Consciousness: Its Neurobiology and the Major Classes of Impairment

Andrew M. Goldfine, MD\textsuperscript{a,b,*}, Nicholas D. Schiff, MD\textsuperscript{a}

Disorders of consciousness encompass a wide range of syndromes whereby patients demonstrate a globally impaired ability to interact with the environment. We briefly review the subset of disorders of consciousness that result from permanent brain injury, such as ischemic stroke, global ischemia, and traumatic brain injury (TBI). Disorders of consciousness may also arise as functional (rather than structural) disturbances of consciousness, including generalized and complex partial seizures as well as metabolic and toxic delirium. These functional disturbances are not discussed here but have been reviewed by Posner and colleagues\textsuperscript{1}.

In this review, we first review brain structures that support the normal conscious state to develop a framework to demonstrate how their dysfunction can lead to disorders of consciousness. We then present the nosology of the different disorders of consciousness, including coma, vegetative state (VS), the minimally conscious state, and akinetic mutism. The pathology and brain imaging data that give insight into the pathophysiology associated with each diagnostic category are reviewed. Knowledge of the underlying mechanisms of the disorders can enhance the ability to prognosticate and promote recovery from these devastating conditions.

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\textsuperscript{a} Department of Neurology and Neuroscience, Weill Cornell Medical College, LC 803, 1300 York Avenue, New York, NY 10065, USA
\textsuperscript{b} Burke Medical Research Institute, Weill Cornell Medical College, 785 Mamaroneck Avenue, White Plains, NY 10605, USA
* Corresponding author. Burke Medical Research Institute, Weill Cornell Medical College, 785 Mamaroneck Avenue, White Plains, NY 10605.

\textit{E-mail address: andygoldfine@gmail.com}
Normal human consciousness is defined as the presence of a wakeful arousal state and the awareness and motivation to respond to self or environmental events. In the intact brain, arousal is the overall level of responsiveness to environmental stimuli. Arousal has a physiologic range from stage 3 non–rapid eye movement (REM) sleep during which strong stimuli are required to elicit a response, to states of high vigilance, during which subtle stimuli can be detected and acted upon. Whereas arousal is the global state of responsiveness, awareness is the brain’s ability to perceive specific environmental stimuli in different domains, including visual, somatosensory, auditory, and interoceptive (e.g., visceral and body position). The focal loss of awareness, such as language awareness in aphasia or spatial awareness in left-sided neglect, does not significantly impair awareness in other modalities. Motivation is the drive to act on internal or external stimuli that have entered conscious awareness. In the next section, we describe the brain regions that support these three aspects of consciousness and show that they are not independent, but rather interact extensively with each other.

Underlying Substrates of Arousal and Conscious Awareness

The initial discovery that specific brain areas could drive overall cerebral activity appeared in the work of Moruzzi and Magoun. These investigators proposed the existence of an ascending reticular activating system (ARAS) in the upper brainstem tegmentum (reticular formation) and central thalamus that promoted widespread cortical activation. Subsequent work has revealed that the ARAS is not a monolithic activating system, but a collection of interdependent subcortical and brainstem areas that have specific roles in arousal and awareness. The core areas for maintaining an awake state seem to be the glutamatergic and cholinergic neurons in the dorsal tegmentum of the midbrain and pons. These areas activate the central thalamus (primarily intralaminar nuclei) and basal forebrain. The central thalamus and basal forebrain subsequently activate the cortex through glutamatergic and cholinergic projections, respectively. In addition to supporting arousal, the basal forebrain is active during REM sleep and the central thalamus plays a role in conscious awareness (below).

Other brain regions are also involved in arousal but have a more modulatory role, including the nuclei in the upper brainstem that use norepinephrine, dopamine, serotonin, and other neurotransmitters. These nuclei act on the basal forebrain, thalamus, striatum, and cortex. The hypothalamus is also involved in the sleep-wake transition and its histaminergic outputs help maintain the awake state. Overall, the large number of regions involved in arousal provide redundancy, so that selective damage to one region, even if bilateral, only rarely results in permanent unconsciousness.

