A Discussion Regarding the Feasibility of Memory Enhancement through Electrical Stimulation of the Paper Circuit

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Mini Review

Abstract

Long Term Potentiation (LTP) is the neurological process that naturally enhances our ability to recall memories that we have formed neural networks for. It commonly occurs in pyramidal neurons, which are abundant within regions of the hippocampus. Since neurons can be stimulated to commit neural activity through electrical stimulation, it can be reasonably assumed that electrically stimulating (pyramidal) neurons within certain regions of the hippocampus and other structures throughout the paper circuit can induce the release of certain neurotransmitters important in LTP at a higher frequency. This increased release of glutamate and subsequent increased diffusion of sodium and calcium ions into postsynaptic neurons' dendrites would theoretically make LTP occur in these same neurons (where LTP had already just naturally occurred) repeatedly, thus adding more AMPA and NMDA receptors to these neurons' dendritic membranes and producing more Brain Derived Neurotrophic Factor (BDNF) which would cause synaptogenesis to occur at an increased rate as well.

Keywords: Long Term Potentiation (LTP); Neurons; Pyramidal; Hippocampus; Neurotransmitters

Introduction

There are multiple approaches to memory enhancement, most of which include using oral supplements (*i.e.* Cognium®), but another theoretical approach is through electrical stimulation of deep gray matter structures involved in memory formation [1]. This theory revolves around the idea of using neural threads in conjunction with microelectrodes planted throughout the brain to deliver electrical pulses. This electrical stimulation will specifically target parts within the paper circuit, a neural loop which is significantly involved in memory formation, and is intended to induce Long Term Potentiation (LTP) at an increased frequency. LTP refers to the strengthening of synapses in that a (postsynaptic) neuron's minimum threshold for an action potential to occur is decreased by adding more AMPA and

NMDA receptors to the dendritic membrane, thus making it easier to access the neural network and retrieve the information contained within it [2].

Brain Derived Neurotrophic Factor (BDNF) is also produced during late phase LTP through gene expression caused by dopamine binding to the metabotropic D5 dopamine receptor, which causes synaptogenesis and expands the neural network. When the recipient of the implant begins to form a memory and the neurons within the hippocampus start firing, the microelectrode designated to that area will detect the neural activity and alert the implant's CPU (either through direct connection or technology similar to Bluetooth) located at the top of the skull (in place of a piece of bone similar to how titanium is used in place of pieces of skull that had to be removed during neurosurgery). The implant will then send electrical stimulation down the neural threads targeting the hippocampus in the form of electrical pulses to make the neurons release more glutamate (which binds to the AMPA receptors) so that an increased amount of sodium and calcium ions can diffuse through the AMPA receptors of each neurons' respective postsynaptic neuron and induce LTP, making it occur more frequently than it would naturally be occurring in that region. This same process will occur at other structures within the paper circuit: The mammillary body, anterior thalamic nucleus, and cingulate cortex.

Literature Review

The hippocampus as it relates to a memory enhancing brain implant

The hippocampus will be of extreme importance in regards to this theoretical implant's purpose of memory enhancement due to the neurons (primarily pyramidal neurons) it contains being specialized to consolidate short term memory into long-term memory [3]. The microelectrode and neural threads designated for detection of neural activity within and electrical stimulation of the hippocampus should specifically target the entorhinal cortex or the subiculum, or both. A difficulty that arises if we target the subiculum or both the entorhinal cortex and the subiculum, though, is we would need to determine the rate of transmission of information throughout the Trisynaptic circuit (includes neurons within the dentate gyrus, CA3 and CA1 regions) perfectly to ensure the subiculum is not stimulated before the information actually reaches it because that could risk Long Term Depression (LTD) a decrease in synaptic strength occuring due to neurons in the subiculum (considered postsynaptic neurons in this context) firing before the neurons contained in the CA1 region (considered presynaptic neurons in this context) stimulate them to fire. Stimulating just the entorhinal cortex may be a better option since it can be considered where neural activity in the hippocampus originates and then spreads throughout the rest of the hippocampus, but it is still important to note that the neurons of the entorhinal cortex can become postsynaptic neurons and present the same concern discussed involving the subiculum if they are somehow naturally stimulated by the neurons extending from the cingulum before they are electrically stimulated by the implant's neural threads [4]. This does not seem likely, though, since memory formation initiates at the entorhinal cortex and would not reach the rest of the paper circuit before quick pulses of electrical stimulation were delivered to it while it is still committing neural activity. It seems reasonable to assume the safer option (safer in terms of less risk of LTD occuring) is electrically stimulating just the entorhinal cortex since it is considered an actual starting point in regards to hippocampal neural activity rather than trying to electrically stimulate the subiculum at all, a structure which can be considered an intermediate in the transmission of information throughout the hippocampus.

