How should functional imaging of patients with disorders of consciousness contribute to their clinical rehabilitation needs?

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Purpose of review
We discuss the problems of evidence-based neurorehabilitation in disorders of consciousness, and recent functional neuroimaging data obtained in the vegetative state and minimally conscious state.

Recent findings
Published data are insufficient to make recommendations for or against any of the neurorehabilitative treatments in vegetative state and minimally conscious state patients. Electrophysiological and functional imaging studies have been shown to be useful in measuring residual brain function in noncommunicative brain-damaged patients. Despite the fact that such studies could in principle allow an objective quantification of the putative cerebral effect of rehabilitative treatment in the vegetative state and minimally conscious state, they have so far not been used in this context.

Summary
Without controlled studies and careful patient selection criteria it will not be possible to evaluate the potential of therapeutic interventions in disorders of consciousness. There also is a need to elucidate the neurophysiological effects of such treatments. Integration of multimodal neuroimaging techniques should eventually improve our ability to disentangle differences in outcome on the basis of underlying mechanisms and better guide our therapeutic options in the challenging patient populations encountered following severe acute brain damage.

Keywords
clinical rehabilitation, disorders of consciousness, functional imaging

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Abbreviations

DBS	deep brain stimulation
DOC	disorders of consciousness
EEG	electroencephalography
ERP	event-related potentials
fMRI	functional magnetic resonance imaging
MCS	minimally conscious state
PET	positron emission tomography
VS	vegetative state

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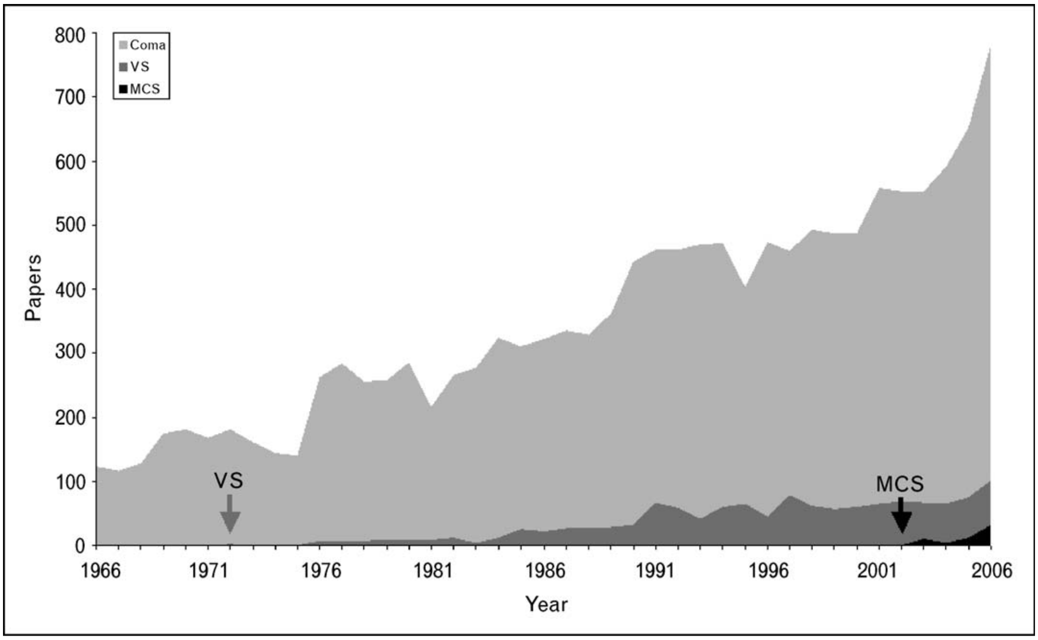
Introduction

The vegetative state (VS) and minimally conscious state (MCS) are disorders of consciousness (DOC) that can be acute and reversible or chronic and irreversible [1••]. A wide variety of traumatic and nontraumatic injuries can result in bedside examinations consistent with VS and MCS that similarly vary in their probability of recovery. Patients in MCS [2] will show more than the mere reflex behavior observed in VS survivors, but they are unable to effectively communicate. Preliminary evidence indicates that MCS patients attain better functional improvement and demonstrate improvement over a longer period of time as compared to those in VS [3••,4]. To date, the vast majority of studies on traumatic or ischemic brain damage have focused on the acute phase of coma (Fig. 1). In our view, there is insufficient attention devoted to the long-term diagnostic, prognostic, therapeutic and social problems of persistent DOC [6–8]. Integration of multimodal neuroimaging techniques may eventually improve our ability to disentangle differences in outcome on the basis of underlying mechanisms and better guide our therapeutic options in these challenging patient populations. Electrophysiological and neuroimaging studies can enable objective assessment of cerebral function in VS and MCS patients, and can therefore overcome some of the difficulties in producing an evidence base for their treatment.

