosis			
MCS	61 (62.2 %)	29 (87.9 %)	90 (68.7 %)
UWS	37 (37.8 %)	4 (12.1 %)	41 (31.3 %)
Stimulation target			
DLPFC (1 session)	45 (45.9 %)	16 (48.5 %)	61 (46.6 %)
DLPFC (5 sessions)	4 (4.1 %)	5 (15.2 %)	9 (6.9 %)
DLPFC (20 sessions)	13 (13.3 %)	4 (12.1 %)	17 (13.0 %)
Motor	6 (6.1 %)	1 (3.0 %)	7 (5.3 %)
Fronto-parietal	30 (30.6 %)	7 (21.2 %)	37 (28.2 %)

We report the sample characteristics. For normally distributed continuous variables we report mean and standard deviation between parentheses; for non-normally distributed continuous variables (i.e., Time Since Injury, CRS-R Index) median and interquartile ranges in square brackets. For categorical variables (e.g., sex, etiology) we report the N and percentage between parentheses.
Abbreviations: Coma Recovery Scale-Revised (CRS-R), Traumatic Brain Injury (TBI), Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS), Dorsolateral PreFrontal Cortex (DLPFC).

definition might be stricter than others (e.g., an increased score in CRS-R), we preferred adopting a more conservative approach to ensure the identification of a behavioral response to tDCS as opposed to spontaneous fluctuations occurring in patients with DoC [29,65]. Patients who participated in more than one trial were considered responders if they responded to at least one protocol. In that case, we considered for the analysis the demographic and behavioral data from the protocol they demonstrated a response to. Patients who participated in more than one trial but did not respond, were included considering the data of the first protocol they participated in.

The CRS-R index of all the participants was calculated from their CRS-R scores based on Annen et al., 2019 method [24]. The CRS-R Index was used instead of the CRS-R because, contrarily to this scale, it is a quantitative measure that allows for accurate differential diagnosis.

Statistical analyses

To characterize responders of tDCS, we first described them with appropriate summary measures of central tendency and dispersion. We predefined a set of available variables that are relevant in clinical practice (i.e., age, sex, time since injury, protocol of stimulation, baseline diagnosis and etiology) and we estimated the proportion of responders and its 95% confidence intervals (95%CI) within each subgroup. To account for the cross-over design, we used Quasi-Poisson regression [30].

We then used a risk-based characterization of responders through predictive modeling [31]. To find the predictors of treatment response we used the Least Absolute Shrinkage and Selection Operator (LASSO) implemented through the glmnet R package [32]. We selected LASSO because it is appropriate for classification, it allows variable selection and it avoids overfitting. While logistic regression could also classify responders and non-responders, it estimates a coefficient for every variable in the model. In generalized linear models, this is achieved by minimizing the mean squared error: the predictions of the model are compared with the observed data and the coefficients that minimize this difference are estimated. LASSO, besides minimizing the mean squared error, shrinks the coefficients of the variables using a penalization term. Then, some coefficients are shrunken to zero, providing a means for variable selection which favors parsimonious models. When models are built without taking into account validation, they risk fitting the data on which they were trained but not new data. With cross-validation, the data are split into folds and divided into a training and a testing set. Each fold, the model is trained in the training set and its performance tested in the validation set [33]. In our binary regularized logistic regression model, response to tDCS was the outcome. We started the development of the model with the above-mentioned variables as predictors. To prevent overfitting and select the minimum regularization parameter, we used 10-fold cross-validation with the area under the curve (AUC) as the loss function. We used the c-statistic as a measurement of discrimination and plotted calibration as shown in Supplementary Fig. S2 and S3.

For each patient included, we defined their predicted probability of treatment response as the linear combination of the value of their predictors with the estimates from our model. We plotted the predicted probabilities against the continuous variables (time since injury, age, and the CRS-R Index at baseline) to display graphically our results. For this purpose, we allowed B-Splines with three knots. Moreover, we stratified our sample according to quintiles of the predicted probability of treatment response and calculated the proportion of responders to tDCS within each quintile and its 95% CIs [31]. Finally, we present the predicted responses for each relevant patient profile.

Results

Out of the 155 patients who participated in the 8 studies on tDCS, 131 patients were included in this retrospective study. The final sample included 44 women, had a mean age of 46.13 years and a mean time since injury (TSI) of 12.84 months. A total of 90 patients were in MCS and 61 patients had suffered a traumatic brain injury (TBI). Thirty-two patients, 90 patients in MCS, mean age 46.13 years, mean time since injury – TSI 12.84 months, of which 33 (25 %) responded to tDCS (see Supplementary Material). The study flowchart and sample characteristics are presented in Supplementary Fig. S1 and Table 1, respectively.

When we contrasted the median age of responders and non-responders, it was 56.1 (IQR: 34.8, 64.8) years and 45.49 (IQR: 31.0, 56.2), respectively. Women were 33.3 % of responders and 33.7 % of non-responders. Responders had a median time since injury of 15.67 (IQR: 5.7, 81.2) months vs. 12.17 (IQR: 4.5, 26.7) months of non-responders. The median CRS-R Index at baseline was 22.55 (IQR: 5.79, 30.30) for responders contrasting with 5.88 (IQR: 3.8, 28.2) of non-responders. The etiology of 54.5 % of responders and 43.9 % of non-responders was TBI. MCS was the diagnosis of 87.9 % of responders and 62.2 % of non-responders. DLPFC was the target of stimulation of 75.8 % of responders and 63.3 % of non-responders. For details, see Table 1.

