Developing a Neuroprosthesis for Memory: The Past, Present, and Future

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N. V. Thakor (ed.), *Handbook of Neuroengineering*,
https://doi.org/10.1007/978-981-15-2848-4_64-2

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Abstract

With our rapidly aging population, dementia and memory loss are increasingly prominent burdens on our global healthcare systems. There is thus a pressing need to quell the memory problems associated with this "silver tsunami" toward healthy and independent living. Neuromodulation technologies are emerging technologies that allow us to directly interact with the brain to possibly restore lost function including memory. In this chapter, we provide an overview of the field of neuromodulation for modulating memory, with a particular focus on invasive, electrical stimulation technologies. Since any successful scientific investigation must begin with an appropriate context, we start this chapter by discussing various memory frameworks and the underlying anatomical structures that are involved in physiological memory processing. Next, we provide a comprehensive overview of continuous and conditional open-loop stimulation techniques, followed by novel closed-loop stimulation technologies that dynamically respond to the underlying brain activity to improve memory function. We conclude the chapter by highlighting the limitations of the current work and point out the fundamental necessities of any real-world neuroprosthesis for memory.

Keywords

Memory · Neuroprosthesis · Hippocampus · Fornix · Theta burst stimulation · Closed-loop stimulation · Open-loop stimulation · Mesial temporal lobe · Fornix

Abbreviations

ACH	Acetylcholine
AD	Alzheimer's disease
ADAS	Alzheimer's Disease Assessment Scale
ATN	Anterior thalamic nucleus
AVLT	Auditory verbal learning and memory task
CA	Cornu ammonis
cOL	Continuous open loop
DBS	Deep brain stimulation
DG	Dentate gyrus
iEEG	intracranial EEG

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LTD	Long-term depression
LTP	Long-term potentiation
MIMO	Multi-input multi-output
MMSE	Mini-Mental State Examination
MTL	Mesial temporal lobe
NBM	Nucleus basalis of Meynert
NGF	Nerve growth factor
OL	Open loop
PD	Parkinson's disease
QoL	Quality of Life
TBI	Traumatic brain injury
TBS	Theta burst stimulation

1 An Introduction to Memory

1.1 Introduction

Memory is an elusive construct that has tantalized philosophers, psychologists, and neuroscientists alike for several millennia. One of the earliest accounts of memory can be traced back to a dialog written by Plato, *Theaetetus*, circa 369 BCE, where he postulated that "there exists in the mind of man a block of wax, which is of different sizes in different men … Let us say that this tablet is a gift of Memory . . . when we wish to remember anything which we have seen, or heard or thought in our own minds, we hold the wax to the perceptions and thoughts, and in that material receive the impression of them … and that we remember and know what is imprinted as long as the image lasts; but when the image is effaced, or cannot be taken, then we forget and do not know [1]." He goes on to describe how false opinion ensues from associating a new experience with the wrong *image* on this wax tablet. This concept of treating memory as a block of wax, one that is pliant, moldable, and even vulnerable, is a powerful one and hints at the concept of *plasticity*, beautifully described by the famous American psychologist William James as "the possession of a structure weak enough to yield to an influence but strong enough not to yield all at once" [2]. In modern behavioral neuroscience, this plasticity refers to the ability of a biological neural network to change and adapt to novel stimuli and experiences. If we were to extend this wax tablet metaphor, we can envision a world where we can develop a scalpel to better carve out new images on this tablet (i.e., improve memory encoding) or a loupe to better interpret the fading images (i.e., improve memory recollection) in order to help individuals with some form of memory loss. The recent endeavors toward developing a neuroprosthesis for memory aim to provide us with the primordia of the scalpels and loupes that we will need to understand human memory and help those suffering from memory deficits.

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1.2 Memory Failure and Its Impact on Healthcare

Dementia is characterized by a decline in memory, language, problem-solving, and other cognitive skills that can affect an individual's ability to perform rou-

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tine activities [3]. The *Diagnostic and Statistical Manual of Mental Disorders* classifies dementia as a major neurocognitive disorder, because it interferes with both cognitive function and performing everyday activities [4]. With a rapidly aging population, the number of individuals with dementia is expected to increase exponentially in the coming years. It is estimated that, in the United States, 14 percent of people aged 71 and older have some form of dementia [5]. Approximately 47 million individuals around the world live with dementia today, a number that is expected to triple in the next three decades [6]. As of 2018, the estimated annual cost of dementia is expected to reach one trillion USD, and it is expected to increase substantially as the population with dementia increases in the near future. Thus, the societal and economic burden of dementia is immense, driving a demand for new drugs and interventional therapies that can help manage the symptoms and slow, if not completely halt, the progression of the disease [7].

Of the many symptoms associated with dementia, memory loss and memory dysfunction is perhaps the most tangible. Memories, as Clark and Martin describe, are "psychological accoutrements of a lifetime of experience" [8]. They form the essence of the human experience, providing us with a sense of self, an ability to store, recall, and learn from past experiences, and allow us to effectively place ourselves in our societal fabric. As a result, memory loss can be truly crippling. In fact, a cross-sectional epidemiological study with over 1600 elderly participants demonstrated a significant correlation between self-reported memory complaints and virtually every dimension of an individual's quality of life (QoL) [9]. Thus, there is an urgent and significant need for technologies and/or therapeutics that can improve memory function.

1.3 Taxonomy of Memory

In order to develop a neural prosthesis to effectively augment or maintain human memory, it is important to understand the underlying anatomical organization of memory systems and different memory models. In its most colloquial sense, a memory is a conscious recollection of a fact (e.g., the capital of Egypt is Cairo) or a past event (e.g., your trip to Cairo last summer). However, over the past several decades, this understanding of what constitutes a "memory" has evolved drastically. Tulving first proposed a categorization of episodic memory in 1972 which has been further refined over the years to include self-experiences and subjective time [10, 11]. Since then, a large impetus for the dissociation between various memory systems and their anatomical correlates stemmed from seminal experiments with an individual named Henry Molaison (H.M.). H.M. had intractable epilepsy and underwent bilateral mesial temporal lobe (MTL) resections in order to control his seizures. Following surgery, H.M. developed severe anterograde amnesia (being unable to form new episodic memories) and mild retrograde amnesia (being unable to access memories from the past). However, most of his intellectual and cognitive capacities were unaffected, along with his ability to learn new procedural skills [12]. This sparked significant interest into understanding and classifying the various

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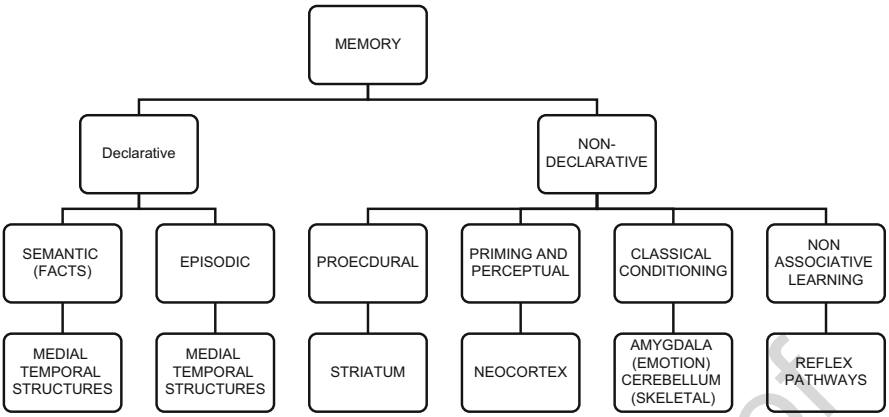

Fig. 1 Example taxonomy of brain systems: This breakdown shows division of memory into declarative and non-declarative forms as well as the respective anatomical locations believed to be primarily associated with each type of memory. Specifically, medial temporal structures are under the declarative memory category and are one of the main targets for neuromodulation for memory. (Adapted with permission from Squire [148]; Copyright 2019; Elsevier)

types of memory systems and the essential role of the MTL in supporting them. Although there remains significant debate regarding the precise classification and categorization of the various memory subsystems, the most robust and simplistic categorization subdivides memory into *declarative* and *non-declarative* forms (see Fig. 1).

One of the key findings from H.M. was the fact that his ability to learn procedural skills was completely intact, suggesting that the type of memory associated with such skills is not MTL dependent. Today, we use *non-declarative memory* as an umbrella term used to categorize the several dispositional and nonrepresentational types of memory. These are types of memory that cannot be consciously recalled and are expressed through performance, rather than through recollection. In addition to procedural skills (such as learning how to ride a bike), non-declarative memories include perceptual learning (differentiating two musical tones), simple classical conditioning (associating the lunch bell with food), and nonassociative learning (an animal learning to ignore a repeating stimulus). As discussed below, the underlying neural network involved in these non-declarative forms of memory is very different from those involved in declarative forms of memory.