Whereas the level of arousal reflects the overall state of activity in the brain, conscious awareness is a more dynamic and complex process involving various cerebral networks at any one time. There are several competing theories on how we become aware of environmental and internal stimuli, although it is widely believed to depend on interactions between the cortex and specific and nonspecific (e.g., intralaminar) thalamic nuclei.

Conscious awareness and arousal states also interact. Without arousal, there is no awareness, and in states of high arousal, awareness can be focused on one modality at the expense of others. For example, animal models have been used to demonstrate that in addition to a core generalized arousal, there are also more specific forms of arousal, such as hunger, sexual behavior, and fear, which enhance responses to
specific stimuli. Conversely, awareness also influences arousal, such as the abrupt increase in arousal when an alarm goes off.

Stimuli are not acted on as reflexes, but typically require motivation to enter conscious awareness through a process called intention or goal-directed behavior. Lesion and functional brain imaging studies demonstrate that goal-directed behavior is primarily driven by the medial frontal and anterior cingulate cortices. These cortical regions are supported in producing goal-directed behavior by striatopallidal-thalamic loops as well as the ventral tegmental area and the periaqueductal gray of the brainstem (Fig. 1). The arousal systems discussed previously also act directly on the goal-directed behavior network, primarily through innervation of the striatum and frontal cortex.

In summary, studies indicate that the normal conscious state includes volition, processing of sensory information, and a generalized level of arousal. As discussed later, brain injury can produce disorders of consciousness from injury at any of these levels.

NOSOLOGY AND PATHOPHYSIOLOGY OF DISORDERS OF CONSCIOUSNESS

The disorders of consciousness discussed in this article are syndromes that are behaviorally defined, and each is thought to reflect a specific pathophysiologic model (Table 1). However, the models are imprecise and do not apply in every case. As such, we will begin with an overview of the behavioral assessment of levels of consciousness, followed by more detailed descriptions for each syndrome. Pathology and imaging data are used to support mechanistic models underlying each behavioral syndrome.

General Concepts in the Assessment of Consciousness

The determination of level of consciousness at the bedside is primarily a judgment of responsiveness across multiple sensory modalities (eg, vision, somatosensation, and
auditory) and cognitive domains (e.g., language and learned movements). The lowest level of behavior to be documented is whether eye opening is spontaneous or requires stimulation (e.g., loud sounds or noxious touch). Higher-level behaviors include responses that are contingent on sensory stimuli. These range from eyes tracking a mirror and withdrawal from painful touch, to accurately following commands and the use of objects (e.g., a comb or toothbrush). The level of effort required to alert the patient and the speed of their response should also be noted, because these observations guide subjective and objective assessments of arousal. Inaccuracy in specific cognitive domains (e.g., aphasia and apraxia) reflects focal impairments in awareness, rather than global disorders of consciousness.

One caveat to behavioral testing of arousal is that all of the patient responses require a capacity for motor output and adequate arousal. Patients with functional or structural interruption of motor systems at any level may not be able to follow the commands, despite full comprehension and intention. Patients with a minimal residual ability to communicate (e.g., eye blinks) but who have generally intact consciousness,
are deemed to be in the locked-in state (LIS).\textsuperscript{1} There are also patients with both impaired motor output and arousal from diffuse brain injury, which contribute to a high misdiagnosis rate in disorders of consciousness.\textsuperscript{22,23} To ensure accurate diagnosis in patients with diffuse brain injury, it is essential to examine patients at maximal levels of arousal using techniques such as deep tendon massage or postural repositioning.\textsuperscript{24} Patients should also be examined at multiple time points or videotaped by family to capture periods of high alertness.