Standards of care for the vegetative state and minimally conscious state

At present, there are no standards of care [9] for DOC. No treatment has been proven to alter the course of recovery from VS or MCS [10••]. Research initiatives aimed at developing therapies to facilitate recovery of consciousness are constrained at a conceptual level by the absence of a universally accepted definition of consciousness [11].

Figure 1 Sole focus on acute coma neglects problems of rehabilitative treatment in chronic disorders of consciousness



Number of scientific papers on coma (light grey), the vegetative state (VS; dark grey) and the minimally conscious state (MCS; black). The last 40 years have witnessed an impressive increase in research efforts in the field of coma as illustrated by the number of publications on the subject. In 1972, the clinical criteria of the VS were published (grey arrow) [5]. Since then there has been a slowly starting but ever-progressive increase in the number of papers on the VS. In 2002, the criteria were published of the MCS (black arrow) [2]. It seems the medical community is rapidly adopting this new clinical entity as witnessed by the number of papers since its definition. The graph, however, also illustrates the huge discrepancy between publications on acute comatose states as compared to chronic (albeit sometimes transient) disorders of consciousness such as the VS and MCS. To date, the primary focus in severe brain damage is on the early phase after the insult. Research will allow clinicians to address the 'silent epidemic' of chronic disorders of consciousness and offer the field evidence based guidelines and therapeutic options. MEDLINE search performed in May 2006.

Existing definitions often invoke the importance of 'purposeful' or 'meaningful' behavior, but it is not clear what type of evidence is sufficient to demonstrate that a specific motor action is imbued with purpose or meaning [12]. Until an objective index is found, the boundary separating consciousness and unconsciousness remains arbitrary [13•]. Recently, diagnostic schemes built around the presence or absence of criterion behaviors have been developed to distinguish MCS from VS [2,14,15]. While behaviorally based diagnostic criteria are useful for characterizing patients clinically, they are inherently flawed because motor responsiveness is often an unreliable proxy for consciousness. Movements that appear to be volitional may actually be reflexive in nature and vice versa. Complicating matters further, patients may exhibit behavioral signs of awareness during one examination and fail to do so on the next. Fluctuations in arousal and motor responsiveness commonly occur in DOC, and may result in diagnostic instability [16,17•]. These factors have conspired to produce rates of misdiagnosis in VS that range from 15 to 43% [18–20].

The effectiveness of an intervention cannot be discerned without a reliable method of evaluation. Until recently, there were few psychometrically sound assessment instruments designed specifically for MCS and VS patients. The psychometric properties of several standardized assessment methods [21–23] useful for monitoring treatment effectiveness have recently been reviewed [24••]. Practical problems have further limited the opportunity to establish a robust base of support for neurorehabilitation. Most extant literature is based on single-center studies with small sample sizes. In the US, limitations in access to care have depleted the available pool of patients as insurers are reluctant to authorize rehabilitation until the capacity to participate actively in treatment can be documented. Ethical issues also contribute to the dearth of controlled trials as clinicians are reluctant to randomize patients with catastrophic brain injury into placebo control groups.

A need for evidence-based neurorehabilitative treatment

Treatment interventions employed in DOC include physical management strategies intended to promote improvements in physical condition and prevent secondary complications, administration of pharmacological agents with putative cognitive-enhancing effects, and multimodal sensory stimulation to elicit a wider range of behavioral responses. Almost all of the published findings on the effectiveness of these treatments are based on poorly controlled (class III) or uncontrolled (class IV) studies. European [25••] and US [26••] evidence-based reviews identified four controlled studies, only one of which was a randomized controlled trial. Consequently, existing data are insufficient to make recommendations for or against any of the neurorehabilitative treatments in VS and MCS.

