Neural Prostheses for Restoring Memory – Looking to the Future

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Abstract

Neural implants are a new tool in the field of medicine, and are becoming increasingly common. Issues with memory are one potential area in which such devices may prove useful. This paper reviews research published to date and explores future possibilities and hurdles in developing a device available to the general population.

Introduction

Memory loss and deficits have long been a major concern among all societies. Traditionally associated with the elderly, conditions such as neural atrophy, Alzheimer’s disease and other forms of dementia not only deprive individuals of cherished memories, but may also remove their independence and reduce capacity to fully function for the rest of their lives. Memory is poorly understood on a biological level, but new ground has been broken and some inroads have been made into understanding its inner workings. Utilising recent advances in our understanding of memory, hypothetical targets and possible neural interfaces have been put forward. Most have yet to see the light of day, but the door has certainly been opened, and restoring, enhancing, or preventing loss of memory are tangible and realistic goals for the future.

Biology

Though well researched in the field of psychology, memory in a purely biological sense is less well understood. Several types of memory exist, which tend to be concentrated in specific parts of the brain. Though not yet conclusively proven, there is a general consensus as to the general principles of memory formation and function.

Implicit procedural memory, i.e. memory of skills and tasks, is retained in the cerebellum at a largely subconscious level[1]. For example, an experienced driver can hold a conversation while driving, but a learner may find this overwhelming as they are dedicating a higher proportion of conscious effort to controlling the vehicle.

Short-term/working memory is concentrated in the parietal and prefrontal cortices[2].

Memories in the traditional sense, as in recalled past experiences and emotions that are stored on a medium to long-term basis, are stored in different locations. Sensory information passes through the hippocampus to the medial temporal lobe. Medium-term memories are stored in the entorhinal, perirhinal, and parahippocampal cortices, whereas longer-term memories are moved to the neocortex, usually during sleep.

Difficulties with memory can affect any or all of the above areas, with correspondingly varying effects. Memory loss is generally broken down into two distinct types: retrograde amnesia, where one cannot retrieve past memories, and anterograde amnesia, where new memories are hard to lay down. The latter is usually trauma-related, but the former can occur not only from trauma, but a wide range of other causes such as Alzheimer's, alcoholism or simply old age.

Memories are laid down using a neurological activation pattern known as long-term potentiation (LTP), with a required growth factor, brain-derived neurotrophic factor (BDNF), which encourages consolidation of new synapses.

Memory retrieval occurs via action potentials (APs) that travel from the prefrontal cortex (where the decision to retrieve information is made), to the basal ganglia and from there to the relevant areas, as outlined above. The former two areas could be considered "gatekeepers" to the memories, so damage here would be devastating, but the memories are likely to remain intact in other areas.

Using this principle, we can consider lost memories not as gone, but currently irretrievable, as the storage locations are theoretically intact. This echoes the description of dementia according to Penny Garner of the Contented Dementia Trust; she describes memory as an ever-expanding photo album where new memories ("photographs") are not always inserted. Similarly, one could describe Alzheimer's as losing specific photographs throughout this album; the patient may be able to tell that there is an empty space in the album, which can cause considerable distress for sufferers[3].

Existing Research

Little research on actual devices has been done to date, though a single piece of literature has put forward a prototype.

This study looked at using a 32-electrode device implanted into the hippocampus of the rat brain. This was placed in the CA1 and CA3 regions, which connect up predominantly to the entorhinal cortex, which controls medium-term memory[4].

Following surgical implantation of the device and a minimum of 7 days' respite, rats were trained using a presentation of two levers. The inappropriate one had been previously presented, and selecting the other resulted in a reward, after which both levers were withdrawn until the rat had moved away for some time.

The implanted device recorded the brain signals in these areas via a computer connection. Using this data, characteristic brain signal patterns were recognised for each decision of the rat. A multi-input/multi-output (MIMO) model of electrical signals was used in this study to characterise the "memories" made during the training. The researchers had previously developed this model for such a purpose in mimicking hippocampal signals[5].