The proportion of responders among MCS patients was 0.32 (95% Confidence Intervals: 0.24, 0.43) compared with 0.10 for UWS (95% CI: 0.04, 0.25). For details on the proportions of responders within each category of pre-defined effect modifiers, see Supplementary Material Table S1.

Regarding the prediction model, we present in Supplementary Material (Supplementary Table S2) the variables selected for the model, performance metrics, graphical results, patient profiles, and proportions within the stratified predicted risk. All the variables tested were selected with the LASSO which offered an area under the curve of 0.77 (95%CI: 0.67, 0.85). We evaluate this finding in the discussion [34].We report the coefficients associated with each variable in the Supplementary Table S2 to avoid their misinterpretation as causal estimates [36]. The predicted proportion of responders (0.25) matched the observed proportion of responders (0.25). Supplementary Material Table S3 and Fig. S3.

As an example for clinical interpretation, a typical profile of a responder is a middle-aged woman diagnosed with MCS, had TBI and is stimulated a year or more after injury. To illustrate better the clinical profiles, we have held the CRS-R Index at its threshold level of 8.315 and analyzed the predicted probability of response varying the diagnosis and the etiology. According to the prediction model, a 40-year-old female patient diagnosed with an MCS due to TBI, who is stimulated 3 years post-injury and undergoing DLPFC tDCS would have a predicted probability of response of 44.5%. In contrast, patients with a similar profile but with a diagnosis of UWS and an etiology other than TBI, would have a predicted probability of responding to tDCS of 7.17 %.

Patients in the first quintile of predicted probability had on average a response proportion of 7.4 % (95%CI: 1.0, 24.0) compared with patients in the fifth quintile whose percentage of response was 57.7 % (95%CI: 37.0–77.0) (Supplementary Table S3).

The influence of the continuous predictors selected by the model (i.e., TSI, age and CRS-R Index) on the probability of response predicted by the model is depicted in Figs. 1–3. As is shown in Fig. 1, the probability of response increased with TSI. Patients with longer TSIs and older ages had increased probabilities of response. Moreover, most patients with higher probability of responses had an initial diagnosis of MCS and TBI etiology. The probability of responding to tDCS was also shown to be influenced by age as well (Fig. 2); with a higher probability of response for patients between 40 and 50 years old. Note that this range was not a pre-specified cut-off and corresponds to what was observed from the data distribution. Patients between 60 and 80 years old also appeared to have a high probability of responding to tDCS. Finally, the CRS-R Index and the probability of response showed a non-linear pattern (Fig. 3); patients at the lower and higher ends of the distribution of the CRS-Index showed lower probabilities of response compared to patients with intermediate indices. The pattern of probability of response showed an increase for patients with scores between approximately 7 and 50, whereas it showed lower probabilities of response for patients with scores outside of this range.