In contrast to non-declarative forms of memory, *declarative memories* constitute our conversational understanding of a memory. These are the types of memories that are thought to be dependent on the MTL and show marked deficits in individuals such as H.M. who have experienced significant damage to their MTL structures. Declarative memories are those that we can consciously recall. They allow us to create internal representations of the world around us, giving us the ability to effectively place ourselves in space and time. Declarative memories can be further divided into *semantic* and *episodic* memories, with the former referring to

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facts about the world and the latter referring to the recollection of an event in its original context. When we speak of memory loss, we typically refer to dysfunction of the declarative memory systems. We associate memory loss as being unable to remember names, or faces, or events, all forms of declarative memory. Since declarative memories are the most compromised in common memory disorders, this chapter will largely focus on the development of neuroprosthesis that improves declarative memory function.

It is important to note that the taxonomy presented above is largely simplistic. There are many new theories that suggest alternate categorizations of memory, for example, memory division based on the underlying neuronal networks that contributes to each memory type [13]. Regardless of the specific categorization or memory model being utilized, the central importance of the MTL structures in human memory function is undisputed.

1.4 Anatomy of Memory

Most neuromodulation approaches, and in particular the invasive, intracranial neuromodulation approaches that will be discussed in this chapter, typically target a spatially specific region of the nervous system. For instance, deep brain stimulation (DBS) for controlling symptoms of Parkinson's disease, which has proven to be a highly successful treatment modality for these patients, specifically delivers high-frequency electrical stimulation to the subthalamic nucleus (STN) or the globus pallidus interna (GPi) [14]. Although the precise mechanism of action of DBS in the context of Parkinson's disease is still a topic of much debate, it is understood that targeting these specific structures of the cortico-basal ganglia loop is of utmost importance, as it alters the pathological network activity in these brain circuits which in turn helps control the symptoms of the disease. Thus, understanding the underlying anatomy of the system one wishes to probe and/or alter is the first step toward developing an effective neuroprosthesis for augmenting or correcting such a system.

While there is emerging evidence that suggests that memory is a widely distributed network phenomena [15], the necessity of the MTL in encoding, consolidating, and recalling declarative forms of memory is largely undisputed. Furthermore, the MTL is also a common target of invasive intracranial electroencephalography in patients with medically refractory epilepsy [16], which has provided psychologists and neuroscientists with unprecedented access to these structures, in order to better understand their role in declarative memory function and in order to develop neuroprostheses that alter or augment the function of these structures. Thus, the following section will provide an insight into the anatomy of the various MTL structures and their relevance in human memory function.

1.4.1 The Mesial Temporal Lobe (MTL)

The human MTL consists of various structures including the hippocampus, parahippocampal, entorhinal and perirhinal cortices, and the amygdala [17]. This section

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provides a brief anatomical overview of the major MTL structures that have been targeted in various memory neuroprostheses.

Hippocampus

The hippocampus is thought to play a critical role in declarative memory [18], with anatomic divisions including the CA fields (CA1 and CA3), the dentate gyrus (DG), and the subiculum that play different roles in memory processing. These subdivisions, much like the majority of the MTL circuitry, are conserved across various mammalian species [19]. These hippocampal subdivisions are connected in a serial, unidirectional manner as follows: The dentate gyrus projects to the CA3, which projects to the CA1 which then projects to the subiculum [20]. Furthermore, the hippocampus is known to receive convergent fibers from virtually all cortical association areas (and numerous subcortical structures) [20], which allows it to process high-level perceptual information from diverse cortical regions. The principal neurons within the CA3 subfield are also known to have broad recurrent connections involving excitatory glutamatergic synapses which can spread out an input across all elements of a previously activated network, enabling the putatively ascribed function of "pattern completion" [18, 21]. The unique architecture of the hippocampus also facilitates rapid, N-methyl-D-aspartate (NMDA)-mediated synaptic plasticity which has been strongly linked to memory [22]. This hippocampal circuitry is thought to endow the hippocampus with a distinct set of characteristics that allow it to mediate elemental cognitive processes such as associative representation, sequential organization, and relational networking [18]. Specifically, these hippocampal substructures seem to be differentially involved during explicit memory testing [18, 23, 24] and in association with spatial location [25–27]. One of the proposed mechanisms of hippocampal function suggests that the hippocampus consolidates information with neocortical representations through matched and mismatched predicted events from sensory input [28]. During the memory encoding process, it is believed information is stored using hippocampal networks that bind together information between neocortical networks, and these networks can strengthen over time [29, 30]. This idea is reinforced through the proposed involvement of amygdala and hippocampus in sensory integration [31]. Specifically, when sensory inputs diverge, the CA1 is thought to be activated in order to compare past and present stimuli [28]. According to Hasselmo's model of hippocampal encoding and retrieval, CA1 is very active in encoding state [32]. The hippocampus, and specifically CA1 and CA3, might also govern comparisons between internal representations from the neocortex and the incoming stimuli [33, 34].

This hippocampal circuitry, in conjunction with the widespread neocortical sites that are activated during memory encoding, underlies what we call a *memory engram*. This engram is yet another elusive construct, which refers to a group of distributed cells that are activated during the encoding of a memory and are then reactivated during recollection of the same memories [35]. In addition to these memory engram cells, other memory-relevant cells discovered in the hippocampus include place cells which fire to a specific location in space [36] and time cells which can fire at separate instances of time in a memory [37] and can be generalized

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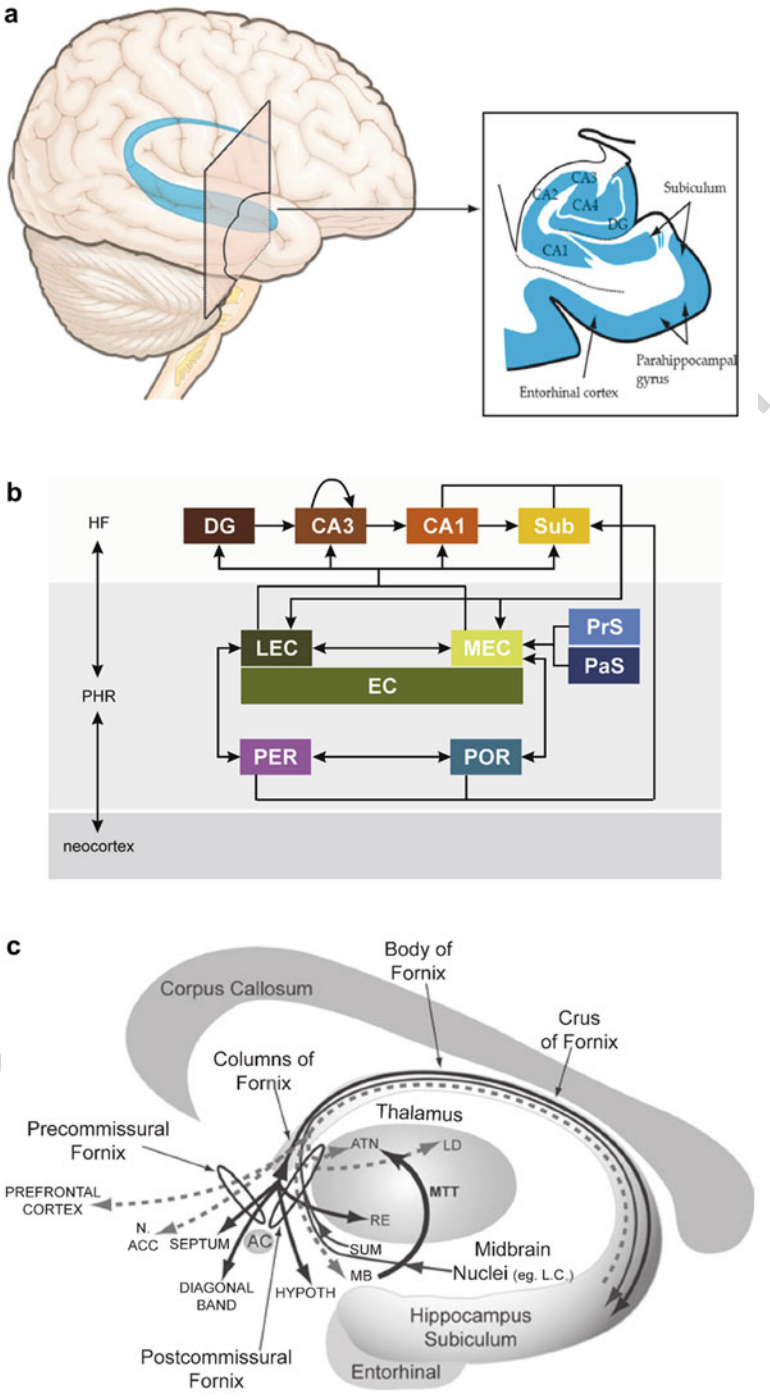

Fig. 2 (continued)

to representations of a task as a whole [38]. The widespread connectivity of the hippocampus to various brain structures, its role as an integrator of information, and the presence of a diverse population of memory encoding cells in the hippocampus make it an obvious and suitable target for developing a neuroprosthesis for memory.