Thus, using this measured pattern as a template, the researchers could accurately predict the rats' choice from the brain output signal.

This MIMO signal pattern was then replicated and delivered to the rats. This had the effect of increasing the success rate of the rat selecting the appropriate lever. This improvement was particularly evident when there was a longer delay between successive presentations of the lever.

A neurological agent, MK801, which significantly impairs neurological transmission within the hippocampus, was also used to simulate an impaired ability to remember. It produced a clearer result in the difference between stimulation and none.

The animals themselves acted as their own controls; stimulated and unstimulated success rates were compared among the same animals.

Significantly, the researchers also delivered a scrambled signal from the MIMO signals. This had no effect on success rate compared to no stimulation (control) success rates. This would suggest that the pattern of signal was important in influencing behaviour.

Implementation

In the context of Alzheimer's or another dementia, this approach may be of limited practical potential. This system requires signal measurement of the brain in advance of memory loss, i.e. "backing up" specific memories.

However, for non-patient-specific memories, such as procedural memory, this approach could be useful. Visual/emotional memories are unique and thus not retrievable without prior recording, but skills such as walking, speaking and bladder control are all learnt neurological responses, usually in areas of the cerebellum. If this approach were taken, a "stock" of skills and procedural memory tasks could be drawn upon to restore basic skills to individuals who may have lost them.

However, this brings up ethical concerns akin to those raised by gene therapy or gene selection. Theoretically, if such a system were to exist, one could essentially "shop" for new skills such as another language, ability to play an instrument, sports skills, etc.

Developing a neural prosthesis for memory is not an easy task, the brain being a highly complex and compact structure. Currently, we know roughly where much of it is stored anatomically, but the underlying mechanisms for memory formation and retrieval are still largely elusive.

Memory is not a uniform entity either, and great variations exist among individuals. One famous example is that of a lady known as AJ, who was one of the first documented cases of highly superior autobiographical memory[6]. She had an innate ability to remember details, banal and emotional, happy and sad, in equal measure all the way back to her formative years. Existing models largely accept that memories are prioritised and stored according to the emotional significance we give them, but AJ, and those like her, make us wonder if there's more to the system.

Proposing a Hypothetical Future Technology

Looking to the future, one would hope that diseases such as Alzheimer's and other forms of dementia would potentially be curable. Medicine and other forms of therapy could offer the answer, but neural implants may be a viable alternative.

As we have seen, different areas of the brain are responsible for different types of memories; some are conscious, some are not, some are unique to the individual, some are not. It is not possible to address them all at once, so specific examples must be selected.

Clinical Needs

There are two key questions to ask in developing a memory implant:

> "What would we need an implant to do?"
> "What can we realistically do?"

The former has virtually endless answers, but the latter has a much smaller cohort of answers. Pushing the boundaries of technology for the future is about taking answers to the first question and seeing if we can make them answer the second. This is a good model for identifying areas for research, but not always for trying to develop a useable product here and now.

One of the unfortunate results of Alzheimer's and other forms of dementia is a loss of independence due to dangerous behaviour, such as leaving the front door open, leaving kitchen appliances on, etc[7,8]. These behaviours are one of the first reasons patients may need a caregiver, or to be moved into a home. If there was some way of mitigating such dangers, patients might remain living independently for that bit longer.

Concept

Berger et al.'s model took a specific behaviour and encouraged the rodent to perform a specific task with an electrical signal. In a similar manner, patients could be "taught" to avoid risky and dangerous behaviour such as leaving a lit gas ring unattended.

Having developed the neural activity as a MIMO signal, these signals could be programmed to a neural implant connected to a wireless receiver/transmitter; similar to cochlear implants, pacemakers, implantable cardioverter-defibrillators, deep-brain stimulation battery packs, etc.

The wireless device could also be controlled via specific signals, such as a proximity alarm. If the patient turns on a gas ring and leaves it unattended, a signal would be sent to the implant, and thus the brain, to go back and turn off the gas. Similarly, if a door was left open, and the patient left, a trigger for a MIMO signal to return and close the door would be generated. A wide range of signals to avoid danger could be programmed in this manner.

