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EDITORIAL

Reconsidering the Many Disorders of Consciousness

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Acute and chronic neurological and psychiatric disorders can disrupt consciousness and cause affected individuals to lose varying degrees of behavior control. In 2002, researchers identified the minimally conscious state (MCS) as a distinct disorder of consciousness.[1] They defined this as "a condition of severely altered consciousness characterized by minimal but definite behavioral evidence of self or environmental awareness."[2] The MCS is distinguished from the vegetative state (VS), where patients show arousal and have sleep–wake cycles but are unaware of themselves and their surroundings. The VS has also been described as "unresponsive wakefulness syndrome."[3] The VS and MCS are prolonged disorders of consciousness (pDOCs) that most commonly result from traumatic or hypoxic brain injury. Some patients with these injuries die from permanent cessation of all integrated brain functions. Others progress from coma to the VS or MCS. Whereas VS patients have no integrated thalamocortical and corticocortical connectivity, some of this connectivity is preserved in MCS patients. This may explain why minimally conscious patients "retain the capacity for cognitive processing."[4] According to some estimates, 100,000 people in the United States alone are minimally conscious.[5] In 1994, the Multi-Society Task Force estimated that approximately 25,000 patients in the United States were in the VS.[6] The subsequent identification of the MCS as a diagnostic category suggests a smaller prevalence of the VS.

There has been much debate about the ethical implications of the diagnosis and prognosis of pDOCs, as well as interventions that might restore cognitive and motor functions of patients with them.[7] One significant development was the 2006 finding from functional magnetic resonance imaging (fMRI) that a patient believed to be in a VS was covertly aware and in the MCS.[8] The imaging showed activity in cortical brain regions indicating a conscious response to verbal instructions. It suggested that the brain activity associated with the patient's response was a potential marker for recovery from the MCS, defined as the "re-emergence of a functional communication system or restoration of the ability to use objects in a functional manner."[9] Around the same time, the first FDA-approved clinical trial using deep brain stimulation (DBS) for a patient who had been in an MCS for seven years after an assault showed some restoration of his cognitive and motor functions.[10] Although to date clinical trial outcomes of DBS for pDOCs have been mixed, MRI-guided DBS and other interventions may "facilitate recovery and quality of life in these patients."[11]

A review of the neuroethics literature might suggest that the VS and MCS were the only disorders of consciousness. There are other conditions in neurology and psychiatry where awareness is acutely or chronically disrupted or impaired. Yet the literature has largely ignored the normative issues they raise. Many of these disorders were identified long before pDOCs. Continued research aimed at gaining a better understanding of the underlying brain mechanisms associated with these disorders could lead to improved detection, treatment, and prevention that could improve quality of life for the many millions of people suffering from them. The neuropsychiatric and psychological burdens that delirium, epilepsy, and other forms of impaired consciousness impose on people make them at least as medically, ethically, and socially significant as the VS and MCS because they affect many more people. Some of these disorders involve the *level* of consciousness, or the degree to which one is aware. Others involve the *content* of consciousness, or what or how one perceives when one is aware. Both types can harm individuals in different ways and degrees over varying time scales.

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In the 19th century, John Hughlings Jackson defined delirium as a disordered level of consciousness.[12] Norman Geschwind later described it as a disorder of global attention involving psychomotor impairment.[13] A more recent definition of delirium is "a severe neuropsychiatric syndrome characterized by the acute onset of deficits in attention and other aspects of cognition."[14] Delirium involves different degrees of psychomotor agitation or retardation.[15] It is the most prevalent syndrome in the general medical setting.[16] "Terminally ill cancer patients, patients with moderate to severe traumatic brain injury, frail elders, and the critically ill are clinical populations generally recognized to have a high incidence of delirium over their course of illness, due to factors such as polypharmacy, comorbid medical conditions, and metabolic dysfunction."[17] This disorder is associated with "increased morbidity and mortality, increased cost of care, increased hospital-acquired complications, poor functional and cognitive recovery, and decreased quality of life."[18] Antibiotics can prevent the development of delirium from urinary tract infections. In most cases, though, delirium can have complex causes that present challenges in detecting and treating it. Reducing sedation and analgesia may mitigate the psychomotor agitation associated with delirium in dying patients and thus be an important component of palliative care. The development of more effective tools to predict which conditions would be more likely to induce delirium, and judicious use of psychopharmacology, could prevent or at least reduce the burdens this disorder imposes on patients. Because of the disorder's effect on cognition, decisions about how to control delirium are not made by patients but by families and healthcare providers presumed to be acting in their best interests.