### Coma and VS Represent Loss of Corticothalamic Function

The most common disorder of consciousness that immediately follows severe brain injury is coma. Coma is a state that is characterized by eyes-closed unresponsiveness: comatose patients fail to respond to even the most vigorous stimulation.\textsuperscript{1} When given noxious stimulation, patients may not move at all or may display stereotyped/reflexive movements only. The pathophysiology of coma is generally the same as VS (discussed below), except that some patients have loss of some or all brainstem function. For patients with loss of all brainstem and cerebral function, the diagnosis is brain death. Coma prognosis is complex and depends on the causes and the severity of injury as well as the multiple medical factors that led to the initial injury.\textsuperscript{1} Brain death does not have a prognosis because it is simply equivalent to death.

If patients survive coma, they either recover consciousness within days or transition to VS within 30 days after injury. VS is a behaviorally-defined state, similar to coma, whereby patients show no evidence of self or environmental awareness.\textsuperscript{25} It is also similar to coma because patients can have spontaneous or stimulus-induced, stereotyped movements, and may retain brainstem regulation of visceral autonomic function that would suggest that the lower brainstem is intact. The only behaviorally salient difference from coma is that VS patients cycle daily through eyes-open and eyes-closed periods. This does not imply that VS patients have normal sleep-wake cycles; rather, their electroencephalograms (EEGs) display a monotonous slow pattern regardless of whether the eyes are open or closed, or they only have fragmented components of normal electrographic sleep-wake phenomenology.\textsuperscript{26,27} The periods of eye opening reflect only a crude arousal pattern that involves upper brainstem nuclei.

VS may represent a transitional state on the way to recovery of consciousness or could be a chronic condition in cases of more severe brain injuries. Persistent vegetative state (PVS)\textsuperscript{25} is a term used for patients who have remained in VS for an arbitrarily defined duration of 30 days.\textsuperscript{26} Another commonly used term is permanent vegetative state, which is applied to patients in VS after global ischemia for 3 months or TBI for 1 year.\textsuperscript{28} Permanent VS is more of a prognosis than a diagnosis, as these time durations reflect only a reduced probability of recovery. We prefer to define patients in persistent VS simply by the etiology and duration, avoiding the use of absolute terms, such as permanent.

There are three main pathologic findings in patients with prolonged VS from structural injury. The most common is diffuse cortical and thalamic cell loss, which occurs in the setting of global ischemia caused by cardiac arrest.\textsuperscript{29} The second is widespread damage to long axons, known as diffuse axonal injury (DAI), which occurs from TBI.\textsuperscript{30} DAI has been shown in animal models to occur as a result of rapid acceleration-deceleration injury of the axons, sometimes in conjunction with delayed axonal disconnections.\textsuperscript{31} The third and least common pattern of injury is extensive damage to the upper brainstem and thalamus, which usually occurs as a result of basilar artery stroke.\textsuperscript{32,33} The common link between these three injury types and VS is the loss of corticothalamic function, either from cell death, disconnection, or loss of brainstem drive.
In vivo imaging studies further support the model of VS that represents diffuse corticothalamic dysfunction. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is a measure of energy consumption, and in the brain it primarily represents the neuronal firing rate at the synapse. Patients in PVS have been shown to have global metabolic rates reduced by 50% or more compared to healthy controls. In general, metabolic rates exhibit less reduction in the brainstem and more reduction in the cortex and subcortical nuclei, with the most consistent reduction occurring in the medial parietal and frontal areas. Comparable reductions in cerebral metabolic rate have been identified during generalized anesthesia and slow-wave sleep in healthy controls.

To examine corticothalamic functioning more directly, investigators have used H$_2^{15}$O-PET, functional magnetic resonance imaging (fMRI), and event-related potential analysis to measure brain responses to sensory inputs. Studies using simple and complex auditory stimuli and noxious stimuli have demonstrated a pattern of activation of brainstem and primary sensory cortical regions in some patients with VS without the activation of higher-order sensory or association areas. These results suggest that patients with VS may have some residual thalamocortical activity, but do not possess enough to produce the global integrative function that is required for conscious awareness.