Parahippocampus and the Perforant Pathway

Although the hippocampus serves as a site of convergence of cortical and subcortical inputs, a majority of these inputs do not directly project to the hippocampus. Instead, the regions adjacent to the hippocampus, including the entorhinal, perirhinal, and postrhinal (or parahippocampal cortex in primates) cortices, serve as the input tier to the hippocampus [19]. Most cortical inputs arrive at the perirhinal and postrhinal/parahippocampal cortices (Fig. 2b) [19, 20]. Information from here is then projected to the entorhinal cortex where it is further processed before being passed onto the hippocampal formation. Interestingly, the parahippocampal region (consisting of the entorhinal cortex, perirhinal cortex, and postrhinal/parahippocampal cortex) receives parallel streams of cortical inputs [19]. One of these streams is largely concerned with spatial content of sensory information and generally projects to the postrhinal/parahippocampal cortex. The other stream is largely concerned with the nonspatial identity of the stimuli and generally projects to the perirhinal cortex. The entorhinal cortex (further subdivided into medial and lateral regions) integrates some of this information and serves as an output tier of the parahippocampal region, projecting in parallel to all of the hippocampal fields. This projection, from the entorhinal cortex to the hippocampal formation, is termed the perforant pathway and is a major input pathway to the hippocampus. Furthermore, similar to the hippocampus, the entorhinal cortex is also

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Fig. 2 (**a**) A schematic of a coronal slice of human hippocampal formation (obtained with permission from [39]; Copyright 2019; Elsevier). (**b**) A flowchart showing anatomical connectivity in the mesial temporal lobe structures, including the parahippocampal-hippocampal circuitry and informational flow as discovered through animal iterature (obtained with permission from [20]; Copyright 2019; Elsevier). Neocortical projections reach the parahippocampal region (PHR), which acts as a main input to the hippocampal formation (HF). From PHR, the perirhinal cortex (PER) projects to the lateral entorhinal cortex (LEC), and the postrhinal cortex (POR) projects to the medial entorhinal cortex (MEC). The entorhinal cortex (EC) has connections from PER and POR. Additionally, MEC receives input from the presubiculum (PrS) and the parasubiculum (PaS). The perforant pathway originates from EC which projects to all HF subregions and provides input to the hippocampus from the external world and can act as output back to the neocortex from hippocampal formation. (**c**) Representation of the location of fornix, its divisions, and its connections to hippocampus (obtained with permission from [40]; Copyright 2019; Elsevier). Dashed arrows indicate solely efferent from the hippocampal formation, the narrow solid arrows represent solely afferent to the hippocampal formation, and the wide solid arrows show reciprocal connections within the fornix. (Abbreviations in the image are AC, anterior commissure; ATN, anterior thalamic nuclei; HYPOTH, hypothalamus; LC, locus coeruleus; LD, thalamic nucleus lateralis dorsalis; MB, mammillary bodies; MTT, mammillothalamic tract; RE, nucleus reuniens; and SUM, supramammillary nucleus)

involved in providing a representation of space in the form of *grid cells*. Unlike the hippocampal place cells, these grid cells increase their firing rate when an organism is sampling information near the nodes of a putative grid that can tile the physical and/or visual world. Thus, since the parahippocampal region and the perforant pathway serve as a major input tier to the hippocampus and since significant evidence points to their significance in providing us with a robust representation of space, these regions may also serve as putative targets for neuromodulation approaches.

Fornix and Other Input Pathways

Another major pathway through which information travels to and from the hippocampus is the fornix (Fig. 2c). The fornix is an anatomical structure that emerges from the hippocampus to form an arch that lies just above the thalamus and just below the corpus callosum. The fornix connects the hippocampus to a large array of cortical and subcortical structures [40]. Some of these connections are unidirectional (either afferents to or efferents from the hippocampus) and others are reciprocal connections. Some of the major unidirectional connections facilitated by the fornix include efferents from the hippocampus to the mammillary bodies, ventral striatum and prefrontal cortex, and afferents from the supramammillary nucleus, raphe nucleus, and the locus coeruleus to the hippocampus [41]. Another structure, called the medial septum, is reciprocally connected to the hippocampus by the fornix. This is critical for propagating the dominant theta rhythm to the hippocampus [40, 42]. This rhythm has been shown to be important for learning and memory, and it has been proposed that oscillatory patterns in this frequency range enable synaptic plasticity [36, 43]. There is also evidence that other major anatomical structures connect to the hippocampus through a parallel nonfornical pathway [41, 44]. These structures include the nucleus basalis of Meynert (NBM), amygdala, claustrum, and thalamic nucleus centralis medialis.

Given the heterogeneity of the various types of memories and the various anatomical structures that are known to play a major role in facilitating one of more of these memory types, the problem of developing a neuroprosthesis for modulating memory performance is an obviously complex one. The complexity of the underlying anatomical structures coupled with our incomplete understanding of the underlying mechanisms that support the various memory systems further increases difficulty of this problem. We now review the various approaches that have been taken toward developing an effective neuroprosthesis for modulating memory function and their advantages and their pitfalls.

2 An Electrical Neuroprosthesis for Memory

The word neuroprosthesis is an amalgamation of the word *neuro*, which refers to nervous tissue, and the word *prosthesis* which refers to an artificial device that can augment or replace the function of a body part. Thus, the word neuroprosthesis refers to technologies that can interface directly with the nervous system in order

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to replace lost function. In the context of the current chapter, a neuroprosthesis for memory refers to a technology that can directly interface with the nervous system in order to improve memory function in those with memory deficits.

Neuromodulation is an umbrella term for technologies that can directly modulate neural activity, through electrical, pharmacological, and, more recently, optical stimulation. Over the past 50 years, there has been an explosion in the field of neuromodulation and, in particular, in the field of electrical neuromodulation, which refers to a subset of these neuromodulation technologies that use invasive or noninvasive electrical (or magnetic) stimulation. This chapter will largely focus on electrical neuromodulation technologies, since electrical neuromodulation is, by far, the most common type of neuromodulation technology. There is a very rich literature on noninvasive stimulation (transcranial alternating current stimulation, transcranial direct current stimulation, and transcranial magnetic stimulation) for modulating memory function and would warrant a chapter in its own right. For the purposes of developing an implantable neural prosthesis that could work continuously in the real world, we have chosen to focus this chapter on invasive, electrical neuromodulation technologies as the most parsimonious approach currently for a memory neuroprosthetic.

Electrical neuromodulation takes advantage of the fact that primary currency of communication in the mammalian nervous system is electricity. Neurons communicate with one another by firing action potentials, which can be thought of as electrical impulses being carried down an insulated wire. By modulating the intracellular and/or extracellular electrical and magnetic fields of this inherently excitable nervous tissue, neuromodulation technologies provide us with the ability to dynamically interact with the brain. These technologies allow us to not only investigate the brain in a causal manner but also provide an avenue through which brain activity can be modulated to mitigate pathological activity. Furthermore, due to their extensive use in treating other neurological conditions such as Parkinson's disease, the safety and efficacy of electrical neuromodulation technologies are well established and well accepted [45–47] (Fig. 3). AU4

2.1 A Continuous Open-Loop Approach

An open-loop (OL) controller refers to a device that does not receive any feedback from the system it is trying to control. It functions in a static or blind dynamic (i.e., changing, but independently of the underlying neuronal activity) manner, in which it cannot respond to the ever-changing state of the brain. A continuous open-loop (cOL) system is an open-loop system in which the stimulus is delivered in a continuous, semicontinuous, or interspersed manner. Such systems are typically the easiest to implement as they do not require a recording or processing element, which would otherwise complicate the system. Furthermore, cOL systems are also highly translatable to the real world, because they can be deployed and tested in the real world, as the complexities of providing feedback to the system are eliminated. As a result, these approaches are the most common when developing a neuroprosthesis to modulate memory performance in humans.

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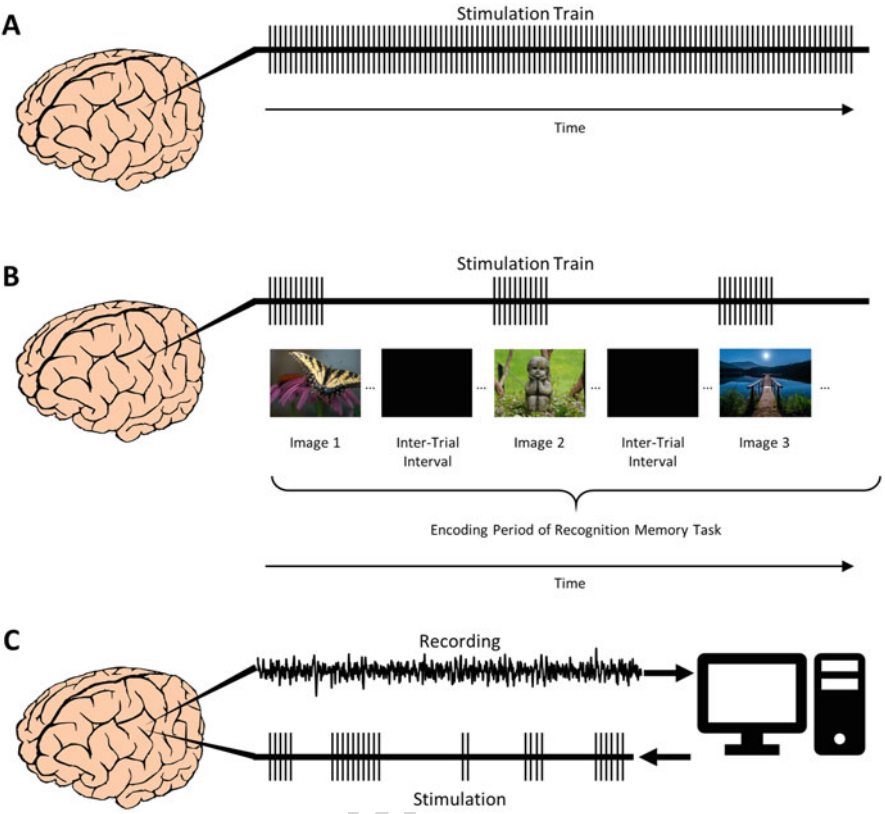