Looking to the future beyond these initial concepts, perhaps this could form the basis of a neurological reminder of important people in the patient's life. Not only is it distressing for family members to not be recognised by their own parents, siblings, etc., but one can only imagine the distress of the patient if they are constantly surrounded by people they perceive to be strangers.

It is likely, though not certain, that Berger et al.'s device signals a memory, not a forced set of actions, though it is unclear if the resulting actions of the rodents were completely autonomous. If the mechanism of Berger et al.'s system triggers a memory of a specific event as a prompt rather than a series of forced actions, this opens up a whole range of possibilities to "back up" other memories.

Benefits

While this would have no effect on the underlying disease process, it would have a significant impact both on the patient and their family/carers. It could provide peace of mind for all involved that, for now at least, the patient would be not likely to hurt themselves, and could be left unsupervised for significant periods of time. The possibility of more time to be trusted to be independent would likely also be very empowering and welcome amongst patients.

Long-term care of the dependent elderly, and concerns for their wellbeing, are well-documented sources of adverse consequences for carers. Depression, stress, poor sleep, anxiety, neglect of personal problems, health deterioration and other issues are commonly seen among the carer population[9,10].

Ultimately, most patients in this group end up in a nursing facility of some description, which is a heavy financial burden on the families, the state, or both. Generally, patients are happier at home, and if we can facilitate this for longer, everyone benefits both psychologically and financially.

Research Challenges

We are a long way from nearing anything resembling this technology being available for the general population. Prototypes of similar technology were first published in rodents only a year ago.

Research into the biology of memories needs much additional development.

Further *in vivo* studies and prototypes of the published neural implant, or similar, are needed, and then advancement to larger in vivo studies if successful. This is both costly and time-consuming, but given time, it is virtually inevitable.

Potential damage to neural tissue also needs to be considered. Potentially devastating side effects of surgical implantation or inadvertent stimulation of other areas is very possible, if not highly likely. This is a very important consideration when looking to apply this technology to humans.

Ethical Implications

Significant ethical hurdles would have to be overcome, particularly in the area of patient autonomy. Triggering a physical response/action in response to a wireless signal questions true autonomy. Whether or not the action is due to a memory prompt, or a direct neurological stimulation over which the patient has no control, is the big question. Neurological "reminders" rather than direct surrendering of bodily control are very different, and may not be possible to identify in rodent models.

Patient autonomy in a damaged neurological state, as prospective patients would be, is questionable. The validity of informed consent and appreciation of the risks in these patients are sometimes hard to determine, and in such an invasive procedure, is especially important to get right.

Due to the progressive nature of these conditions, this device would have an inherently short period of use. The time from diagnosis to required placement in a home or under full-time care could be only a few years. It begs the question of whether or not such a procedure is warranted.

However, if this technology were to progress to aid in recognition of family members and beyond as previously described, one could argue it never becomes obsolete.

However, one does need to bear in mind whether or not such an implant might fundamentally change the personality of the patient. For many people, their condition forms who they are, and major treatment in a non-immediately life-threatening situation may be somewhat unpalatable to many.

As with any wireless technology, the possibility of outside interference must also be considered. It has been found that pacemakers containing patient data can be accessed by an unauthorised operator, so privacy and protection issues would need to be safeguarded.

Ultimately, if we keep the patient's best interests at heart, and follow the four principles of autonomy, beneficence, non-maleficence and justice, we should find ourselves on the right path.

Conclusions

Memory is a complex neurological process, and science has barely scratched the surface. In light of recent discoveries and successful in vivo models, we can hypothesise on what possibilities lie ahead. No doubt there is a market, especially with a large proportion of the elderly population experiencing memory difficulties. In an ever-aging society, these issues are not going away. An implant of some description is inevitable, but how it might work, or when it may become a reality, we can only speculate.

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