Waking Up from Coma: New Treatments, New Hope

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The movie *Men in Black* ends with a sequence where Tommy Lee Jones' character is reported in the popular press to have awakened miraculously after 20 years in a coma. Although clinicians traditionally have scoffed at such reports, such cases do make the news now and again, and raise the question of whether and how that can happen. Recent advances provide some answers, and suggest some treatments that might promote such an outcome.

To understand how coma occurs, it is first necessary to have a basic understanding of how wakefulness is maintained in a normal brain. We now know that there are collections of nerve cells in the lower part of the brain, called the brainstem, which are responsible for maintaining a waking state. These nerve cells use excitatory neurotransmitters such as acetylcholine, norepinephrine, dopamine, and glutamate, to turn on cell groups in the upper part of the brain, called the forebrain.

The ultimate target of this arousal system is the cerebral cortex, the part of the brain responsible for perception, thought, and behavior. During wakefulness, the activity of the cerebral cortex can be measured by the electroencephalograph, or EEG, which shows waves of electrical activity that are relatively fast (12 to 60 waves per second). During sleep, specialized sleep-promoting cell groups in the brain shut down the arousal system, and the waves in the cerebral cortex slow down to the range of 1-7 waves per second.

Anything that disrupts this arousal system, by either damaging the origin of the pathway in the brainstem, its targets in the forebrain, or the connection between the two, will cause loss of consciousness. This is typically accompanied by slow EEG waves, similar to those during sleep, except that such patients cannot be awakened by stimulation (calling their name, shaking them). If the disruption is temporary, such as the brief loss of consciousness that occurs after mild head trauma, the individual may awaken very quickly. If the unconsciousness persists, it is called coma.

After a couple of weeks in coma due to damage to the arousal system, the remaining structures in the brainstem and the forebrain reorganize their activity, and the patient recovers apparent wake-sleep cycles, with eye opening and faster EEG waves during the day. However, if the cerebral cortex itself has been damaged, for example by severe traumatic brain injury or a period of not getting enough oxygen, then the patient will go through "empty" wake-sleep cycles, where the eye opening is not accompanied by signs of cognition (responding to events in the environment). After a month in such a state, the patient is said to be in a "persistent vegetative state."

Some patients, however, show clear although minimal signs of cognitive recovery. These responses may be as small as tracking people in the room with their eyes, or squeezing someone's hand, and the responses may not even be consistent. These patients are said to be in a "minimally conscious state" (MCS) and it is this group that has recently received attention as having the potential for more substantial recovery.

Some of the evidence for the preservation of function in the brains of patients in MCS comes from functional imaging, which allows mapping of brain activity by magnetic resonance imaging (MRI) scanning. Several groups of investigators have used functional MRI (fMRI) to evaluate residual function in the brains of MCS patients. In intact individuals who are resting in the MRI scanner, characteristic patterns of activity within the brain can be detected when the subject is asked to imagine watching a tennis match (which, for example, engages the visual cortex). This pattern is different from what is seen in a subject who is asked to imagine walking through a house, or performing another task (which typically engages parts of the cerebral cortex involved in control of movement). Saying a person's name produces a different pattern of brain activation from repeating a string of meaningless syllables. Tests of this type on MCS patients show that some demonstrate patterns

of brain activation, which indicate that they are indeed processing the task using areas of the brain appropriate for that task, despite their appearance of non-responsiveness.

Interestingly, there is another smaller group of patients in whom this technology has been able to detect brain function, despite the appearance of complete unresponsiveness. Such patients, in whom damage to the upper brainstem has completely severed the outputs from the cerebral cortex that cause movement, may be completely unable to move, a condition called the "locked-in syndrome." If there is some preservation of movement, even of the eyelids or eyes, the patient can communicate by those movements. Previously, in completely paralyzed patients, there was no way to be sure if the patient was cognitively intact. Now, studies using fMRI have not only detected normal patterns of brain activation, but by allowing the patient to imagine either a tennis match (meaning a yes answer to the question) or a walk (signifying a no answer), the patients have even been able to establish a crude means of communication.

Long term follow up studies of the patients in MCS, however, have discovered that they may occasionally undergo remarkable recovery. A few people have even recovered to the point where they could perform some of their activities of daily living and communicate verbally. Surprisingly, this "waking up from coma" can occur over a relatively brief period of time, after months or even years of minimal responsiveness. Neurologists now hypothesize that parts of the brain are awake and processing information even during the minimally responsive period, but how the switch gets thrown one day to allow return of clear wakefulness is not understood. It is also not known whether repetitive daily cognitive stimulation, despite apparent lack of response, may contribute to coaxing the brain to recover. We need long term studies that provide such stimulation to MCS patients, to determine its efficacy in restoring function.

Several new treatments in the last few years suggest that recovery can be promoted. One new treatment that was demonstrated in a large scale controlled clinical trial was the use of amantidine. This drug is most frequently used to treat tremor in Parkinson's disease, but was given to a group of 87 patients in persistent vegetative state or MCS, for four weeks, beginning 4-16 weeks after severe traumatic brain injury. Compared to 97 patients who received a placebo, the ones that received amantidine showed a more rapid improvement in disability scores during the four weeks of treatment. It is not yet known whether this treatment with amantidine resulted in better long-term outcomes, nor whether treatment for a longer or different period in their course would have been more effective. We need more trials to determine these answers.

Another promising treatment in a few MCS patients has been the use of zolpidem. Although zolpidem is usually used as a sleeping aid, in a few cases it has been found to "wake up" patients in MCS temporarily, allowing them reproducibly to perform better on cognitive tasks. The mechanism by which either amantidine or zolpidem works is not understood, but both require further attention.

Finally, the use of deep brain stimulation (DBS) has received considerable attention in patients with MCS. This therapy, in which wires are placed in the brain and attached to an electrical stimulator that is implanted under the patient's skin like a cardiac pacemaker, is in its infancy. However, if DBS is used to activate a part of the brain that has been deprived of important inputs by a brain injury, there is reason to believe that it may be useful. This method requires further study.

Meanwhile, for the families of patients in MCS, these studies signal some hope. For too long we have disparaged the value of rehabilitation and functional improvement in such patients. These studies indicate that some patients in the MCS group can in fact "awaken from a coma," sometimes even after many years, and they stimulate us to do more research to find out which patients may benefit, from which treatments, and at which stages of recovery.

Further Reading:

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