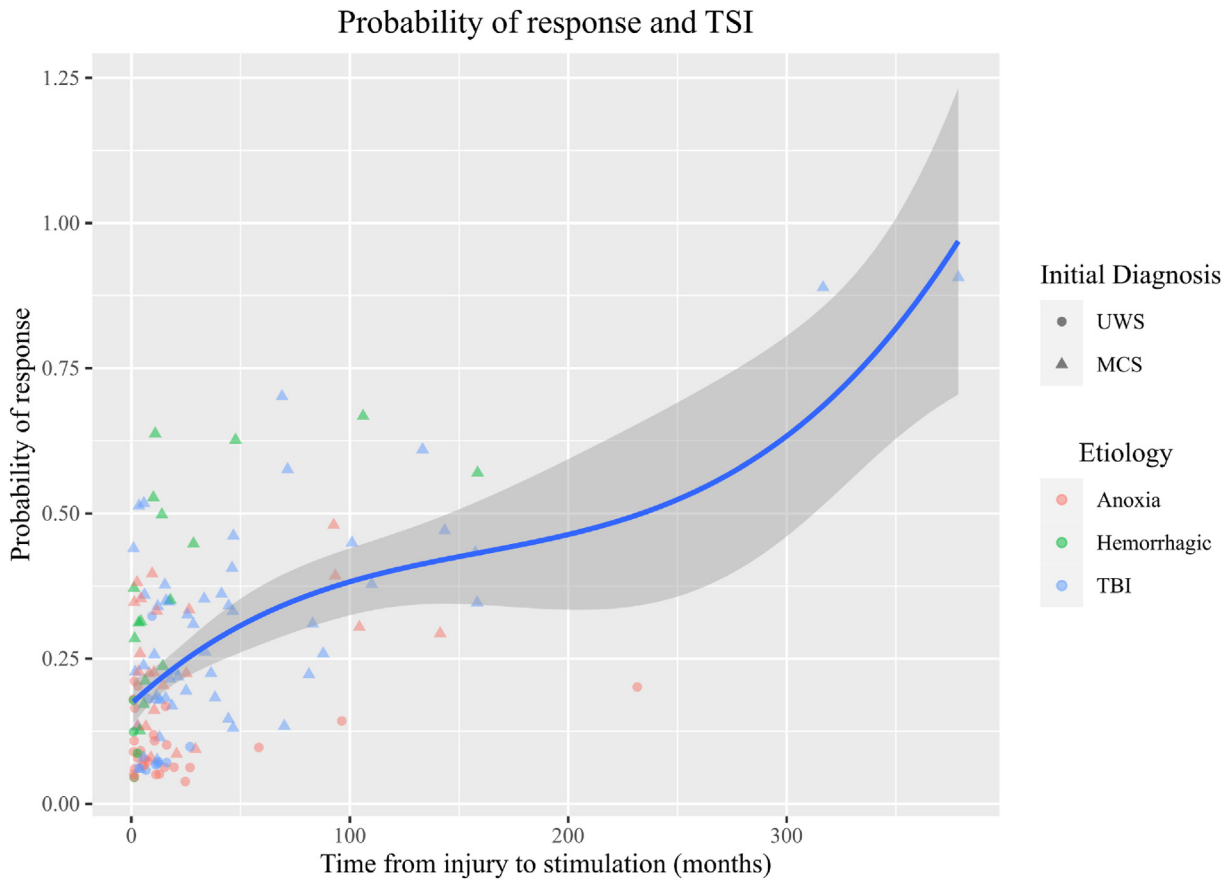

Fig. 1. Probability of response predicted by the model plotted against observed values of the time since injury in months. Initial diagnoses are differentiated by different shape; different etiologies by color. **Abbreviations**: Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS), Coma Recovery Scale-Revised Index (CRS-R), Traumatic Brain Injury (TBI), Time Since Injury (TSI).

Discussion

In this study, we combined data from 8 RCTs using tDCS as a therapeutic tool for patients with DoC (N = 131). We then applied a regularized logistic regression model to find predictors of response to tDCS and we found that initial diagnosis, age and TSI influences response to tDCS. Through the characterization of responders to tDCS, we addressed a relevant gap in precision neurotherapeutics [1].

The impact of diagnosis

The fact that MCS patients have higher chances of responding to tDCS is in line with previous results. Past studies [16,35,36] have shown significant effects (i.e., both clinical and physiological improvement) of tDCS in patients in MCS and not in patients with UWS. Recent meta-analyses have also shown that these patients experience significantly more behavioral improvements compared to UWS in response to tDCS [25,37]. Our quantification of the proportion of responders to tDCS according to the initial diagnosis not only confirms what researchers have observed but also strengthens our knowledge of the most reactive group of patients with DOC to target for this non-invasive treatment. Many studies have shown that patients in MCS have better prognosis than patients in UWS and can show recovery even years after the injury [38–40]. These findings hint at the possibility of underlying intact mechanisms of neuroplasticity in patients with MCS, which would explain the cases of late recovery as well as sensitivity to tDCS that results in behavioral improvement. Two main studies have been performed to gain a better understanding of the brain activity profiles of responders. One study [41] using Positron Emission Tomography (PET) and Voxel-Based Morphometry (VBM) based on magnetic resonance imaging (MRI) found that grey matter atrophy and brain metabolism in consciousness-related regions (e.g., the precuneus and the thalamus) and regions below stimulation electrodes (i.e., left prefrontal cortex) were significantly different between responders and non-responders [41]. Several studies using high-density electroencephalography (EEG) [42,43] found that responders to tDCS were characterized by stronger connectivity in the theta band compared to non-responders. Based on the findings of these studies we can hypothesize that responders would have more preserved structural brain tissue and functional brain activity in regions that have been related to consciousness (e.g., thalamus, cingulate cortex, precuneus) as well as higher activity in the theta frequency band. Many studies [43–47] have used EEG to distinguish between patients in MCS and in UWS and have found that low oscillations coupled with higher oscillations, typical of MCS patients, are a sign of partial preservation of corticothalamic circuit integrity [48]. Furthermore, a case report showed that tDCS might have promoted the behavioral response to commands of a patient who was unresponsive at the bedside [49], suggesting that tDCS may facilitate the patient's ability to demonstrate signs of consciousness, thus improving their diagnosis. In this context, we can assume that tDCS is able to enhance the activation and connectivity of these regions because their baseline functionality is somehow more likely to be preserved for MCS patients, which might not be the case for patients in UWS [50]. To support this hypothesis, several studies on stroke populations have shown that patients with larger brain lesions [51] and white matter deterioration [52] experienced less benefit from tDCS. Another interesting aspect about the difference in frequencies of responders between patients in MCS and patients in UWS is the insight it provides in understanding the mechanisms of action of tDCS treatment itself. For instance, theta power and connectivity have been found to differ between responders and non-responders in several studies [13,49,53] showing more preserved neural activity within central and posterior

Fig. 2. Probability of response predicted by the model plotted against observed values of age (years). Initial diagnoses are differentiated by different shape; different etiologies by color; longer TSI by the size of data point. **Abbreviations**: Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS), Coma Recovery Scale-Revised Index (CRS-R), Traumatic Brain Injury (TBI), Time Since Injury (TSI).

networks and frequency bands in MCS patients compared to UWS. One study [54] exploring tDCS effects with TMS-EEG has found that tDCS reduced slow-wave activity (i.e., delta power) but this was not followed by a behavioral improvement. When a behavioral improvement was observed, there was not only a decrease in slow-wave activity but also an increase in high-frequency power. This suggests that the clinical result may be due to the combination of these two factors, rather than the decrease in delta power alone Overall, the above-mentioned results define clear differences in the neural preservation and activity between patients in UWS and patients in MCS and these could be at the origin of the observed differences in terms of responsiveness, as it appears that tDCS has stronger effects on more preserved neural pathways and substrate.

