The Brightening Future of Locked-in Persons

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Abstract

The gradual descent into paralysis and mutism over several years in Amyotrophic Lateral Sclerosis and the sudden descent following a brainstem stroke are medical tragedies. But the advances in technology indicate a relatively bright future for such locked-in patients. This isolated state of living has inspired researchers around the world to find several ways to restore some aspects of living a fuller life. Examples include: 1] Restoration of speech. 2] Restoration of movement. 3] Robotic helpers making life a lot easier for the person and the caregivers. 4] Speaking robots allowing for an intelligent conversation. 5] The Multiverse enabling a person to enjoy another world and be active within that world. 6] Finally, opening a business on the Internet and earning a living.

Not only technology is advancing, but medical therapies are too for ALS people. Recently, Amylyx has been approved by the Federal Drug Administration (FDA) and added to Radicava and Rilutex medications that prolong and improve the quality of life for the locked-in person. There are as many as 53 medications being trialed that will expectantly slow the progression of the disease and eventually cure the disease.

Review

1] *Speech Restoration:* Amyotrophic lateral sclerosis (ALS), also called motor neuron disease, is a two to five years descent into full paralysis and mutism. Respiratory muscles become involved so that ventilator assistance is required to avoid death. About 90% of patients choose to die by refusing the ventilator because of the bleak outlook (1). Some decide to stay alive such as Stephen Hawking (2) who contributed to the world of science by speaking through an assistive device that restores slow typing and slow speech. Half of ALS patients have frontal lobe involvement so that a fronto-temporal dementia develops. The other half continue with full cognition. There are 30,000 ALS patients in the USA with approximately 6,000 each year having to decide to live or die as they become fully paralyzed and mute (3). To be able to speak again would make them “feel human” as the late ALS patient (DJ) wrote to me over 20 years ago. He said he “would be able to speak to my children again”!

Silent speech has been a challenge that is now being overcome. Silent speech is defined as a mute person attempting to speak, speaking as they used to in the past, but not imagining speech. Various researchers have used different techniques. For example, Dr. Ed Chang's group records using electrodes placed over the cortical speech area with patients successfully producing phrases in real time (9). Stravisky et al have produced silent speech from an arm motor area using an array of electrode pins that are inserted into the cortex (10). Kennedy et al have decoded silent speech offline using an electrode that grows the brain neuropil into the electrode tip (12a). The electrodes were implanted into the speech motor cortex.

Critical remaining issues include longevity of the neural signals that need to be decoded to produce the speech. Ideally, the electrodes and recording systems should never have to be replaced. Placing electrodes over the cortical surface leads to loss of signal over several years (11). Arrays of pin electrodes also lose signal quality after many years with single units deteriorating to multi-units and finally noise (4d). Only one system has been shown to last as much as 13 years until the locked-in patient died, with continuation of the same signals without needing recalibration (12a,b). Thus, if those researchers can achieve on-line decoding of the signals, their system would be preferred. The alternative is to replace electrodes that have lost signal and have scarred the brain, but that will only produce further scarring and subsequent loss of signal.

2] *Movement Restoration:* Locked-in patients would welcome restoration of movement to at least to one arm to allow writing and use of utensils. Researchers are using access to cortical signals to control a muscle stimulator that would restore movement to a paralyzed dominant arm (4a-d). Restoring full body movement using an exoskeleton is more problematic but is theoretically possible (5).

Early studies were used to control robotic arms that provided a way for the patient to feed herself (4a). An array of electrodes from Blackrock Micro Inc. was used for several years. Controlling paralyzed limbs by cortical control of a muscle stimulator is still in progress (13). One major difficulty is that there is absence of sensory feedback in most brainstem stroke or tetraplegic patients, so accurate control of the arm is extremely difficult. Efforts are underway to supply feedback to the sensory cortex to provide the closed loop between motor intent, muscle stimulation and sensory feedback that will operate in less than a hundred milliseconds (14).