These imaging tools have also been used to provide insight into an ambiguous area between VS and consciousness. Schiff and colleagues described 3 patients who demonstrated complex motor behaviors but were still considered to be in VS. All were found to have an overall low resting metabolism (20–50% of normal by FDG-PET), yet had residual islands of cortical and subcortical higher metabolism in areas consistent with their behaviors. In all patients, these brain structures showed marked abnormalities at the level of response to simple sensory stimuli as measured by magnetoencephalography, which demonstrated a loss of the integrity of even early cortical processing. These patients, similar to those studied by Laureys and colleagues, revealed that some preservation of basic corticothalamic processing may coexist with behavioral unconsciousness and this does not contravene a clinical diagnosis of VS.

The Minimally Conscious State Represents a Low Level of Residual Corticothalamic Integrity or an Inability to Maintain Cerebral Integrative Function

The next level of recovery on the continuum from VS to full consciousness is the minimally conscious state (MCS). The Aspen Neurobehavioral Workgroup defined MCS in 2002 as “a condition of severely altered consciousness in which minimal but definite behavioral evidence of self or environmental awareness is demonstrated.” This condition has been operationally defined by a set of behavioral tests known as the JFK Coma Recovery Scale Revised (CRS-R), and is discussed by Hirschberg and Giacino elsewhere in this issue. MCS includes a more heterogeneous group of patients than VS, because the operational definition allows for a wide range of behaviors, whereas VS only includes reflexive movements. In MCS, low-end behaviors include visual tracking to a mirror, localization of noxious touch, and inaccurate verbalization, whereas high-end behaviors include consistent movement to command and choosing correctly between 2 objects. Patients with only low-end behaviors can be difficult to differentiate from VS, because these behaviors may be subtle and infrequent. This differentiation is essential because patients in MCS have significantly better prognoses for recovery than those in VS.

Pathology and anatomic imaging literature have revealed that MCS is typically associated with similar injury patterns as VS, but with sufficient surviving neurons and connectivity between cortex, thalamus, and brainstem arousal centers to support some level of behavioral responsiveness. In the setting of TBI, one study found...
that across the continuum of VS to MCS to full consciousness, patients were less likely
to have severe DAI and more likely to have focal brain injuries, such as hematomas
and contusions. Notably, these investigators reported overlap in pathologic find-
ings across all levels of consciousness, which demonstrated that current anatomic
methods cannot completely account for the variances in behavior.

Functional imaging (fMRI and H$_2^{15}$O-PET) and neurophysiologic methods have
proved to be more sensitive than anatomic methods in distinguishing patients in VS
from those in MCS, because they measure corticothalamic function. For example,
when presented with sensory stimuli, MCS patients activate higher-order association
cortices, similar to healthy controls, whereas VS patients, at best, activate primary
sensory cortices. However, compared to healthy controls, MCS patients require
a higher level of arousal (ie, more alerting stimuli) to produce similar patterns of acti-
vation. This requirement for a higher level of arousal is consistent with behavioral
data, which show that these patients fluctuate in their level of responsiveness and
suggest an underlying inability to maintain cerebral integrative functioning.

**Akinetic Mutism and Related Syndromes are Disorders of Goal-Directed Behavior**

Akinetic mutism, in its originally described form, fits in the category of MCS, although
milder variants, including abulia, are categorized as fully conscious states. Patients with these conditions have intact arousal and often the appearance of vigilance, but have severe poverty of movement despite lack of damage to motor systems. Severe cases can only be distinguished from VS by the preservation of visual tracking through smooth pursuit eye movements. The underlying cause in most cases is injury to the bilateral medial frontal lobes and anterior cingulate cortex from a mass lesion or anterior cerebral artery infarct. These syndromes can also arise from bilateral injury to the basal ganglia, dorsal and central thalamus, or midbrain, as these areas are tightly integrated with the frontal lobes in the generation of goal-directed behavior. As discussed below, the circuits involving these areas play a significant role in recovery of consciousness from a wide range of injuries.