Fig. 3 Schematics showing different types of stimulation approaches used currently for memory neuroprostheses. (**a**) A continuous open-loop approach in which high- or low-frequency stimulation is delivered in a continuous manner. (**b**) A conditional open-loop approach in which the stimulation is delivered in an open-loop manner, but contingent on a particular memory task being employed. For instance, this schematic shows stimulation being delivered at the onset of new images in the encoding period of a recognition memory task. (**c**) A closed-loop approach in which the stimulation being delivered is contingent on some underlying brain activity

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Since cOL systems do not respond to any real-time feedback, the main parameters that can be altered in these systems are (1) the anatomical location at which the stimulus is being delivered (in order to target a specific underlying memory network) and (2) the characteristics of the stimulus being delivered in order to affect the said network. This section provides examples of various open-loop neuroprosthesis for memory developed over the last two decades (Fig. 4).

Table 1 provides a summary of all the continuous open-loop stimulation studies discussed in this chapter, including an overview of the methods implemented in each study along with the relevant behavioral outcomes. California Verbal Learning Test (CVLT), Rey Auditory-Verbal Learning Task (RAVLT), the Rey Visual Design Test (RVDT), the Verbal and Visuospatial Supraspan, Alzheimer's Disease Assessment

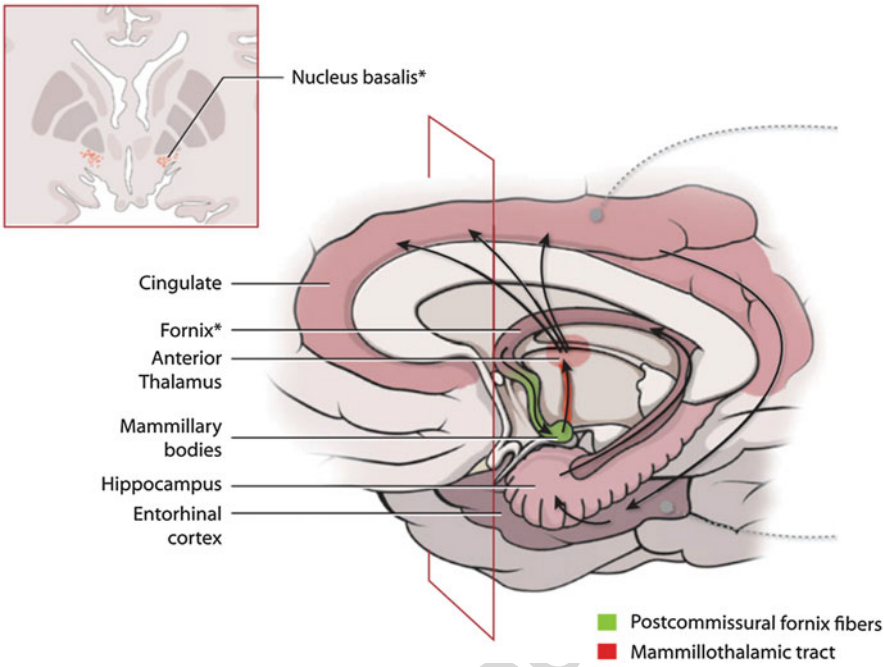

Fig. 4 Common targets for developing a neuroprosthesis for memory (obtained with permission from [48]; Copyright 2019; Elsevier). Many of these anatomical locations, as part of the Papez circuit, are considered good targets for deep-brain stimulation for memory. The fornix is a major pathway to hippocampus governing memory and cognition. Neocortical projections from cingulate to components of the default mode network (parietal, temporal, and frontal) feed back to the hippocampal formation. The portion of the fornix beyond the anterior commissure is known as the postcommissural fornix and is shown in green. Just inferior to the anterior commissure is the acetylcholine rich nucleus basalis which can cholinergically innervate the hippocampal formation. The mammillothalamic tract shown in red identifies connections from mammillary bodies to the anterior thalamic nucleus. These target locations are discussed in detail, specifically the fornix, nucleus basalis, anterior thalamus, and medial temporal lobe structures as part of stimulation for improving memory

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Scale, Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), Coetsier Story Recall Test (CSRT), nucleus basalis of Meynert (NBM), Wisconsin Card Sorting Test (WCST), subthalamic nucleus (STN).

2.1.1 Fornix Stimulation

The fornix, as identified earlier in this chapter, is a major input pathway to the hippocampus, and it lies in close proximity of the hypothalamus, a collection of nuclei that serve to regulate a variety of metabolic and autonomic processes within the body. In 2008, a group of researchers in Toronto attempted an experimental procedure to treat morbid obesity by delivering bilateral, hypothalamic stimulation in an attempt to help control the individual's appetite. Serendipitously, they observed

Table 1 Continuous Open-Loop Stimulation Studies

Year	n	Memory-related outcome	Memory task/Memory type	Stimulation location	Stimulation parameters	Additional notes/details	Ref
1996	9	Impairment	Recognition task (words and block designs)	MTL structures	3 V, 2.5 ms pulse width at 2 Hz	Stimulation applied starting 3 h prior and during task	[49]
2007	9	Improvement	Rey verbal learning, digit counting, logic memory, and Wind Mill visual-spatial Bezarez Test	Hip	0.3 mA, 0.45 ms pulse width at 130 Hz	Stimulation was delivered for 1 min every 5 min. In half of the subjects, stimulation started immediately after implant and others 1 month later. Testing was done every 3 months for 18 months	[50]
2008	1	Improvement	CVLT, Spatial Associative Learning Task, Wechsler Memory Behavioral Evaluation	Hypothalamus	2.8 V, 0.06 ms pulse width at 130 Hz	Performance on CVLT improved significantly after 3 weeks of continuous stimulation Effect of stimulation was further characterized using tasks with high sensitivity and specificity for hippocampal function. These tasks were completed in a double-blind manner, with on-stimulation and off-stimulation periods separated by 1 week or 1 h. In both these tests, the recollection index was significantly higher in the on- vs. off-stimulation period	[51]

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Year	n	Memory-related outcome	Memory task/Memory type	Stimulation location	Stimulation parameters	Additional notes/details	Ref
2009	1	Improvement in AVLT	Letter-Number-Span Test, Digit Symbol Test, Trail Making Test Part B, Rey Auditory Verbal Learning Test (AVLT)	STN and NBM	4.2 V at 0.06 ms pulse width at 130 Hz (STN) 1 V at 0.12 ms pulse width at 20 Hz (NBM)	Testing 1 week before implantation of the electrodes, after DBS in four double-blind phases: STN stimulation, combined STN and NBM stimulation, STN stimulation, and combined STN and NBM. Taking away the NBM stimulation in phase 3 resulted in significant decline in cognitive and memory performance, which was rescued by resuming NBM stimulation in phase 4	[52]
2010	6	No change (increases in metabolic activity structural volume of MTL structures)	ADAS-Cog	Fornix	3–3.5 V, 0.09 ms pulse width at 130 Hz	Testing before and after 12 months of continuous stimulation	[53] [54]
2010	2	No change	Standardized Tests – Objective Hopkins Verbal Learning Test-Revised, and the Brief Visuospatial Memory Test-Revised, and Memory Assessment Clinic Self-Rating Scale	Hippocampus	0.5 V, 0.09 ms pulse width at 185 Hz	Three-month baseline period after implantation with no stimulation and then stimulator on/off 3 months	[55]

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Table 1 (continued)

Year	n	Memory-related outcome	Memory task/Memory type	Stimulation location	Stimulation parameters	Additional notes/details	Ref
2011	5	Neutral/impairment	Verbal and Visuospatial Supraspan RAVLT RVDT	Hip and amygdala	<2 V, 0.45 ms pulse width at 130 Hz	The patients were followed up between 12 and 74 months after continuous stimulation. Reducing stimulation intensity reduced impairments	[56]
2011	10	Improvement (complex figure) Impairment (verbal with left stimulation)	Many standardized tests including RAVLT, RVLT, CSRT Complex figure test	Hip and amygdala	1–2.5 V, 0.45 ms pulse width at 130 Hz Voltage	Standardized tests delivered after first 6 months of continuous stimulation	[57]
2012	9	Improvement (in delayed verbal memory)	(IQ, MMSE), information processing (digit forward and backward, trail A, and digit symbol), or executive function (trail B and WCST)	Anterior thalamic nucleus	1.5–3.1 V, 0.09–0.15 ms pulse width at 100–185 Hz	Testing before and after 12 months of continuous stimulation. Some participants had minor changes in their medications during this period	[58]
2015	6	Stable/impairment	Cognitive subscale of the ADAS-Cog	NBM	2–4.2 V at 0.09–0.15 ms pulse width at 10–20 Hz	Four-week double-blind sham stimulation period, followed by a subsequent 11-month stimulation period	[59]
2015	2	Stable	ADAS-Cog	NBM	2–4.2 V at 0.09–0.15 ms pulse width at 10–20 Hz	Improvement in one, stable in the other	[60]

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that delivering such stimulation resulted in sensations that the patient described as "déja vu," in which he had vivid recollections of memories from his early adulthood [51]. Further testing with the same patient revealed that acute stimulation in this region (likely through forniceal stimulation) improved his recollection memory (i.e., ability to recall details associated with a previously experienced event) on various verbal memory tasks, the effect of which was correlated with activation of the hippocampus and parahippocampal gyrus, regions that are known to play a crucial role in declarative memory.