Our results regarding the CRS-R Index at baseline show a clear pattern of probability of response in line with the results regarding the MCS diagnosis. The probability of responding remains high throughout the range of scores that identify patients in MCS. The odds of responding start to decrease around scores of 50 on the CRS-R Index which could be explained by a plateau effect, as the CRS-R might be not sensitive enough to detect changes in patients that show high scores and are more compatible with a confused post-traumatic syndrome [55]. Indeed, the CRS-R does not test for residual cognitive abilities in confused patients and was designed to assess the presence of signs of consciousness. Consequently, patients that score above 50 on the CRS-R Index could be better suited for other tools indicating the use of other instruments, such as the Confusion Assessment Protocol or the Galveston Orientation and Amnesia Test, to detect the effects of tDCS [56].

The impact of time since injury

The results of TSI on responding to tDCS in our sample, which included both subacute and chronic patients (ranging between 1 and 251 months post-injury), might seem counterintuitive as they reveal that the longer the time between the injury and the stimulation, the greater the chances of responding to tDCS. However, it is compatible with longitudinal studies on DoC [5,39] which show that recovery is possible even years after the injury, especially in TBI etiologies [57]. This might be partially explained by a survival bias, in which patients with longer TSI have comparatively better health conditions and fewer comorbidities than those who do not survive long after the injury [58]. Importantly, one study also found that some patients showed improvements only weeks or months after the tDCS intervention, which might support the hypothesis that longer TSI might favor tDCS improvements. One possible explanation for this is the re-organization of the brain after severe brain injury [59,60]. There is evidence that the brain re-organizes itself throughout time after TBI [61], especially in the motor areas [62,63]. In the present figure for TSI, most patients who show higher probabilities of responding with long TSI have TBI etiologies. Another factor that could play a role in this interaction might be that patients with chronic DoC receive fewer hours of rehabilitation (e.g., physiotherapy, occupational therapy) compared to patients in other clinical conditions, who can participate in more extensive rehabilitation programs, usually lasting up to a year after the injury [27,28]. For this reason, it might be easier to detect tDCS effects in settings where the patients are less stimulated.

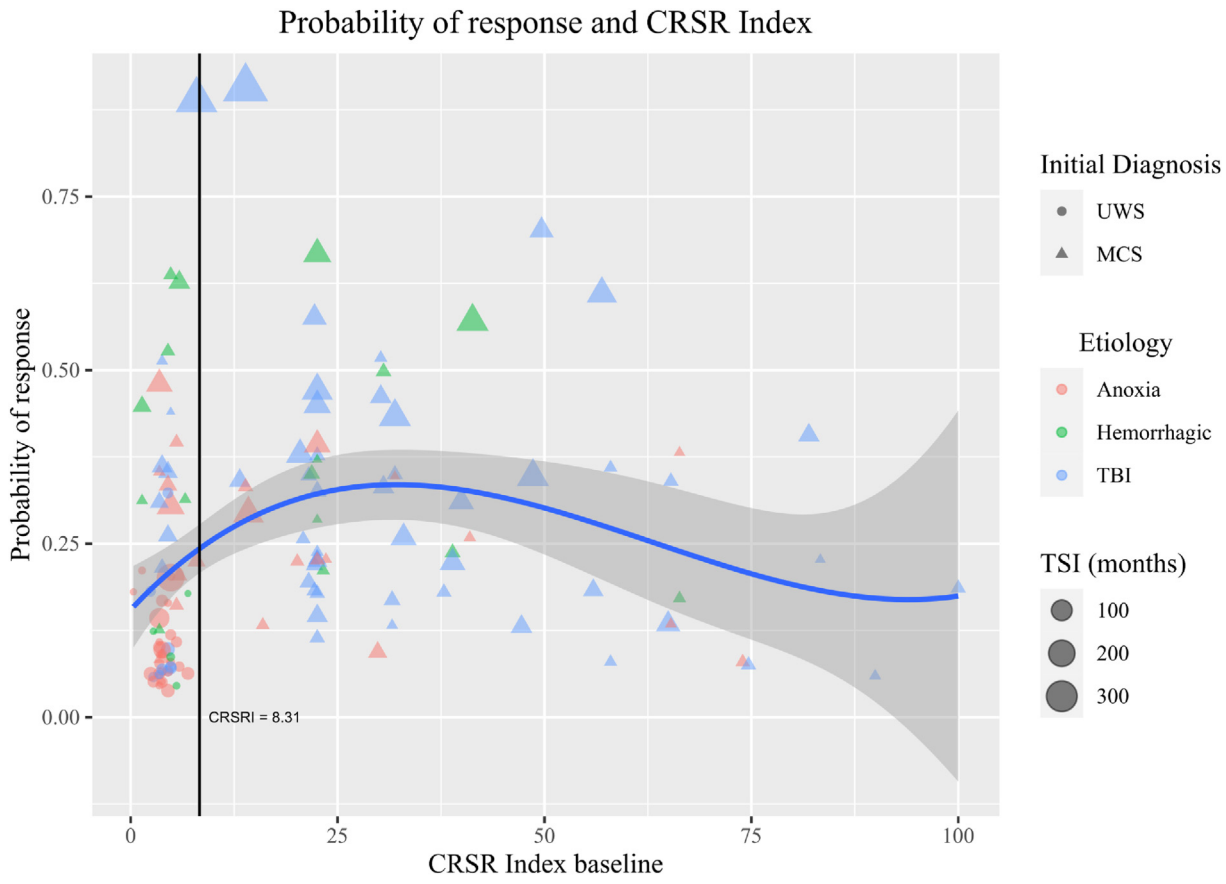

Fig. 3. Probability of response predicted by the model plotted against observed values of the Coma Recovery Scale Index at baseline. Initial diagnosis and etiology are differentiated by shape and color, longer TSI by the size of data point. The vertical black line indicates the cut-off point of CRS-R index scores (i.e., 8.315) that distinguishes between MCS and UWS. **Abbreviations**: Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS), Coma Recovery Scale-Revised Index (CRS-R), Traumatic Brain Injury (TBI), Time Since Injury (TSI).