**Patients with Severely Damaged Motor System may be Widely Miscategorized**

Functional brain imaging studies have led to a new but currently undefined category of disordered consciousness: patients who are behaviorally in VS or MCS, yet demonstrate imaging evidence of high-level cognitive processes, including command following and, in 2 instances, communication. These studies used fMRI (although EEG may also be used) to reveal changes in cortical activity when patients are asked to imagine a motor performance or spatial navigation task (Fig. 2 shows example results). The most striking example of covert conscious function came from a patient who initially fulfilled the behavioral criteria for VS, but was able to answer 5 out of 6 autobiographical questions correctly using the mental imagery of playing tennis as a ‘yes’ response and walking around his house as a ‘no’ response. Only a few such patients have been identified, because there are no obvious historical or anatomic imaging markers to predict covert consciousness. Furthermore, the assessments currently used require levels of memory and attention not present even in some fully conscious subjects. The clinical implications of these findings are also not clear, because it is not yet possible to turn these fMRI or EEG paradigms into a bedside communication device. Moreover, it is not known if the ability to follow commands identified through fMRI predicts an emergence to full consciousness. However, once these measurements are obtained, it is clear that the patients have interacted with their environment, thereby placing them in a vague category between high-level MCS and LIS.
MECHANISTIC CONSIDERATIONS IN THE PROGNOSIS AND TREATMENT OF PATIENTS WITH DISORDERS OF CONSCIOUSNESS

Prognosis from Disorders of Consciousness

The pathophysiologies described earlier help to explain the mechanisms by which some patients recover and why others do not, and give an interpretive framework for the successes of specific interventions in improving arousal. In brief, the three types of pathophysiologies linked to disorders of consciousness from permanent brain injury discussed earlier are: (1) loss of cortical and thalamic neurons from global ischemia, (2) DAI in the setting of rapid acceleration/deceleration that leads to the disconnection of corticothalamic loops, and (3) damage to the upper brainstem and central thalamic neurons leading to loss of arousal tone for corticothalamic loops. In addition, dysfunction of medial frontal systems from any of these three mechanisms, as well as others, may result in MCS and globally impaired levels of function near the operational criteria for MCS (ie, akinetic mutism).

Global ischemia generally has the worst prognosis of the injury types discussed because of the marked sensitivity of cortical and thalamic neurons to hypoxia and ischemia.29 In this setting, the key issue is typically the prediction of recovery to avoid futile attempts at sustaining life in patients who are often otherwise quite ill.69 Previously, this declaration could be made purely on clinical grounds within 3 days after an injury,70 but with the addition of therapeutic hypothermia,71,72 these criteria no longer apply.73 Prognosis after hypothermia is difficult, most likely because the neurons spared by hypothermia remain functionally impaired for long time periods, leading to a later demonstration of recovery. As a result, new prognostic algorithms need to be developed, which will likely require more time after injury as well as new imaging and electrophysiological techniques. If patients survive and transition to MCS, treatment strategies are similar to those discussed below.

Patients with DAI presenting with coma have a wide range of outcomes, from prolonged VS to independent functioning.28,69 The time course of recovery is also variable, ranging from days to years. Interestingly, one patient regained full consciousness and language after 19 years in MCS.74 There are no reliable predictors of recovery in this population, although rough guidelines suggest that patients in MCS have a higher likelihood of recovery than those in VS, especially if MCS occurs within the first year.51,52 This is a better prognosis than for patients with global ischemia, for whom recovery to independence is exceedingly rare if the patient remains in VS for 3 months. The mechanism by which the brain recovers from DAI is still not clear.75 Possible contributors to recovery include the regrowth of corticothalamic axons74–77 and the remapping of intracortical connections to maximize spared pathways.78