Following this seminal discovery, a phase I clinical trial of deep-brain stimulation of the hypothalamus/fornix was initiated, in which six patients with Alzheimer's disease were implanted with DBS electrodes in the hypothalamus, in contact with the anterior border of the vertical portion of the fornix [53]. Although the study was unable to claim any clear benefits with regard to improving memory performance in these patients, they demonstrated increased cerebral glucose metabolism relative to baseline in brain regions that typically demonstrate reduced metabolism in Alzheimer's disease. Furthermore, the study also suggested a moderate but not significant reduction in the overall rate of cognitive decline in the patients with continuous fornix/hypothalamic DBS when compared to traditional rates of decline reported in literature. Finally, the authors also demonstrated a robust activation of the Papez circuit (a neural circuit proposed by James Papez in 1937 which is thought to be responsible for declarative memory function, of which the fornix, hypothalamus, hippocampus, and anterior thalamic nuclei are key elements [61]) during fornix/hypothalamus stimulation [53].

The stimulation parameters used in these studies (60–90 μs pulse width, 130 Hz frequency) were similar to those currently used in deep-brain stimulation implants for individuals with Parkinson's disease [53]. Successive animal and human studies investigated the role of the stimulation parameters on the corresponding memory performance [62, 63]. Hescham and colleagues showed that both high- and low-frequency stimulation of the fornix can lead to improved spatial memory performance in rats, with the effects being more dependent on amplitude of the stimulation, than on the frequency [62]. Such effects have been translated to humans where Koubeissi and colleagues showed that continuous, 4-h low-frequency stimulation of the fornix led to improved performance on a clinical cognition test (Mini-Mental State Examination or MMSE), driven primarily by improvement of recollection memory [63].

Subsequently, post hoc analysis of the volumetric changes in the brains of the patients implanted in the phase I clinical trial showed that, when compared to age-matched controls, their mean hippocampal atrophy was slowed [54]. In fact, two of the patients in the phase I cohort who had the best clinical response to the DBS actually showed increase in hippocampal volume. This finding is consistent with earlier reports that demonstrate significantly larger hippocampal volumes in London taxi drivers who are, by the nature of their jobs, required to have very high-performing spatial memory [64, 65].

Having established the safety of this implant procedure [53], and along with promise of improved glucose metabolism [53], positive volumetric changes [54],

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and a potential slowing of the cognitive decline supported by the DBS implants [51, 53], a phase II trial of fornix DBS was completed [66]. In this study, 42 individuals suffering from Alzheimer's disease were all implanted bilaterally with DBS electrodes in the hypothalamus/fornix in a manner similar to that described in the phase I trial. These individuals were randomly assigned to a control group (who received no stimulation) and a test group (who received continuous stimulation in a manner identical to that described earlier). The cognitive performance and cerebral glucose metabolism for these individuals were analyzed at baseline, 6 months following implant, and 12 months following implant. The results of this trial showed no significant differences in the primary cognitive outcomes between the two test groups. The test group did show significant and widespread increases in cerebral glucose metabolism at 6 months following implant, but these changes were nonsignificant at 1 year post-implant. This may point toward some potential adaptation mechanism in the brain that may alter the brain's response to the continuous deep-brain stimulation. Interestingly, the metabolic and cognitive benefits of the stimulation were more pronounced in individuals aged >65, whereas those aged <65 showed a trend toward decreased cognitive capabilities compared to corresponding controls. Alzheimer's is in fact a progressive disease, and continuous open-loop stimulation may alleviate symptoms but does not seem to slow the underlying pathological process. As a result, a future phase III clinical trial has been scheduled and will only recruit individuals aged 65 and older [67].

2.1.2 Nucleus Basalis of Meynert (NBM)

Atrophy of the nucleus basalis of Meynert (NBM), a group of cholinergic neurons located in the basal forebrain, is one of the characteristic pathological features of Alzheimer's disease [68]. As a result, the NBM may be a suitable candidate for neuromodulation/deep-brain stimulation, in an attempt to reverse the neuronal atrophy and/or improve glucose metabolism in this region.

In fact, one of the earliest reports of deep-brain stimulation for Alzheimer's disease can be traced back to a case study conducted in 1985, where stimulation of the left NBM was able to rescue decreases in metabolic activity in the ipsilateral temporal and parietal lobe, in much the same way as the hypothalamic/fornix stimulation [69]. However, this study reported that no clinical benefit was observed following 9 months of continuous stimulation. A more recent case study used low-frequency stimulation (20 Hz) in a patient with Parkinson's disease dementia [70]. In this patient, bilateral stimulation of the subthalamic nucleus (the most common site for stimulation for controlling Parkinsonian motor symptoms) and the NBM for a period of 13 weeks significantly improved the participant's performance on an auditory verbal learning and memory task (AVLT). Interestingly, ceasing stimulation of the NBM, even for a short period of time (24 h), led to dramatic worsening of the participant's memory performance (to levels even worse than his performance at baseline). Although this may be an anomaly, it may also hint at a chronic or subacute change in the underlying neuronal circuitry, in a manner that makes it somewhat dependent on exogenous stimulation.

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In 2015, Kuhn and colleagues performed a phase I clinical trial with NBM stimulation in six patients suffering from moderate Alzheimer's disease [59]. Following 12 months of continuous, low-frequency (10–20 Hz) stimulation, they reported that four of the six patients that they tested responded to the treatment, on the basis of stable or improved primary outcome parameters such as overall score on the ADAS-Cog Scale and on the MMSE. Interestingly, they reported that, on the whole, participants actually improved on the memory component of the ADAS-Cog Scale following 12 months of stimulation. Although there was an overall deterioration of cognition on the ADAS-Cog Scale for the whole group [71], this deterioration was shown to be smaller than the deterioration observed in a much larger group of patients who were only treated with anticholinergic medications. Although no conclusive mechanism of action was reported in this study, the authors attributed the findings to one of three hypotheses: (1) an excitatory effect of the low-frequency stimulation on the NBM cholinergic neurons which may cause acetylcholine (ACH) release in the cortex resulting in higher levels of ACH, leading to improved cognitive performance, (2) potential changes in oscillatory activity in mesial temporal lobe circuits as a result of the low-frequency stimulation, and (3) putative neurogenesis and/or plasticity effects of the NBM stimulation (since NBM neurons are known to express nerve growth factor (NGF), the production of which is generally increased by increased neural activity). The neurogenesis hypothesis is intriguing, because an earlier study investigating NGF-based gene therapy also showed similar improvements in the rate of cognitive decline in patients suffering from mild Alzheimer's disease [72]. In that study, autologous fibroblasts, genetically modified to express the human NGF gene, were implanted in the basal forebrain, in an attempt to stimulate cholinergic function by promoting sprouting of cholinergic axons.

Although these preliminary clinical trials all implemented continuous stimulation of the NBM, later work in nonhuman primates has suggested that intermittent stimulation of the NBM actually improves performance on a working memory task when compared to continuous stimulation [73]. This improvement was also correlated with ACH release in these animals. In a similar manner, stimulation of the medial septum, another afferent pathway to the hippocampus, has also been shown to increase ACH release while promoting hippocampal neurogenesis, which may share a common underlying mechanism of action as the NBM stimulation [74].

It should be noted, however, that despite the promise of NBM stimulation for modulating memory performance and cognition, a recent, randomized, double-blind, crossover clinical trial investigating stimulation of the NBM in six patients with Parkinson's disease dementia showed no improvements in primary outcome measures (verbal learning, verbal fluency, etc.) [75]. Akin to fornix/hypothalamus stimulation, outcomes of NBM stimulation are quite heterogeneous, with relatively little consistency in the primary outcome measures, stimulation parameters, study design, and even patient population. The mechanism of action, although more substantial than that of fornix stimulation, remains nonspecific and vaguely described in the literature. However, the relative promise does warrant further investigation in this field.