Epilepsy affects 50 million people worldwide. It is characterized by recurrent seizures disrupting both experience and behavior due to abnormal electrical discharge in large groups of neurons in the upper brainstem and medial thalamus.[19] Hippocrates described epilepsy as "The Sacred Disease." The work of Hughlings Jackson, and of Wilder Penfield and others in the 20th century, has increased our understanding of its pathophysiology.[20] Not all seizures cause impaired consciousness. But consciousness is transiently lost for shorter periods in absence seizures (less than 10 seconds) and longer periods in generalized tonic–clonic and focal impaired consciousness seizures (1–2 minutes). Approximately 30% of people with this disorder fail to respond to antiepileptic medications. Improved brain-mapping techniques using neuroimaging and electrocorticography have led to more precise identification of the source of seizures at the earliest sign of hyperactive electrical brain activity and improved monitoring of this activity.[21] Guided by these techniques, DBS and responsive neurostimulation (RNS) have reduced seizure frequency in otherwise treatment-resistant epilepsy for some patients.[22]

Hal Blumenfeld describes the psychological harm from the fear and anxiety in anticipating a seizure: "Imagine that at any moment you might suddenly become unconscious and lose control of your behavior. This is the burden carried by many people with epilepsy who face their lives each day not knowing when all their plans and activities will be devastated by seizures."[23] He adds: "When consciousness is lost, patients may be injured, lose work or school productivity, suffer social stigmatization, or lose their lives."[24] Although the acute disturbance of consciousness in epilepsy does not involve the same chronic cognitive and motor impairment as the MCS, Blumenfeld's comments suggest that epilepsy could be more harmful because patients in the MCS probably lack the level of awareness to have these negative experiences. Advances in epilepsy research could improve DBS and RNS for this disorder or lead to other interventions that might reduce the incidence of or prevent seizures and improve the quality of life of those who have it. These include both adults and children. The latter group raises such ethical questions as whether parents could give proxy consent for a child to undergo an intervention that is more brain-invasive than pharmacotherapy, and how to weigh the benefits against the risks.

One of the characteristics of the MCS is cognitive motor dissociation. This is a state in which there is awareness and cognitive function but no motor behavioral responses.[25] This has precluded minimally conscious patients from communicating and indicating gesturally or verbally that they are aware.[26] It is not only an obstacle to confirming awareness, but also to patients wanting to express their experience and preferences for medical care. In some neurological disorders, cognitive and motor functions are not so separable. Consider ideomotor apraxia. This may result from a parietal lobe stroke. It is characterized by the inability to execute certain learned movements. An affected patient may be able to perform some

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motor functions without thinking about them but cannot perform them when consciously trying to follow instructions because of difficulty in processing information. At least one researcher has described apraxia as a disorder "on the cognitive side of motor control."[27] The psychomotor impairment in apraxia suggests that cognitive and motor functions intersect in normal and abnormal brain processing. Regardless of whether one describes apraxia as a disorder of the level or content of awareness, its psychomotor symptoms suggest that some disorders of consciousness impair behavior control through interacting cognitive and motor dysfunction. Therapies need to target the neuropsychological bases of these two aspects of behavior.

Ischemic and hemorrhagic strokes cause other neuropsychiatric sequelae involving the content of consciousness. Some people with hemispheric strokes may experience hemispatial neglect.[28] The deficit in attention and awareness toward the space opposite the brain damage can limit their ability to navigate physical space and interact with others. Poststroke syndromes are one area where different forms of neurostimulation might have therapeutic potential in activating endogenous repair and growth mechanisms in the brain. The goal would be not to increase the level of awareness but to increase or restore the content of awareness to enable patients to reengage with and readapt to the natural and social environment.

Psychiatric disorders, specifically schizophrenia and major depression, may be the most prevalent chronic disorders of the content of consciousness. Georg Northoff explains that they are "disorders of the *organization* or *form* of consciousness."[29] This distinguishes them from the VS and MCS, which are disorders of the *level*, *degree*, or *state* of consciousness. The disturbed cognitive and affective contents of these disorders and their adverse impact on behavior are symptomatic of varying degrees of dysfunction in neural circuitry and neurotransmission. Referring to the positive subtype of schizophrenia, Stanislas Dehaene states that it "drastically alters the conscious integration of knowledge into a coherent belief network, leading to delusions and confusions…. [30] He further states that "schizophrenics' main problem seems to lie in the global integration of incoming information into a coherent whole."[31] This is consistent with the earlier view of Emil Kraepelin, who in 1896 described schizophrenia as a "disunity of consciousness," or an "orchestra without a conductor," based on clinical observation of his patients.[32] Disruption of resting-state connectivity in anterior cortical midline structures appears to be a major factor in the pathophysiology of this disorder. "The occurrence of abnormal contents and an abnormal self in phenomenal consciousness in schizophrenia can ultimately be traced back to their resting state activity's abnormal self-specific and pre-intentional organization and its subsequent carryover and transfer to any kind of stimulus-induced activity and its associated phenomenal states, that is, consciousness."[33]