The influence of postural changes has been explored in a small prospective case series completed in the UK [27]. Twelve patients (VS = 5; MCS = 7; etiology unreported) were assessed using the Wessex Head Injury Matrix [21] while positioned upright or lying supine. Improvements in the highest ranked behaviors elicited and in the total number of behaviors prompted were observed for the upright position, although postural change did not elicit conscious behavior in the VS group. A Dutch retrospective study [28] included 26 young patients diagnosed with traumatic or nontraumatic VS or MCS on admission to rehabilitation. Group A was exposed to an 'intensive' interdisciplinary neurorehabilitation program within 50 days of injury and received treatment for 3–5 months. Specific treatment protocols were reportedly utilized, although no description was provided. In Group B, formal rehabilitation was initiated more than 50 days after initial injury. Intense early rehabilitation resulted in fewer cases of permanent VS (A = 0; B = 3) and less residual disability (A = moderate; B = severe) at 2 years postinjury. Among Group B, however, 83% (10/12) had Extended Glasgow Outcome Scale scores [29] of 5 or less on admission as compared to 50% (7/14) in Group A. Greater injury severity may also have accounted for the delayed onset of rehabilitation in Group B. Studies from Singapore [30] and Sweden [31] have investigated outcome following a comprehensive inpatient rehabilitation program. Treatment activities were not standardized, but involved physical management strategies such as a range of motion exercises, postural control techniques, skin care, nutritional management, sensory stimulation and restoration of sleep–wake cycles. Both studies reported a higher incidence of recovery at 1 year postinjury relative to historical data [32] (i.e. 71 and 81 vs. 35%, respectively). Unfortunately, the lack of treatment controls, inclusion of both traumatic and nontraumatic cases, and reliance on gross outcome measures limit the conclusions that can be drawn based on these findings.

Finally, some groups have attempted to use electrical deep brain stimulation (DBS) to facilitate recovery from VS. A Japanese study has recently reviewed their experience with 25 patients initially classified as vegetative and followed for 10 years after DBS in the centromedian-parafasicularis nucleus and mesencephalic reticular formation [33]. The authors describe eight patients who recovered consistent communication. These uncontrolled studies enrolled all patients prior to 1 year (most between 3 and 6 months), however, and five of these patients were reclassified to MCS based on current criteria [2]. As a result, no conclusion about the efficacy of DBS can be drawn as spontaneous recovery rates for VS following traumatic brain injuries are significant past 6 months and further recovery from MCS may be relatively common even 1–2 years following injury [4]. No improvement was identified in patients who had suffered cardiac arrest. Schiff *et al.* [34] have proposed specific selection criteria and DBS targeting strategies for MCS. Without future controlled studies and careful patient selection criteria, however, it will not be possible to evaluate the potential of therapeutic interventions in DOC. There is also an imperative need to elucidate the neuropsychological effects of such interventions.

Electrophysiological assessments

Sensory and cognitive event-related potentials (ERPs) offer an objective method for assessing residual cognitive functions and outcome in DOC (see previous review [35]). 'Exogenous' ERPs are tightly time-locked to the presentation of an external stimulus and depend on the physical properties of the sensory stimuli used to elicit them (e.g. brainstem auditory, somatosensory and visual evoked potentials). Early components of these potentials arising within 100 ms are known to persistent even in unconscious states. The later components of exogenous potentials and other so-called 'endogenous' ERP components (e.g. P3b, P600, contingent negative variation, readiness potential) are more reliably related to the (conscious or unconscious) cognitive processing of the information and less frequently observed in DOC (for reviews, see [36•,37•]).

With regard to prognosis, the absence (or presence) of some ERP components indicates known prognostic factors for bad (or good) outcome in comatose patients [38•,39]. Most importantly, the absence of somatosensory evoked potentials is a potent indicator of death or irreversible VS [36•,40•]. In contrast, an intact mismatch negativity effect has recently been suggested to have a strong positive predictive value, i.e. its presence predicts an outcome better than death or VS [40•,41].