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2.1.3 Thalamic Nucleus

The anterior thalamic nucleus (ATN) is also a component of the previously described Papez circuit which plays a role in modulating declarative memory performance [61]. Short (1 h), high-frequency, and not low-frequency, stimulation of this region in rodents has been shown to promote hippocampal neurogenesis [76, 77] and can also rescue corticosterone-induced memory deficits in these rats [77]. Interestingly, similar stimulation of the ATN has been shown to have an anticonvulsant effect in several seizure models [78] and in clinical practice [79–82]. Medically refractory epilepsy patients undergoing ATN-DBS therapy not only showed a significant decrease in their seizure frequencies at 1 year post-implant but also showed improvements in verbal recall and oral information processing [58]. A larger clinical trial showed no cognitive or mood differences with subjective changes [80].

Although the positive effects of ATN stimulation on memory can be partly attributed to hippocampal neurogenesis, animal work has also shown that ATN stimulation induces metabolic activation of the hippocampus and the thalamus in a manner akin to stimulation of the hypothalamus/fornix [83], which may drive increased metabolic activity of the Papez circuit, leading to improved memory function.

2.1.4 MTL Structures

At the heart of the Papez circuit and the declarative memory network in humans lies the medial temporal lobe, specifically the hippocampal and parahippocampal regions. Since these regions are thought to play a critical role in declarative memory performance, they have often been neuromodulation targets. Interestingly, however, although cOL stimulation of the mesial temporal lobe structures has been investigated as a means of controlling seizures in individuals with medically refractory epilepsy [50], it hasn't been extensively investigated in patients with dementia. In patients with medically refractory epilepsy, high-frequency cOL stimulation of the hippocampus has been shown to significantly reduce seizure frequencies but has also shown a slight, but not significant, trend toward improved memory performance [50]. McLachlan and colleagues performed a double-blind, randomized, controlled, cross-over trial with two patients and again demonstrated no consistent change in any objective or subjective changes in memory [55]. With a larger patient population, Miatton and colleagues also reported no consistent changes in memory or cognitive performance following chronic, cOL stimulation of the amygdalohippocampal formation [57]. At the same time, however, such stimulation at an amplitude sufficient to trigger afterdischarges has been shown to significantly retard late-recall performance in a verbal memory task [84]. Similarly, a more recent study has shown that high-amplitude stimulation of the hippocampus can indeed lead to impairment of visual and verbal memory, which can be rescued simply by reducing the amplitude of stimulation [56]. This may be attributed to the fact that direct stimulation of the hippocampus at an amplitude high enough to evoke afterdischarges may interrupt normal hippocampal function and its crucial

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role in encoding and retrieving memories. Alternatively, one might suggest that based on animal evidence, high-frequency stimulation may be beneficial. Such high-frequency stimulation of the entorhinal cortex (which serves as a major input structure to the hippocampus) in rodents has been shown to drive hippocampal neurogenesis [85, 86] and has been shown to rescue memory performance in animal models of Alzheimer's disease [86, 87].

It should be noted however that investigation of cOL stimulation in MTL structures has primarily been performed in patients with medically refractory epilepsy, and not those suffering from Alzheimer's- or Parkinson's-related dementia. Since the underlying pathologies in these diseases are drastically different, it may be inappropriate to compare the efficacy of cOL stimulation on various anatomical locations given the underlying bias of the patient populations used for each stimulation site.

Currently it can be concluded that direct electrical stimulation of the hippocampus, in a continuous, open-loop manner, has not been shown to improve memory performance.

2.2 A Conditional Open-Loop Approach

Human memory function can typically be grossly divided into three stages: stimulus encoding, maintenance, and retrieval. The encoding stage involves the presentation of a stimulus and formation of a representation that persists longer than original presentation. Maintenance is the time period involved in transforming this representation and preserving/storing it over time. Retrieval is the stage where a previously encoded memory is retrieved. The hippocampus and other mesial temporal lobe structures are thought to use specific mnemonic processes during each of these stages, and direct electrical stimulation of the hippocampus may affect these processes in a differential manner. Although continuous open-loop DBS approaches for modulating memory have shown some promise, they exacerbate the fundamental problem of open-loop technologies by stimulating the brain regardless of the current brain state. Thus altering the underlying neuronal activity in the same manner during both of these distinct processes may not be conducive to improving overall memory function. For instance, an early study by Halgren and colleagues showed that delivering electrical stimulation to the hippocampus during the different stages of the memory task, encoding, retrieval, or both, had distinct effects on memory performance [88]. Thus, conditional open-loop approaches where open-loop stimulation is delivered but only during specific memory stages may be more effective. Although these conditional open-loop approaches are difficult to implement and test in the real world, where the memory encoding and retrieval processes occur in a continuous, dynamic manner, they have been the mainstay of much neuromodulation memory research.

The clinical scenario that has undergird so much of the conditional open-loop research is epilepsy, where patients undergo intracranial electrode implants to localize their seizure foci [89]. While these individuals are in the hospital,

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they often graciously consent to participate in a variety of memory tasks, which provide researchers with the ability to test conditional open-loop (and closed-loop) neuroprostheses for memory. These individuals are an ideal cohort for investigating memory processes and the effect of novel memory neuroprostheses on underlying memory function because (1) a large fraction of individuals with chronic epilepsy already suffer from memory and cognitive deficits [90] and (2) since a majority of individuals with medically refractory epilepsy tend to have temporal lobe epilepsy [16], the anatomical locations where their electrodes are implanted often overlap with mesial temporal lobe structures that are also known to play a critical role in declarative memory processes.

This section will discuss such conditional open-loop approaches that have been developed and tested in recent history. We will identify the different types of stimulation that has been used and the varying anatomical locations that have been targeted (Table 2).

2.2.1 Acute, High-Frequency Stimulation of the Hippocampus Degrades Memory

Over the past two decades, researchers around the world have attempted to understand the effect of acute, conditional open-loop stimulation on hippocampal-dependent memory. One of the most cited, conditional open-loop stimulation studies for modulating memory performance in the past decade was published in 2012 by Suthana and colleagues [93]. In this study, the authors delivered high-frequency stimulation to the hippocampal or entorhinal region in an intermittent fashion (5 s on, 5 s off) but only during the encoding phase of a spatial navigation task. The authors claimed that such stimulation of the entorhinal cortex during the encoding phase was effective at improving spatial memory, whereas direct hippocampal stimulation was not effective at modulating (improving or worsening) memory performance. However, a later study by Jacobs and colleagues refuted these claims with a much larger cohort of patients and demonstrated that in fact, both hippocampal and parahippocampal stimulation during the encoding phase of a spatial navigation task and of a verbal memory task significantly degraded memory performance [97]. Most of the other studies that have investigated contingent, open-loop stimulation of the hippocampal and adjacent cortices have demonstrated a significant degradation in memory function, over a broad spectrum of memory types [91, 92, 96]. Although there is a lot of heterogeneity between these studies, the greatest common denominator is that direct stimulation of the hippocampus appears to degrade memory performance. This isn't entirely surprising since high-frequency stimulation (which is the type that is used in most of these studies) is thought to introduce a spatially specific, reversible lesion [106]. Despite these reported negative effects of hippocampal stimulation on memory function, the heterogeneity of these studies do provide us with a clearer picture of the dynamic nature of the underlying hippocampal memory network.

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Table 2 Conditional open-loop stimulation studies. This table provides a summary of all the conditional open-loop studies discussed in this chapter, providing an overview of the methods implemented in each study, along with insights into putative mechanisms of action (as suggested by the authors of the respective studies). Theta burst stimulation (TBS), high-frequency stimulation (HF), low-frequency stimulation (LF), mesial temporal lobe (MTL), hippocampus (Hip), entorhinal cortex (EC), Rey Auditory-Verbal Learning Task (RAVLT), parahippocampal gyrus (PHG), dorsolateral prefrontal cortex (DL-PFC), temporal cortex (TC), intertrial interval (ITI)

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
1985	3	HF	Impairment	Recognition (paired associate words)	MTL structures	<2 mA, 0.1 ms pulse width at 51 and 30 Hz	Encoding	Stimulation, delivered during list of paired item presentation.	Impairment of memory due to the spread of afterdischarges from stimulation	[84]
1985	4	Single Pulse	Impairment	Recognition (complex scenes)	MTL structures	<1.5 mA, 0.1 ms pulse width (during image presentation)	Encoding, retrieval, encoding + retrieval	Stimulation was delivered for each individual stimulus presentation.	Stimulation-induced impairment was rescued with a delay, suggesting stimulation impairs the memory trace consolidation	[88]
2004	5	HF	Impairment	Recognition (faces, words, and objects)	Hip	1.9–5 mA with 1 ms pulse width at 50 Hz	Encoding	Electrical stimulation was alternated based on block and delivered throughout visual stimulus presentation (1.2 s)	HF stimulation perhaps acts as a functional lesion. Laterality of stimulation is evident, with left stimulation impairing words, right impairing faces	[91]

(continued)

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Table 2 (continued)