The mammillary body as it relates to a memory-enhancing brain implant

The next structure in the paper circuit that receives information from the hippocampus is the fornix, but since it is purely white matter (white matter tract) it will not be electrically stimulated. When the mammillary body receives information from the hippocampus after that information travels through the hippocampal mammillary tract and begins committing its own neural activity, the microelectrode designated for the mammillary body will retrieve the escaped electrical signals released by the neurons when they fire and cause the implant to electrically stimulate the structure through its neural threads. While there is no specific structure within the mammillary body that is best to target the electrical stimulation towards (since the anatomy of the mammillary body is not as detailed as that of the hippocampus), it is reasonable to assume that focusing the stimulation where the fornix directly connects to the mammillary body would have the highest chance of inducing LTP since a majority of the stimulation would be targeted (or at least try to be targeted as close as possible) specifically near the soma of the neurons (structure of neurons directly before axon hillock where action potentials begin). A concern with this approach, though, is that the electrical field of the stimulation delivered by the neural threads would cover a certain amount of surface area on the mammillary body so that, no matter where on the structure you stimulate, many neurons not in the specific area of interest within the mammillary body will still fire and potentially fire before each of those neurons designated presynaptic neurons stimulate them, thus causing LTD to potentially occur more throughout the mammillary body than LTP [5]. This was less of a concern in regards to the hippocampus since the structures within it are extremely localized and the hippocampus itself is a bigger structure than the mammillary body, so it is easier to focus a microelectrode and neural threads directly on top of and directly penetrating structures such as the entorhinal cortex.

Discussion

The anterior thalamic nucleus as it relates to a memory enhancing brain implant

Like the hippocampus with the hippocampal mammillary tract, the mammillary body sends information through a white matter tract (mammillothalamic tract) to the Anterior Thalamic Nucleus (ATN). The ATN follows the same process of being electrically stimulated as the hippocampus (entorhinal cortex) and mammillary bodies in that when the area of interest that its designated microelectrode is focused on detects neural activity, it will inform the implant and electrical stimulation will be delivered to the structure to induce LTP in the neurons localized to that area of interest. In regards to the area of interest in the ATN, it could be most beneficial to focus as much electrical stimulation on the anterodorsal subnucleus of the ATN (ATN is comprised of three nuclei: anteromedial, anteroventral, and anterodorsal subnuclei) since most neurons extending from the mammillary body through the mammillothalamic tract to the ATN specifically extend to the anterodorsal subnucleus 2. While most mammillary neurons extend to this specific subnucleus, though, its primary function is controlling the head direction system to orient our head to aid in spatial navigation1, so stimulating it may not be as helpful in regards to enhancing memory. The anteromedial subnucleus, on the other hand, contributes indirectly to memory due to it sending information to neurons that contribute to the functionality of the prefrontal cortex1, which is responsible for high level cognitive functions; it is reasonable to assume that better cognition/cognitive function is associated with increased memory recall,

so prioritizing the anteromedial subnucleus in regards to electrical stimulation seems more beneficial for memory enhancement purposes [6].

The cingulate cortex as it relates to a memory enhancing brain implant

The neurons in each subnucleus within the anterior thalamic nucleus comprise the thalamocingulate tract and extend to the cingulate cortex. The cingulate cortex is the fourth and final structure within the paper circuit that will be electrically stimulated. Similar to the process of electrically stimulating the hippocampus, mammillary bodies, and anterior thalamic nucleus, a microelectrode designated for detecting neural activity within the cortex will send a signal to the implant's CPU and pulses of electrical stimulation will be sent back to the structure to induce LTP while natural neural activity is occurring. The microelectrode and neural threads will specifically target the posterior part of the cortex since it has outputs to the hippocampal system (through the cortohippocampal fibers of the cingulum). The posterior fibers form the cingulum and extend to the entorhinal cortex to complete the loop, and the microelectrode focused on the hippocampus's area of interest will once again detect neural activity in that area like it did in the beginning and the neural threads will stimulate the area.

Conclusion

By using neural threads to electrically stimulating the four primary structures in the paper circuit (hippocampus, mammillary body, anterior thalamic nucleus, and cingulate cortex) upon initial detection of naturally occurring neural activity within each of those areas through a microelectrode, we can theoretically induce LTP at an increased frequency in these structures. Neurons throughout the paper circuit would possess an increased number of AMPA and NMDA receptors (due to them being stimulated to release the neurochemicals that initiate LTP at an increased rate than their natural release) along their dendritic membranes and produce BDNF at an increased rate, which would also make synaptogenesis occur at an increased rate. The idea of neurons releasing a significantly increased amount of neurochemicals relevant to the function of LTP in conjunction with the increased expansion of networks encoding different memories (following the increased occurrence of LTP) could theoretically be achieved by electrical stimulation and lead to enhanced memory recall.

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