The impact of age

Finally, the results regarding age are difficult to interpret as there was no linear relationship between age and probability of response. It appears from the distribution of the data that the odds of responding to tDCS are higher for patients between approximately 40 and 50 years old and that they remain quite elevated after 66 years old. One study showed that tDCS effects tend to decrease with age, especially after 66 years old as a result of decreased long-term potentiation plasticity [64]. Our findings are consistent with these hypotheses, as we have observed an increased probability of response for older patients too. It is interesting to note that some of the patients who have higher probabilities of responding also have TSI longer than 10 months. Since we have observed that patients with longer TSI also have increased probabilities of responding this might play a role in the probabilities observed. Another relevant characteristic of our data is that many of the patients falling between ~35 and ~57 years old (with lower odds of responding) appear to have anoxic etiologies. Anoxic patients with DoC usually present poorer prognosis [38,58], which might partially explain why their probability of response is lower than other age ranges. These hypotheses are all based on the distribution of our data, however, given the many factors adding to our observed results, their non-linearity, and inconsistencies with previous studies we must remain cautious when interpreting this finding.

Clinical relevance

Our findings outline a specific clinical profile as the most responsive to the tDCS treatment. Patients that are more likely to benefit from this treatment are in MCS, with a CRS-R Index between 7 and 50 and a long TSI. We have discussed above the reasons behind that might underlie the observed sensitivity to tDCS. Patients with some or all of these characteristics should be considered as a priority for tDCS treatment. Moreover, future tDCS clinical trials should favor inclusion of patients with such profiles to increase observed effectiveness and push the field of tDCS in DoC research forward.

The AUC of our model was 0.77. Although this discrimination is fair, a higher value could be obtained with neurophysiologic measurements. For instance, patients with major depressive disorder were classified as responders and non-responders to tDCS according to the current intensity predicted with magnetic resonance imaging (MRI) and obtained an AUC = 0.90 [34]. Therefore, it is likely that incorporating neurophysiologic variables in the model could increase its performance. However, our model has the advantage of using variables readily available in the clinic.

Limitations

Our study presents several limitations. Firstly, the data used in this study were all collected by a single research group. This could introduce bias into the analysis, as it may not be representative of all tDCS studies, nor DoC population. The limited source may affect the generalizability of the findings. Secondly, the definition of responders in our study might differ from the definition of other studies. Therefore, these analyses may not capture the full range of potential outcomes, especially subclinical changes. Thirdly, the heterogeneity of clinical features of the patients and tDCS protocols included could also limit the findings of this study. The nature of included tDCS protocols (i.e., both single session tDCS and repeated/longitudinal studies) also contributes to heterogeneity since it was shown [25,37] that multiple sessions of tDCS produce stronger and

longer-lasting results. Furthermore, some patients might need multiple tDCS sessions to show improvement [20] thus also influencing our characterization of responders. Finally, the lack of neurophysiology and neuroimaging data also limits the scope of the findings. As previously mentioned, some studies [41,44] have found significant differences between responders and non-responders in these variables, thus to better characterize responders to tDCS we should explore brain characteristics. For instance, one recent study [46] found response to tDCS not only on behavioral measures but also on EEG measures of cognition, such as P300 latency. This provides a good example of how response to tDCS should be investigated in a multimodal fashion, including both behavioral and neurophysiological measures, and the characterization of it should be similarly explored.

Conclusions

Since 2014, tDCS studies in DoC patients have explored safety, feasibility and different montages. However, the rates of responders are still low and a better insight on which patients are more likely to respond to tDCS could optimize the targeting of future studies. Our findings identified age, TSI, initial diagnosis, and CRS-R index at baseline as predictors of the response to tDCS in patients with DOC. Based on these results, a better response to tDCS can be expected in patients in MCS, with CRS-R Index scores between 7 and 50 and with a long TSI. This patient profile should be preferred for inclusion in future tDCS clinical trials as we can expect higher effectiveness of the intervention. Our predictors are readily available and hence relevant when selecting patients for open-label therapy in rehabilitation clinics and in research centers. Future studies should focus on the patient profile of responders our study identified, to validate and replicate our clinical and demographic predictors. Moreover, further research should include biomarkers and other neurophysiological measures to complement the patient profile for optimal tDCS responsiveness.

Contributions

AB (conceptualization, data curation, formal analysis, interpretation of results, funding acquisition, investigation, methodology, project administration, validation, visualization, writing – original draft, writing – review and editing), RHG (conceptualization, formal analysis, interpretation of results, methodology, project administration, software, validation, visualization, writing – original draft, writing – review and editing), JA (conceptualization, formal analysis, funding acquisition, investigation, methodology, interpretation of results, project administration, resources, supervision, writing – review and editing), GM (conceptualization, funding acquisition, data curation, investigation, methodology, interpretation of results, project administration, validation, writing – review and editing), SL (conceptualization, funding acquisition, methodology, resources), RL (conceptualization, methodology, interpretation of results, supervision, writing – review and editing), TK (conceptualization, methodology, interpretation of results, supervision, writing – review and editing), AT (conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, interpretation of results, project administration, resources, supervision, validation, visualization, writing – original draft, writing – review and editing).