Using ERPs as an indicator of a patient's cortical information processing capabilities, severely brain damaged but conscious patients showed much greater electrophysiological signs of intact cortical processing as compared to VS or MCS patients. This underlines the fact that ERPs not only reflect lesions in underlying tissue, but importantly also reflect aspects of interacting neuronal networks which give rise to awareness [42•]. Hinterberger *et al.* [43•] have proposed a five-stage assessment involving a standard oddball paradigm, a semantic oddball (patient's name vs. other words and pseudo words), associated word pairs (vs. nonassociated pairs), semantically congruent sentences (vs. semantically incongruent sentences) and instructed imagined hand movement. To illustrate this methodology, data from five seemingly VS patients and five healthy volunteers were presented. Several of the patients showed normal or near-normal ERP responses to some of the tasks, although results were most constant at the lower levels of the suggested processing hierarchy (e.g. semantic oddball). On the basis of these findings, two of the patients were selected for training on a brain computer interface (also called a 'thought translation device') with some success in one of these cases. Similarly, Kotchoubey *et al.* [37•] have reported that some allegedly VS patients might be capable of processing semantic stimuli, indicating some comprehension of meaning. Thus, P3 and N400 components were observed, but were often abnormal (e.g. slow negative response instead of a P300) in patients considered to be VS [44••]. Perrin *et al.* [45•] reported a P300 response to salient stimuli such as the patient's own name as compared to other names in MCS, but also in some VS patients. Evidence is also building up indicating that noncommunicative patients respond more to complex emotionally salient stimuli than to simple stimuli, suggesting some response to meaningfulness of information even in these DOC. None of these studies, however, demonstrates that finding evidence of residual complex processing predicts further recovery.

With regard to the validity of the reviewed data, it should be noted that reliable ERP evaluation in DOC is a challenge in itself, calling for trained electroencephalography (EEG) experts on site. EEG signal quality at the bedside is often affected by various undesirable artifacts, emanating from the surrounding medical equipment and from patients' paroxysmal sympathetic storms (i.e. episodic hyperhidrosis, extensor posturing, changes in temperature, blood pressure, heart and respiratory rate, and level of arousal [46]). Rapidly fluctuating vigilance and quickly exhausted attention make long experimental runs (requisite for reasonable signal-to-noise ratios) impossible, and require a cautious approach to EEG preprocessing and analysis. This restriction should be overcome by using multiple recordings in the same patient. Under these conservative conditions it is often hard to acquire a sufficient number of 'clean' EEG trials for reliable interpretation at the individual patient level. Inferences on a single subject basis – an absolute necessity in clinical settings – are not even easily achievable in healthy controls [44••]. Averaging the results from groups of VS or MCS, on the other hand, can be problematic as the varying etiology and underlying location of brain lesions often give rise to abnormal and quite heterogeneous ERPs.

Data analysis breaking down the EEG in its various frequency bands may make it easier to evaluate which responses can be considered to be real or artificial. Band power and coherence analysis are examples of such analyses, not solely investigating the EEG in the time domain. Coherence measures provide an index of the level of 'functional integration' of the distributed neuronal networks. Unfortunately, such measures are rarely used in DOC. The few available studies ([17•] for review) support the view – gained from functional neuroimaging – that in VS and MCS the interaction between different cortical, as well as with subcortical, brain areas is impaired, e.g. as indicated by reductions in interhemispheric coherence or coherence decrements over affected hemispheres. In addition to conventional ERP analysis, quantitative analyses of the EEG in the frequency domain might thus provide a valuable, and until now mostly unexploited, wealth of information for the evaluation of residual cognitive processing in DOC. Until recently, the bispectral index of the EEG has been exclusively used to assess the depth of anesthesia and sedation [47]. In a preliminary study the bispectral index has been evaluated for its usability in DOC [48•]. Interestingly, an empirically defined bispectral index cut-off 50 differentiated unconscious patients (coma or VS) from conscious patients (MCS or emergence from MCS) with a sensitivity and specificity of 75% each. These findings call for a more extensive evaluation of whether such measures might be helpful in assessing awareness or even outcome [49] in coma survivors.