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2010	12	Pulse	Impairment	Recognition (faces, words, objects, geometric shapes)	Hip	4–6 mA, monophasic pulse width 1 ms	Encoding, retrieval, encoding + retrieval	Stimulation locked to variable delays with stimulus presentation and varying targets.	Unilateral stimulation of hippocampus failed to impair memory, whereas bilateral impaired memory. Thus hippocampi can be though to act independently, and memory formation/retrieval can only be disrupted with bilateral stimulation	[92]
2012	7	HF	Improvement	Visuospatial	Hip and EC	1–2 mA, pulse width 0.3 ms at 50 Hz for 5 s on and 5 s off during trials	During all phases	Stimulation was delivered during a spatial navigation task in half the trials. The shorter the subsequent path to the previously navigated locations, the better the spatial memory.	EC stimulation improved spatial memory performance perhaps due to enhanced theta phase resetting leading to ideal conditions for LTP	[93]

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Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2013	11	HF	In-phase stim: improve-ment; out-of-phase stim: impairment	Word recall	Hip/rhinal	0.01 mA sine wave at 40 Hz	Nonstop during encoding, distraction/ delay and recall phases	Stimulation was delivered to both the hippocampus and the rhinal cortex simultaneously, either in-phase or out-of-phase, or not delivered at all.	Stimulation may entrain synchronization of gamma activity between rhinal cortex and hippocampus which has been correlated with memory formation through either promotion of neuronal communication or facilitation of synaptic plasticity	[94].
2015	4	TBS	Improvement	Visuospatial	Fornix	7 mA, pulse width 0.1 ms with 5 bursts a second on for 100 ms at 200 Hz	Continuous across entire testing period	Three tasks with 50% stimulation in each task: Verbal memory (RAVLT), visual spatial(Georgia Complex Figure Test) and visual confrontational naming (Boston Naming Task)	Theta burst replicates naturally occurring firing patterns in hippocampus	[95]

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Table 2 (continued)

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2016	5	HF	Impairment	Word recall	Hip and EC	<6 mA, pulse width 0.3 ms at 50 Hz for 5 s on and 5 s off during trials	Encoding, distractor, or recall	Stimulation was delivered at onset of stimulus presentation for the respective period of the trial	Impairment across all, but significant in distractor period. Stimulation may alter circuitry through membrane potential alterations and mimic a forgetting cue	[96]
2016	49	HF	Impairment	Word recall and visual spatial	Hip and EC	0.5–1.5 mA, pulse width 0.3 ms at 50 Hz for 5 s of presentation	Encoding	Stimulation was delivered either during 5 s of encoding period of placement of object in virtual arena (Morris water maze) or lists of words	Impairment in both verbal and spatial tasks was elicited regardless of hemisphere and only trended in improvement in parahippocampal stimulation. Suggests MTL structure involvement in encoding.	[97]

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2017	102 (r) 36 (s)	HF	Improvement based on encoding state	Word recall	Hip, EC PHG, Perirhinal DL-PFC	0.5–1.5 mA, pulse width 0.3 ms at 50 Hz for 5 s of presentation	Encoding	iEEG data from 102 patients was used to develop a model capable of differentiating good vs. bad encoding states. 32 patients were then tested with stimulation, which was delivered randomly 200 ms prior and lasting for 4.6 s extending until after second word of the pair disappeared.	In general, stimulation impaired memory. However, post hoc analysis showed that stimulation during the trials that were subsequently marked as being “bad encoding states” actually improved memory	[98]

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Table 2 (continued)

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2017	13	TBS	Improvement	Recognition (people)	Hip and EC	0.05 mA, 5 bursts a second, 4 pulses per burst at 0.2 ms pulse width, delivered at 100 Hz frequency	1 s 2.2–2.7 s prior to picture onset in encoding	Stimulation was delivered on 50% of the images, and the memory of these images was compared with those that were not stimulated	Improvement only with right entorhinal cortex angular bundle suggesting laterality. Theta burst stimulation may be eliciting LTP-like protocols suggesting temporal and spatial specificity. Specifically, white matter stimulation may excite downstream regions	[99]
2018	7	HF	No change	Associative object and word	EC	0.1 mA, pulse width 0.3 ms at 50 Hz for 15 s on 15 s off	Encoding	Stimulation was delivered during 5-minute encoding period in a 15-s, on-off cycle. During this period, participants learned noun-color associations that were later tested	While EC stimulation led to more positive deflections of ERPs in the anterior hippocampus, no behavioral effects of the stimulation were seen, perhaps due to the low stimulation intensities	[100]

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Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2018	22	HF	Improvement with lateral TC stimulation	Word recall	Hip, PHC, neocortex, PFC, and lateral TC	0.5–1.5 mA, pulse width 0.3 ms at 50 Hz for 5 s of stimulation	Encoding	Stimulation applied to 50% of words 200 ms prior to word onset and lasted for 4.6 s extending until after second word of the pair disappeared	Only lateral temporal cortex stimulation improved behavioral performance in the task, and also increased high gamma power as a correlate of memory. Full mechanism needs to be explored further. There may also be an underlying modulation of attention or perception	[101, 102]

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Table 2 (continued)

Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2018	4	TBS	Impairment	Spatiotemporal	Customized per subject based on network activity	4–6 mA, 4 bursts a second, 3 pulses per burst at 0.2 ms pulse width, delivered at 50 Hz frequency	2 s prior to retrieval (delay/ ITI)	Two target stimulation nodes that exhibited strong coupling for spatial vs. temporal memory were identified using iEEG data from a spatiotemporal memory. TBS stimulation was delivered in a subsequent session to these target nodes with a fixed phase-lag (0° or 180°), in a similar spatiotemporal memory task	Only spatial memory was impaired. This impairment was accompanied with theta decoupling of the spatial retrieval network	[103]

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Year	N	Stim type	Memory-related outcome	Memory type	Stimulation location	Stimulation parameters	Stimulation period	Stimulation protocol	Putative mechanism of Action	Ref.
2018	14	TBS	Improvement	Recognition	Amygdala	0.5 mA, 8 trains of 4 pulses per burst at 0.2 ms pulse width, delivered at 50 Hz frequency	1 s at offset of image (delay/ITI)	Theta burst stimulation at the end of the encoding period (image offset). Memory was tested immediately after and following a 1-day delay	Increased memory performance a day later and increased theta gamma interactions. Perhaps through glutamatergic release from amygdala and slower robust molecular changes and plasticity that can only be seen with a long delay	[104]
2019	6	HF	Improvement	Associative word recall	Hip	0.5–1.5 mA, pulse width 0.3 ms at 50 Hz for 5 s of stimulation	Encoding + ITI (not distractor)	Stimulation was applied during 5 s of encoding and was randomly assigned to blocks of stimulation	Improvement in memory was dependent on task. Theta power increased in lateral middle temporal cortex in stimulation trials that were later remembered. Synchronous membrane fluctuations and enhanced long-range communication facilitated by stimulation may enhance recollection and theta power across network	[105]

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Effects of Stimulation Depends on the Stages of a Memory Task

Since continuous open-loop stimulation would be unable to elicit such stage-dependent effects of stimulation, conditional open-loop stimulation has been used to address this problem. The earliest example of such stage-dependent stimulation can be traced back to Lacruz and colleagues in 2010, where they delivered unilateral or bilateral single pulse stimulation to the hippocampi during the encoding and retrieval phase of a recognition memory task [92]. They showed that bilateral stimulation must be delivered during the encoding phase of the task in order to degrade memory performance, as no degradation was observed when the stimulus was only delivered during the retrieval phase. This study suggested that even a single pulse is capable of disrupting processes that underlie memory encoding in the hippocampus, but this stimulus is not effective at degrading memory performance when delivered during the memory retrieval or recognition phase. A more recent study implemented a similar protocol (albeit with high-frequency unilateral stimulation) and introduced a maintenance phase between the encoding and retrieval phases in which the subjects were presented with a distractor (such as an arithmetic problem) [96]. This study showed that stimulation during the maintenance stage, and not during the recall or encoding phase, was most effective at degrading memory performance. The authors suggest that stimulation during the maintenance phase degrades memory by causing one to forget previously encoded memories. The authors suggest that MTL electrical stimulation may alter the neural circuitry representing internal context [96]. Hence it may work by increasing the rate at which the brain changes its internal representation from one context to another, which obscures contextual representation of the recently encoded memory engram and thus causes one to *forget*.

Effect of Stimulation Lateralization

Unilateral hippocampal stimulation studies have provided us with some insight on the lateralization effects of stimulation. For instance, a study performed by Coleshill and colleagues in 2004 showed that delivering high-frequency stimulation (50 Hz) during the encoding phase of a recognition memory task showed material-specific memory deficits [91]. They observed that when the left hippocampus was stimulated during the encoding phase, recognition memory was degraded for previously presented words, and when the right hippocampus was stimulated, recognition memory was degraded for faces. This may be an important factor since earlier studies have shown the left hippocampus to be involved in word-memory [107] and the right hippocampus to be involved in face-memory [108]. Other studies have shown that when using single pulse stimulation, stimulation of both hippocampi is necessary in order to produce episodic memory deficits (although this study did not investigate differences in different types of memories) [92], whereas when using high-frequency stimulation, stimulation of either hippocampi is sufficient for inducing verbal and spatial memory deficits [97].