Data availability

Upon reasonable request, data supporting our study could be provided via the corresponding author.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tobias Kurth reports outside the submitted work has received personal compensation from Eli Lilly and Company, the BMJ, and Frontiers. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2025.e00587.

References

[1] Edlow BL, Sanz LR, Polizzotto L, Pouratian N, Rolston JD, Snider SB, et al. Therapies to restore consciousness in patients with severe brain injuries: a gap analysis and future directions. Neurocritical Care Jul. 2021;35(S1):68–85. https://doi.org/10.1007/s12028-021-01227-y.

[2] Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 2010;8:2–5. https://doi.org/10.1186/1741-7015-8-68.

[3] Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state. Neurology Feb. 2002;58(3):349–53. https://doi.org/10.1212/WNL.58.3.349.

[4] Nakase-Richardson R, Yablon SA, Sherer M, Nick TG, Evans CC. Emergence from minimally conscious state: insights from evaluation of posttraumatic confusion. Neurology Oct. 2009;73(14):1120–6. https://doi.org/10.1212/WNL.0b013e3181bacf34.

[5] Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology 2010;75(3):239–45.

[6] Estraneo A, Magliacano A, Fiorenza S, Formisano R, Grippo A, Angelakis E, et al. Risk factors for 2-year mortality in patients with prolonged disorders of consciousness: an international multicentre study. Eur J Neurol Feb. 2022;29(2):390–9. https://doi.org/10.1111/ene.15143.

[7] Gosseries O, Charland-Verville V, Thonnard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. Curr Pharm Des Sep. 2014;20(26):4167–84. https://doi.org/10.2174/13816128113196660654.

[8] Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med Mar. 2013;366(5):819–26. https://doi.org/10.1056/NEJMoa1102609.

[9] Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul 2008;1(3):206–23.