3] *Robotic Assistants:* Recent developments in the field of robotics indicate that robots may act as assistants that provide medication, food, drink, and so on. Reviews in (6a, b) indicate that they are not yet adequate except in simple tasks such as reaching for an item (plate of food, for example) and placing it as planned. Nevertheless, it is clear that improvements in robotic assistants will be available in the future.

4] *Speaking Robots:* Even more remarkable is that robots can converse intelligently (7). This recent publication describes a unique means of training the AI by not giving it rules, but allowing it to derive its own programming paradigm by feeding information into the AI system. In a competition playing the game of *Diplomacy,* the robot, playing and speaking anonymously, scored in the top 10% of human players. What is truly remarkable is that the robot had to converse with the other players and was not recognized as a robot! So, it seems that conversational robots are here, well, almost here.

5] *The Metaverse:* Being able to access virtual reality using the Metaverse would also enhance the life of the locked-in patient. Wearing a headset, such as Oculus Rift (8a), the locked-in person can immerse themselves in the 3D world of the Metaverse. Using eye movements that are tracked by the headset, the person's avatar can move under control of the eye movements and explore any part of the world. In addition, virtual reality involving active sporting events will eventually be realized. The use of the Metaverse has helped people during pandemic lock down to support their mental health (8b). It is being considered a useful tool in healthcare (8c) and certainly would be useful tool for locked-in persons.

6] *Run a business:* There is no reason why locked-in people cannot open a business on the Internet once they can communicate quickly with the Internet using speech. If they do open a business, they would earn some funds and restore the sense of personal achievement. They might earn enough to pay taxes!

Therapies for ALS people:

Rilutek, generic name riluzole, is a glutamate blocker. Excess glutamate damages neurons it is believed. Two studies indicated that it prolongs time to needing a tracheostomy by 60 to 90 days. The dosage is 50 mg twice per day. It was FDA approved in 1990s.

Radicava, generic name edaverone, is given by infusion or orally. Oral dose is 105 mg. per day. Four trials have indicated that it improves strength. Long term trials are underway.

Relyvrio, generic name amylyx, was recently approved by the FDA. It is a combination drug containing sodium phenylbutyrate and taurursodiol. Studies indicate it slows down the progress of ALS and slows down functional decline. Thus, it extends survival. It is an oral medication.

Physical therapy: Some clinicians advise against it so as to preserve what muscle strength remains. Others advise to do it to strengthen the normal muscle fibers. It is controversial.

ALS Therapies on the horizon:

There is a recent review of drugs being trialed for ALS (15). There are as many as 53 drugs under investigation! Some have shown positive results but are not yet approved by the FDA. Here is a sample of those that have good results in early trials. Let me summarize here:

A] Anti-inflammatory group such as Tegoprubart, tocilizumab, ANX005, Mastinib and others.

B] Neurotrophic and neuroprotection such as CNM-Au8 (gold), ILB, Inosine and others.

C] Anti-excitotoxicity include Mexilitine, Ezogabine, Memantine.

D] Immune system regulation drugs such as Guanabenz, Trazadone and others.

E] Anti-aggregation medications such as Rapamycin, Colchicine and others.

F] Gene therapy includes Engensis, BIIB105, Torfersen and others.

G] Anti-apoptotic: Methylcobalamin and others.

You may have noticed that some medications are already FDA approved for other uses, such as colchicine for gout, rapamycin for tumors, trazadone for depression and sleep, memantine for memory loss, inosine as a nutritional supplement, proleukin for melanoma cancers, and so on.

Conclusion

Thus, the typical future day for the locked-in person will be as follows. When the locked-in person wakes in the morning, his or her activities of daily living (such as bathroom activities, breakfast and so on) are performed by a robot. The robot then gives the patient the prescribed medications. The person can ask the robot to use the Internet, listen to music, watch television, or read a book. The person can also have an intelligent conversation with the speaking robot using the person's silent speech facility. Conversation with family and friends is now easy and rewarding. The person can choose to enjoy the Metaverse, or decide to study or run a business on the Internet. These technologies apply to people with brainstem stroke as well as to ALS persons. The range of medications being trialed for ALS persons does suggest that the disease will be controlled and eventually, I expect, a cure!

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