Functional neuroimaging

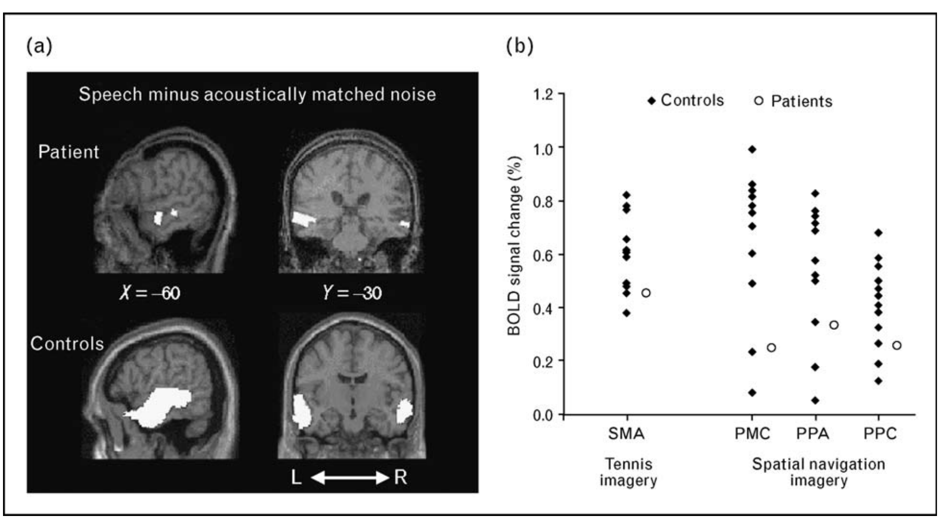
Few studies to date have used functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to monitor and record the recovery of consciousness in VS and MCS [50,51]. Beckinschtein *et al.* [52•] described an interesting case who, after 2 months in a VS, progressed to MCS and then, over the next 18 months, to partial independence. An fMRI was performed involving passive listening blocks of real words, white noise or silence. During VS, the word vs. silence comparison revealed small clusters of activity in temporal-lobe regions, although activity was increased significantly in speech and auditory areas following recovery.

Among the most challenging problems in DOC are the sporadic reports of late recovery following stable behavioral levels consistent with MCS that continue to arise, although few of these patients receive careful evaluation. Voss *et al.* [53••] presented remarkable findings in an unusual case of late emergence from MCS using a combination of diffusion tensor MRI and PET techniques. A 40-year-old male who fully recovered expressive and receptive language after remaining in MCS for 19 years following a severe traumatic brain injury showed very severe diffuse axonal injury along with unusual large regions of increased connectivity (as measured by fractional anisotropy) in posterior medial brain structures not seen in normal subjects. The large, bilateral regions of posterior white matter anisotropy reduced in directionality when measured in a second diffusion tensor imaging study 18 months later, whereas marked increases in anisotropy arose within the midline cerebellar white matter in the same study that correlated with evident clinical improvements in the patient's motor function. Both areas showed relatively increased resting metabolism measured by PET. These findings suggest that slow axonal regrowth may have played a role in the patient's recovery. Most likely, improvements occurring over long time periods in severely brain-injured patients involve both functional and associated structural changes in the brain.

Recent PET and fMRI studies demonstrate that some patients with bedside exams consistent with MCS retain widely distributed large-scale somatosensory [54] and language [55••] responsive networks despite their failure to reliably communicate. Several pathophysiological mechanisms may occur against a background of significant structural brain injuries to limit the expression and use of such wide functional connectivity in MCS patients (see discussion in [56•]). In order to reveal the pathophysiological sequelae underlying VS and MCS, Coleman *et al.* [57•] combined PET and EEG to determine the integrity of neurometabolic coupling. This coupling relationship, which had not been investigated previously in this patient group, seems to be a vital homeostatic function ensuring adequate energy provision to active neuronal groups. The normally tight coupling was preserved in four patients with MCS, but was absent in the six VS patients.

In order to most effectively define the degree and extent of preserved cognitive function in VS, Owen *et al.* [58•] have argued that a hierarchical approach to cognition is required, beginning with the simplest form of processing within a particular domain (e.g. auditory) and then progressing sequentially through more complex cognitive functions. To illustrate this point, a series of paradigms in the auditory domain were investigated, which systematically increase in complexity in terms of the auditory and/or linguistic processes required and, therefore, the degree of preserved cognition that can be inferred from 'normal' patterns of activation in DOC. For example, speech perception was assessed by comparing cortical responses to spoken sentences with those to acoustically matched noise sequences (Fig 2a). At the next level, phonological processing of speech was assessed by comparing responses to degraded ('less intelligible') sentences vs. normal (intelligible) sentences. Finally, speech comprehension was tested by comparing cortical responses to sentences containing ambiguous words (e.g. 'the creak/creek came from a beam in the ceiling') and matched unambiguous sentences. Increases in neural activity during ambiguous sentences reflect the operation of semantic processes that are critical for speech comprehension. The authors illustrated this approach in a patient diagnosed as vegetative who showed activation in response to speech relative to signal correlated noise, potentially reflecting some perception of speech. A significant response was also observed to speech of increasing intelligibility, suggesting that these perceptual processes are recruited more strongly for speech that