[10] Thibaut A, Bruno MA, Ledoux D, Demertzi A, Laureys S. TDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. Neurology 2014;82(13). https://doi.org/10.1212/WNL.0000000000000260.
[11] Bai Y, Xia X, Kang J, Yang Y, He J, Li X. TDCS modulates cortical excitability in patients with disorders of consciousness. Neuroimage Clin 2017;15:702–9. https://doi.org/10.1016/j.nicl.2017.01.025.
[12] Martens G, Fregni F, Carrière M, Barra A, Laureys S, Thibaut A. Single tDCS session of motor cortex in patients with disorders of consciousness: a pilot study. Brain Inj 2019;33(13–14):1679–83. https://doi.org/10.1080/02699052.2019.1667537.
[13] Carrière M, Mortaheb S, Raimondo F, Annen J, Barra A, Binda Fossati MC, et al. Neurophysiological correlates of a single session of prefrontal tdcs in patients with prolonged disorders of consciousness: a pilot double-blind randomized controlled study. Brain Sci 2020;10(7):1–17. https://doi.org/10.3390/brainsci10070469.
[14] Cavinato M, Genna C, Formaggio E, Gregorio C, Storti SF, Manganotti P, et al. Behavioural and electrophysiological effects of tDCS to prefrontal cortex in patients with disorders of consciousness. Clin Neurophysiol 2019;130(2):231–8. https://doi.org/10.1016/j.clinph.2018.10.018.
[15] Mancuso M, Abbruzzese L, Canova S, Landi G, Rossi S, Santarnecchi E. Transcranial random noise stimulation does not improve behavioral and neurophysiological measures in patients with subacute Vegetative-Unresponsive Wakefulness State (VS-UWS). Front Hum Neurosci 2017;11(November):1–10. https://doi.org/10.3389/fnhum.2017.00524.
[16] Huang W, Wannez S, Fregni F, Hu X, Jing S, Martens G, et al. Repeated stimulation of the posterior parietal cortex in patients in minimally conscious state: a sham-controlled randomized clinical trial. Brain Stimul 2017;10(3):718–20. https://doi.org/10.1016/j.brs.2017.02.001.
[17] Martens G, Kroupi E, Bodien Y, Frasso G, Annen J, Cassol H, et al. Behavioral and electrophysiological effects of network-based frontoparietal tDCS in patients with severe brain injury: a randomized controlled trial. Neuroimage Clin Jan. 2020;28:102426. https://doi.org/10.1016/j.nicl.2020.102426.
[18] Martens G, Lejeune N, O'Brien AT, Fregni F, Martial C, Wannez S, et al. Randomized controlled trial of home-based 4-week tDCS in chronic minimally conscious state. Brain Stimul Sep. 2018;11(5):982–90.
[19] Thibaut A, Piarulli A, Martens G, Chatelle C, Laureys S. Effect of multichannel transcranial direct current stimulation to reduce hypertonia in individuals with prolonged disorders of consciousness: a randomized controlled pilot study. Ann Phys Rehabil Med 2019;62(6):418–25. https://doi.org/10.1016/j.rehab.2019.05.009.
[20] Thibaut A, Wannez S, Donneau AF, Chatelle C, Gosseries O, Bruno MA, et al. Controlled clinical trial of repeated prefrontal tDCS in patients with chronic minimally conscious state. Brain Inj 2017;31(4). https://doi.org/10.1080/02699052.2016.1274776.
[21] Barra A, Monti M, Thibaut A. Noninvasive brain stimulation therapies to promote recovery of consciousness: where we are and where we should go. In: Seminars in neurology. New York, NY: Thieme Medical Publishers, Inc. 333 Seventh Avenue, 18th Floor; 2022. p. 348–62.
[22] Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 2004;85(12):2020–9.
[23] Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil Dec. 2010;91(12):1795–813. https://doi.org/10.1016/j.apmr.2010.07.218.
[24] Annen J, Filippini MM, Bonin E, Cassol H, Aubinet C, Carrière M, et al. Diagnostic accuracy of the CRS-R index in patients with disorders of consciousness. Brain Inj 2019;0(0):1–4. https://doi.org/10.1080/02699052.2019.1644376.
[25] Liu Z, Zhang X, Yu B, Wang J, Lu X. Effectiveness on level of consciousness of non-invasive neuromodulation therapy in patients with disorders of consciousness: a systematic review and meta-analysis. Front Hum Neurosci 2023;17:1129254.
[26] Barra A, Rosenfelder M, Mortaheb S, Carrière M, Martens G, Bodien YG, et al. Transcranial pulsed-current stimulation versus transcranial direct current stimulation in patients with disorders of consciousness: a pilot, sham-controlled cross-over double-blind study. Brain Sci 2022;12(4):429.
[27] Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Practice guideline update recommendations summary: disorders of consciousness. Neurology Sep. 2018;91(10):450–60. https://doi.org/10.1212/WNL.0000000000005926.
[28] Kondziella D, Bender A, Diserens K, van Erp W, Estraneo A, Formisano R, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur J Neurol May 2020;27(5):741–56. https://doi.org/10.1111/ene.14151.
[29] Papadimitriou C, Weaver JA, Guernon A, Walsh E, Mallinson T, Pape TLB. "Fluctuation is the norm": rehabilitation practitioner perspectives on ambiguity and uncertainty in their work with persons in disordered states of consciousness after traumatic brain injury. PLoS One 2022;17(4):e0267194.
[30] Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159(7):702–6.
[31] Kent DM, Rothwell PM, Ioannidis JPA, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials 2010;11(1):85. https://doi.org/10.1186/1745-6215-11-85.
[32] Friedman J, Hastie T, Tibshirani R. Regularization paths for generalized linear models via coordinate descent. J Stat Software 2010;33(1):1.
[33] Tibshirani R. Regression shrinkage and selection via the lasso. J Roy Stat Soc B Jan. 1996;58(1):267–88. https://doi.org/10.1111/j.2517-6161.1996.tb02080.x.
[34] Albizu A, Indahlastari A, Suen P, Huang Z, Waner JL, Stolte SE, et al. Machine learning-optimized non-invasive brain stimulation and treatment response classification for major depression. Bioelectron Med 2024;10(1):25. https://doi.org/10.1186/s42234-024-00157-2.
[35] Thibaut A, Bruno M-A, Ledoux D, Demertzi A, Laureys S. tDCS in patients with disorders of consciousness Sham-controlled randomized double-blind study. Neurology 2014;82(13):1112–8. https://doi.org/10.1212/WNL.0000000000000260.
[36] Estraneo A, Pascarella A, Moretta P, Masotta O, Fiorenza S, Chirico G, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: a double-blind cross-over study. J Neurol Sci 2017;375:464–70. https://doi.org/10.1016/j.jns.2017.02.036.
[37] Feng Y, Zhang J, Zhou Y, Bai Z, Yin Y. Noninvasive brain stimulation for patients with a disorder of consciousness: a systematic review and meta-analysis. Rev Neurosci Nov. 2020;31(8):905–14. https://doi.org/10.1515/revneuro-2020-0033.
[38] Estraneo A, Moretta P, Loreto V, Santoro L, Trojano L. Clinical and neuropsychological long-term outcomes after late recovery of responsiveness: a case series. Arch Phys Med Rehabil Apr. 2014;95(4):711–6. https://doi.org/10.1016/j.apmr.2013.11.004.
[39] Estraneo A, De Bellis F, Masotta O, Loreto V, Fiorenza S, Lo Sapio M, et al. Demographical and clinical indices for long-term evolution of patients in vegetative or in minimally conscious state. Brain Inj 2019;33(13–14):1633–9.
[40] Thibaut A, Fregni F, Estraneo A, Fiorenza S, Noe E, Llorens R, et al. Sham-controlled randomized multicentre trial of transcranial direct current stimulation for prolonged disorders of consciousness. Eur J Neurol Oct. 2023;30(10):3016–31. https://doi.org/10.1111/ene.15974.
[41] Thibaut A, Di Perri C, Chatelle C, Bruno MA, Bahri MA, Wannez S, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul 2015;8(6):1116–23. https://doi.org/10.1016/j.brs.2015.07.024.
[42] Thibaut A, Chennu S, Chatelle C, Martens G, Annen J, Cassol H, et al. Theta network centrality correlates with tDCS response in disorders of consciousness. Brain Stimul 2018;11(6):1407–9. https://doi.org/10.1016/j.brs.2018.09.002.
[43] Tarantino V, Fontana ML, Buttà A, Ficile S, Oliveri M, Mandalà G, et al. Increase in EEG alpha-to-theta ratio after transcranial direct current stimulation (tDCS) in patients with disorders of consciousness: a pilot study. NeuroRehabilitation 2024:10538135241296372.
[44] Chennu S, Annen J, Wannez S, Thibaut A, Chatelle C, Cassol H, et al. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. Brain Aug. 2017;140(8):2120–32. https://doi.org/10.1093/brain/awx163.
[45] Sitt JD, King JR, El Karoui I, Rohaut B, Faugeras F, Gramfort A, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain Aug. 2014;137(8):2258–70. https://doi.org/10.1093/brain/awu141.
[46] Gangemi A, De Luca R, Fabio RA, Bonanno M, Cardile D, Mignacca MR, et al. Cognitive effects of transcranial direct current stimulation plus robotic verticalization in minimally conscious state. Biomedicines Oct. 2024;12(10). https://doi.org/10.3390/biomedicines12102244.
[47] Wang Y, Liu W, Wang Y, Ouyang G, Guo Y. Long-term HD-tDCS modulates dynamic changes of brain activity on patients with disorders of consciousness: a resting-state EEG study. Comput Biol Med 2024;170:108084.
[48] Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol Mar. 2020;17(3):135–56. https://doi.org/10.1038/s41582-020-00428-x.
[49] Thibaut A, Chatelle C, Vanhaudenhuyse A, Martens G, Cassol H, Martial C, et al. Transcranial direct current stimulation unveils covert consciousness. Brain Stimul 2018;11(3):642–4. https://doi.org/10.1016/j.brs.2018.02.002.
[50] Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain Sep. 2015;138(9):2619–31. https://doi.org/10.1093/brain/awv169.
[51] Bolognini N, Convento S, Banco E, Mattioli F, Tesio L, Vallar G. Improving ideomotor limb apraxia by electrical stimulation of the left posterior parietal cortex. Brain 2015;138(2):428–39.
[52] Bradnam LV, Stinear CM, Barber PA, Byblow WD. Contralesional hemisphere control of the proximal paretic upper limb following stroke. Cerebr Cortex 2012;22(11):2662–71.
[53] Hermann B, Raimondo F, Hirsch L, Huang Y, Denis-Valente M, Pérez P, et al. Combined behavioral and electrophysiological evidence for a direct cortical effect of prefrontal tDCS on disorders of consciousness. Sci Rep 2020;10(1):1–16. https://doi.org/10.1038/s41598-020-61180-2.
[54] Mensen A, Bodart O, Thibaut A, Wannez S, Annen J, Laureys S, et al. Decreased evoked slow-activity after tDCS in disorders of consciousness. Front Syst Neurosci Sep. 2020;14:62. https://doi.org/10.3389/fnsys.2020.00062.
[55] Bodien YG, Martens G, Ostrow J, Sheau K, Giacino JT. Cognitive impairment, clinical symptoms and functional disability in patients emerging from the minimally conscious state. NeuroRehabilitation 2020;46(1):65–74.
[56] Caplan B, Ponsford J, Jones H, McKay A. Comparing the Westmead posttraumatic amnesia scale, Galveston orientation and amnesia test, and confusion assessment protocol as measures of acute recovery following traumatic brain injury. J Head Trauma Rehabil 2021;36(3):156–63.
[57] Estraneo A, Trojano L. Prognosis in disorders of consciousness. In: Schnakers C, Laureys S, editors. Coma and disorders of consciousness. Cham: Springer International Publishing; 2018. p. 17–36.