Fig. 2. Noninvasive imaging evidence of command following in a patient with severe brain injury who was behaviorally locked in. (A) fMRI demonstrating increased activity (orange) in supplementary motor and other cortical areas when the patient was asked to imagine swimming versus a resting baseline. (B) Spectral analysis of EEG in the same patient performing the imagination of the swimming task at a different time. Example power spectra for 2 channels are on the right; the image on the left summarizes significant spectral changes across all channels and frequencies tested. Head maps below summarize amplitude of power change across all channels at the frequencies listed directly above. (Adapted from Bardin JC, Fins JJ, Katz DI, et al. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. Brain 2011;134(Pt 3):769–82; Goldfine AM, Victor JD, Conte MM, et al. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin Neurophysiol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21514214. Accessed July 17, 2011; with permission.)
In cases of upper brainstem and central thalamic injury, recovery of function depends on the ability of the remaining arousal centers to restore patterned cortico-thalamic activity. If return of consciousness occurs, patients may be left with severe cognitive deficits, depending on the degree of thalamic injury. Similar to DAI, there are a wide range of reported outcomes, but anatomic and functional imaging techniques do not allow prediction of the potential for recovery in most cases.

TREATMENT STRATEGIES FOR PATIENTS WITH DISORDERS OF CONSCIOUSNESS

Akinetic mutism offers a model for approaches that improve the level of consciousness (see Fig. 1). In akinetic mutism, the injury to the cortico-striatopallidal-thalamocortical circuit involving the medial frontal lobe can produce dysfunction as severe as in patients with much more widespread injury. Increasing the function of this circuit through medication or brain electrical stimulation can drive activity widely through the cerebrum. For example, dopaminergic agents (eg, amantadine, levodopa, bromocriptine, or apomorphine) that enhance striatal background activity, have been shown to raise the level of consciousness and improve recovery rates in patients with various severe brain injuries (reviewed by Hirschberg and Giacino elsewhere in this issue). Zolpidem, an agonist of a subset of \( \gamma \)-aminobutyric acid (GABA\( \_A \)) receptors, has also been demonstrated to dramatically improve consciousness in patients with diffuse brain injury. The mechanism of action of zolpidem is thought to occur through cortical activation, both directly and indirectly, by inhibiting the globus pallidus interna from inhibiting thalamocortical firing. Another successful approach through the same network, although only reported in a single patient, is direct activation central thalamic outflow via deep brain stimulation (DBS).

There are no clear guidelines for medical management to attempt to speed recovery of consciousness, as almost all data are from case series. Accordingly, we offer some approaches that have been proved to be successful in our experience. For a medically stable patient with a disorder of consciousness, the first goal is to rule out potential inhibitors of recovery. This includes undiagnosed seizure disorders, particularly because they can be difficult to detect behaviorally in patients with impaired motor output. Medications can also be culprits in worsening arousal, especially those with anticholinergic, antihistaminergic, barbiturate, and benzodiazepine properties as well as some antiepileptic and antispasticity agents.

To promote recovery of consciousness, we recommend amantadine 200–400 mg, split between early morning and early afternoon doses. Amantadine has a relatively benign safety profile and is the only medication tested to date in patients in VS and MCS in a well-powered, randomized, double-blind, clinical trial, although the results have not yet been published. A selective serotonin reuptake inhibitor may also be added, based on animal model and clinical trial evidence for enhancing plasticity, although there is no strong evidence in patients with disorders of consciousness. Zolpidem can be given as 5 or 10 mg doses with a response expected within 1 hour, though only rarely. Zolpidem is apparently safe, though there are no long-term data and the potential for habituation exists. Medications should be trialed individually, with a gradual titration of doses. Patients should have well-documented formal examinations using the CRS-R before and after initiation and dose changes, and any side effects should be noted. In addition, physical, occupational, and speech therapy should be used when appropriate, including daily joint stretching to avoid contractures, which can severely limit movement when the motor system recovers.
SUMMARY

Fins\textsuperscript{92} has argued against a nihilistic approach to patients with chronic disorders of consciousness, as if the loss of function is invariably permanent and there is nothing more to be gained from diagnostic testing and treatment. We agree that these patients deserve a more systematic approach to assessment, prognosis, and treatment. The evidence described in this review shows that these conditions include a wide range of pathologies, causes, prognoses, and proven treatments. Diagnostic testing can be used to determine the degree of injury and suggest residual capacity for cognitive function. Future work will allow the use of imaging modalities to predict recovery and development of tools to communicate with those who have lost all motor function.

REFERENCES