Figure 2 Searching for a neural correlate of consciousness in the vegetative state (VS)



(a) Cerebral activation when hearing sentences vs. signal correlated noise in superior and middle temporal gyri in a VS patient [59••], potentially reflecting some perception of speech, and in a group of healthy volunteers [60]. (b) Blood oxygen level dependent (BOLD) signal intensity changes in supplementary motor area (SMA), premotor cortex (PMC), parahippocampal area (PPA) and posterior parietal cortex (PPC) in the same VS patient while imagining playing tennis or moving around a house plotted against BOLD changes measured in 12 healthy volunteers performing the same tasks. Owen *et al.* [59••] have recently proposed such a 'command following' functional magnetic resonance imaging paradigm for unequivocally demonstrating consciousness in patients lacking reliable motor command following behavior. Reprinted with permission from the AAAS [59••].

can be more readily understood. Finally, ambiguous sentences yielded a partially normal response, interpreted as evidence that some semantic aspect of sentence processing was intact; in other words, not only did the patient's brain recognize speech as speech, but it seemingly was being processed at a level which, in the healthy brain, is equated with comprehension [61•].

In some of the EEG [42•,43•,45•] and functional imaging [61•] studies described above, 'normal' evoked potentials or activation patterns in predicted regions of cortex have been used to infer residual cognitive processing in patients diagnosed as vegetative. The question that invariably arises is whether such signs indicate awareness. It is important to stress that there is a wealth of data in healthy volunteers, from studies of implicit learning and the effects of priming, to studies of learning during anesthesia that have demonstrated that many aspects of human cognition can go on in the absence of awareness. In the examples discussed above (including speech perception and the detection of semantic ambiguous sentences), under normal circumstances cognitive processing is relatively automatic. That is to say, it occurs without the need for willful intervention – you cannot choose to not understand speech that is presented clearly in your native language.

Owen *et al.* [59••] have elegantly addressed this concern by applying an fMRI paradigm where noncommunicative patients are asked to perform mental imagery tasks at specific points during scanning. In one exceptional VS patient studied 5 months after a traumatic brain insult, activation was observed in the supplementary motor area after being asked to imagine playing tennis. In contrast, when asked to imagine visiting all of the rooms of her house, activation was observed in premotor cortex, parahippocampal gyrus and posterior parietal cortex (Fig. 2b). Similar activation patterns were seen in 34 healthy volunteers studied in Cambridge and Liège. Importantly, because the only difference between the conditions that elicited task-specific activation was in the instruction given at the beginning of each scanning session, the activation observed can only reflect the intentions of the patient (which were, of course, based on the remembered instruction), rather than some altered property of the outside world. In this sense, the decision to 'imagine playing tennis' rather than simply 'rest' is an act of willed intention and, therefore, clear evidence for awareness and command-following in the absence of voluntary motor responsiveness. Interestingly, when re-examined 6 months later the patient showed inconsistent visual tracking – the most frequently encountered clinical sign of recovery from VS.

Conclusion

Neurorehabilitative treatment in VS and MCS poses distinctive conceptual, methodological and practical challenges that currently defy efforts to establish a strong evidence base in these challenging patient populations. The quest to generate empirical support for the effectiveness of rehabilitation has been in part hampered by the lack of suitable clinical measurement tools. Recovery from traumatic brain injury is influenced by many variables, all of which need to be controlled or accounted for. Failure to build-in adequate controls for these covariates significantly limits generalizability of the results and diminishes the clinical importance of neurorehabilitation studies in DOC. The relatively long time course of recovery following severe brain damage underlines the importance of developing objective markers for identifying patients with further potential for meaningful therapy and functional improvement. To help differentiate effective from ineffective interventions, rehabilitation research must shift from small, single-center studies to large multicenter clinical collaborations. Research collaborations and partnerships need to be developed and fostered to accomplish this objective. Ultimately, bringing electrophysiological and neuroimaging studies into the clinical evaluation process will enable frameworks to be developed for the longitudinal assessments of cerebral function. Such frameworks should fully consider outcome probabilities and uncertainty in the context of the known constraints that exist when making sensitive and sophisticated measurements.

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- •• of outstanding interest

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