[58] Estraneo A, Loreto V, Masotta O, Pascarella A, Trojano L. Do medical complications impact long-term outcomes in prolonged disorders of consciousness? Arch Phys Med Rehabil 2018;99(12):2523–31.
[59] Milosevic M, Nakanishi T, Sasaki A, Yamaguchi A, Nomura T, Popovic MR, et al. Cortical re-organization after traumatic brain injury elicited using functional electrical stimulation therapy: a case report. Front Neurosci 2021:1046.
[60] Chen R, Cohen LG, Hallett M. Nervous system reorganization following injury. Neuroscience 2002;111(4):761–73.
[61] Ramanathan P, Liu R, Chen MH, Kennedy MRT. Memory and executive functions subserving judgments of learning: cognitive reorganization after traumatic brain injury. Neuropsychol Rehabil 2021;0(0):1–24. https://doi.org/10.1080/09602011.2021.1929345.
[62] Batschelett M, Gibbs S, Holder CM, Holcombe B, Wheless JW, Narayana S. Plasticity in the developing brain: neurophysiological basis for lesion-induced motor reorganization. Brain Commun 2022;4(1):1–15. https://doi.org/10.1093/braincomms/fcab300.
[63] Moreau-Debord I, Serrano É, Quessy S, Dancause N. Rapid and bihemispheric reorganization of neuronal activity in premotor cortex after brain injury. J Neurosci 2021;41(44):9112–28. https://doi.org/10.1523/JNEUROSCI.0196-21.2021.
[64] Ghasemian-Shirvan E, Farnad L, Mosayebi-Samani M, Verstraelen S, Meesen RL, Kuo MF, et al. Age-related differences of motor cortex plasticity in adults: a transcranial direct current stimulation study. Brain Stimul 2020;13(6):1588–99. https://doi.org/10.1016/j.brs.2020.09.004.
[65] Barra A, Bodien YG, Tan CO, Martens G, Malone C, Giacino JT. Behavioral fluctuation in disorders of consciousness: a retrospective analysis. Arch Phys Med Rehabil 2025.