Resting-state dysfunction in the midline network has also been associated with the cognitive and affective disturbances in major depression. These disturbances negatively influence how a depressed person perceives and responds to the world. In severe cases, the phenomenology of this disorder can make one feel disengaged and disconnected from the social environment. Among other deficits, disrupted information in the content of consciousness in psychiatric disorders can impair the ability to form and execute action plans and thus impair agency.

A substantial number of people with these disorders either receive no therapy, or their symptoms are resistant to it. One psychopharmacological treatment paradigm for depression has been challenged by a recent meta-analysis questioning the efficacy of selective serotonin reuptake inhibitors for major depression.[34] Studies of ketamine and psilocybin have shown promising positive results in some patients whose symptoms fail to respond to other treatments.[35] But more studies are needed to establish their safety and efficacy. Despite widespread misinformation about electroconvulsive therapy (ECT) and actual cases of amnesia and other adverse events, it has been effective in relieving symptoms in severe unipolar and bipolar depression.[36] Still, its positive effects may be limited. DBS has been studied in many clinical trials for treatment-refractory depression, though it remains experimental for this disorder. Clinical trials are being conducted to test DBS as a potential treatment for schizophrenia.[37]

Psychiatry is an area where more patients can be harmed from disordered consciousness, and where more can benefit from interventions that modulate neural functions mediating the content of consciousness, than any other area of clinical neuroscience. Mental illness constitutes the main global

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burden of disease in terms of years lived with disability.[38] As a matter of distributive justice, research priority in neuroscience should be given to gaining a better understanding of how genetic, epigenetic, biological, and environmental factors disrupt normal brain–mind interaction. This could lead to therapies that could improve the lives of the many millions of people affected by psychiatric disorders.

There are many disorders of consciousness in neurology and psychiatry. They involve varying degrees of impairment in the level, content, and duration of awareness. These disorders cause substantial harm to patients and their families. Accordingly, they all deserve attention from researchers, clinicians and ethicists in discussing the burdens they impose on people and how those affected by these disorders could benefit from interventions that could relieve or prevent them.

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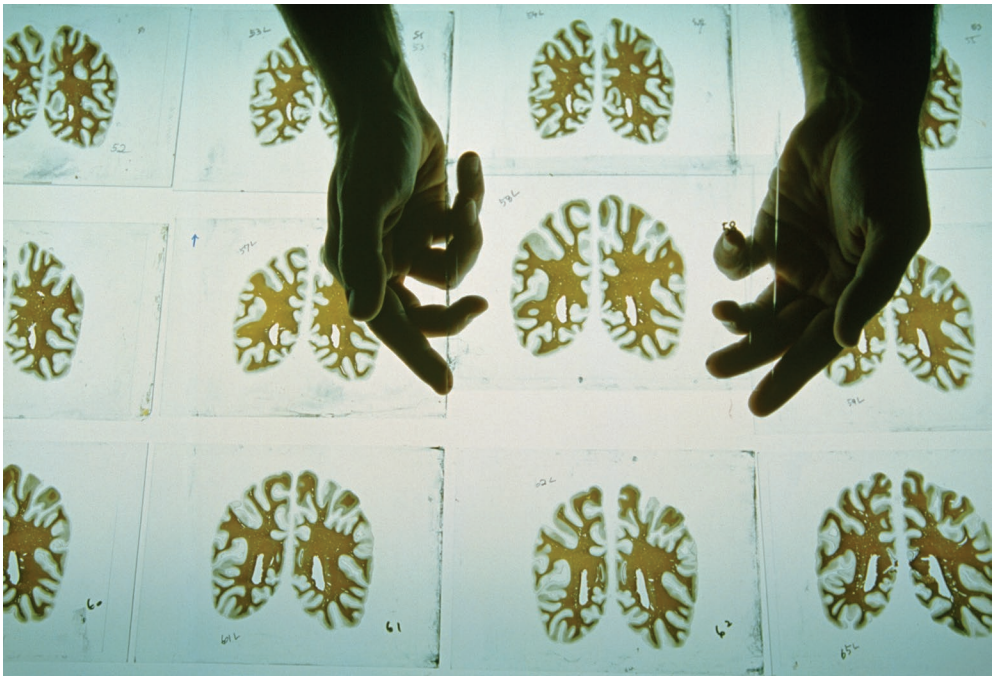

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