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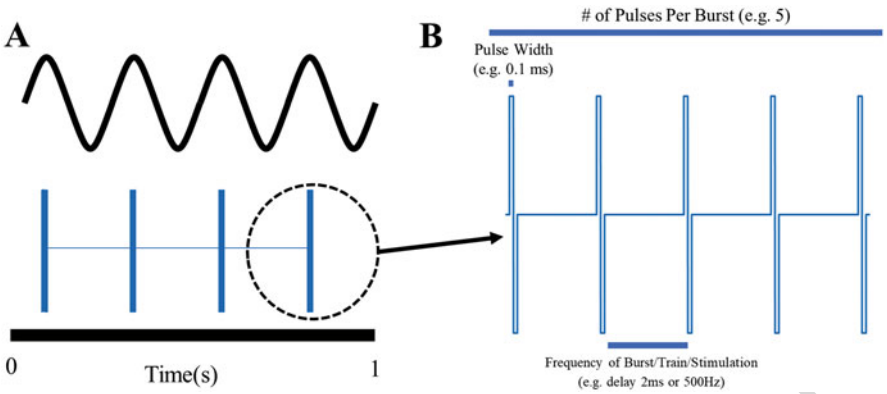

Fig. 5 Example of theta burst stimulation protocol identifying the parameters that can change across studies including the pulse width, number of pulses per burst, frequency of stimulation pulses, and how many bursts per second (i.e., targeted theta frequency). (**a**) We see one cycle of stimulation. (**b**) Zoomed in version of the five pulses delivered in one burst. As evident here, theta burst stimulation entails delivering a high-frequency burst (depicted here as a 500 Hz burst) in a theta envelope (depicted here as 4 Hz). Typical theta burst protocols can have anywhere between 3 and 8 bursts per second, 200 and 500 Hz bursts, and 3 and 8 pulses per burst and a pulse width between 0.1 and 0.3 ms. *It*

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2.2.2 Theta Burst Stimulation of Hippocampal Inputs Can Improve Memory

Since non-customized, high-frequency single pulse stimulation of the hippocampus has been consistently shown to degrade memory performance, an alternative stimulation paradigm, named theta burst stimulation, a delivery of stimulation of multiple pulses/short bursts at high frequency being applied multiple times a second, has been recently investigated (see Fig. 5).

Rationale Behind Theta Burst Stimulation

In their contingent open-loop stimulation study using high-frequency stimulation, Suthana and colleagues proposed that the improvement in spatial memory observed following high-frequency entorhinal stimulation was associated with an increase in theta band (typically 3–8 Hz) power in the hippocampus [93]. The role of theta band activity in memory function is certainly not a recent one. Long-term potentiation (a long-lasting strengthening of synapses following certain activity patterns and a form of plasticity) is believed to play a major role in effectively storing and retrieving memories [22]. It is believed that theta burst stimulation mimics in vivo firing in the hippocampus and is the most effective way of inducing LTP [109]. This can in turn be related to calcium regulation that actually specifically enhances spatial learning [110] and is most optimal around the lower bound of the theta frequency band [111]. Work in animal models has shown that stimulating the hippocampus with intermittent high-frequency bursts aligned with the peaks and troughs of the endogenous theta oscillations can produce LTP and LTD, respectively [112–115].

Thus, theta burst stimulation can be a powerful tool to modulate hippocampal plasticity and thus modulate memory. As a result, theta burst stimulation has been used in various human and animal studies to modulate memory performance.

Entorhinal Theta Burst Stimulation

Perhaps the most comprehensive investigation of theta burst stimulation for modulating memory performance in humans has been conducted by Titiz and colleagues, where they delivered theta burst microstimulation (i.e., stimulating using microelectrodes at current levels that are more similar to physiological levels rather than those used in macrostimulation) unilaterally to the entorhinal areas during the encoding phase of a face-based memory task. Interestingly, the theta burst stimulation during the stimulation trials was delivered roughly 2 s prior to image presentation. The authors reported a substantial and significant increase in memory accuracy and specificity, only when stimulating the right and not the left entorhinal region. This is a captivating finding because a study that was discussed earlier, employing simple high-frequency macrostimulation of the right hippocampus during the encoding phase, showed a face-specific memory deficit [91]. This suggests that while high-frequency stimulation is thought to introduce a functional lesion of the hippocampus, theta burst stimulation of the adjacent entorhinal region (which serves as a major input structure to the hippocampus) prior to image presentation (i.e., prior to the start of the encoding phase) can facilitate better encoding of the subsequently presented image. The spatial specificity of this stimulation is also of importance. Titiz and colleagues demonstrated that such theta burst stimulation delivered to the right angular bundle of the entorhinal region, which is where axons of the perforant pathway are most dense [116], is much more effective at improving memory accuracy and specificity [99]. Contrary to this, theta burst stimulation of the entorhinal gray matter may interfere with underlying neuronal computations which seems to introduce a response bias in the face-based memory task [99]. The differences observed in this study, compared to the previously reported contingent open-loop stimulation literature, may also be attributed to use of microstimulation. Microelectrodes provide significantly greater spatial specificity, allowing the prosthesis to interact with the underlying neuronal networks at a spatial scale that better resembles the underlying neuronal architecture. Furthermore, due to the high impedance of such electrodes, the current delivered during stimulation is much closer to physiological levels when compared to the large currents delivered during macrostimulation. Thus, utilizing microstimulation may have provided Titiz and colleagues with the spatial specificity necessary to interact with the intricate anatomy of the hippocampus and the surrounding structures. However, why such focal stimulation can modulate the vast circuity required to encode a spatially and temporally distributed engram remains largely enigmatic and wanting for future research.

Amygdala Theta Burst Stimulation

The amygdala is a medial temporal lobe structure which is thought to play a key role in processing emotional memories (see [117] for a review). In addition to the role

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that the amygdala plays in emotional processing, it is also thought to play a role in emotional arousal [118]. Thus, it may be possible, by modulating amygdala activity, to enhance memory encoding by associating an emotional valence to a particular stimulus. Recently, Inman and colleagues investigated this exact hypothesis by delivering low amplitude, theta burst stimulation to the amygdala, immediately following the completion of the encoding phase (i.e., immediately following a 3-s image presentation) [104]. Their results demonstrated that amygdala theta burst stimulation was able to significantly improve long-term (i.e., 1 day following image presentation session), but not short-term (i.e., immediately following image presentation session), memory of emotionally neutral images. In fact their stimulation elicited no subjective or objective emotional response, suggesting that amygdala stimulation can enhance memory separate from emotional experience. This is consistent with the presumed role of the amygdala in modulating the consolidation of long-term memory processes [119]. Interestingly, the authors also showed that during the recognition of images that were initially followed by amygdala stimulation, a significantly increased gamma frequency power was observed in the perirhinal cortex, along with significantly increased hippocampal-perirhinal theta band coherence, hinting at the physiological underpinnings of how amygdala stimulation influences the physiology of MTL structures involved in declarative memory. Furthermore, the authors also showed significantly higher theta-gamma phase amplitude coupling between the amygdala (theta phase) and the perirhinal cortex (gamma amplitude) during the recognition phase of images that were followed with amygdala stimulation when compared to images that were not. This finding is fascinating because the theta burst stimulation in and of itself encompasses a high-frequency stimulation burst in a theta envelope. Thus, the reappearance of this theta-modulated gamma activity in the perirhinal cortex during the recognition phase suggests a potential reactivation of an amygdala-induced network state during which the memory was initially encoded.

Fornix Theta Burst Stimulation

While continuous, high-frequency open-loop stimulation of the fornix has shown to be ineffective at improving memory function, forniceal theta burst stimulation may hold some promise. In fact, in a rat model of traumatic brain injury (TBI), forniceal theta burst stimulation delivered during the memory encoding phase was able to rescue spatial memory deficits, whereas high-frequency (130 Hz) and low-frequency (5 Hz) stimulation were not able to induce the same effect [120]. The same group also attempted to stimulate the fornix during the encoding phase in epilepsy patients while they performed various memory tasks [95]. They demonstrated that forniceal theta burst stimulation was able to significantly improve short-term and long-term visuospatial memory; however, improvement was not observed on verbal memory tasks. Although the authors did not report extensive electrophysiological data from the hippocampal memory network, theta burst stimulation of the fornix likely induced robust activation of the hippocampus in a manner that was more physiological and unlike that achieved by high-frequency stimulation of the fornix.

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2.2.3 Limitations of Conditional Open-Loop Approaches

As discussed previously, conditional open-loop stimulation for memory has only been tested in patients with medically refractory epilepsy who have been implanted with electrodes for the presurgical evaluation of their epilepsy. As a result, the translatability of the (often promising) results reported in this section to other diseases and to a healthy brain remains a pressing question. Specifically, such results may not translate as effectively since recorded brain activity can fluctuate and have increased variability weeks after implantation [121]. Furthermore, conditional open-loop studies have to be, by definition, conducted in a controlled experimental environment using one of many available memory tasks. However, there is a significant amount of heterogeneity in this field with regard to the specific type of task used and the underlying mnemonic processes in the brain that this task depends on. As a result, it is extremely difficult to generalize the results of the various studies to real-word application. In fact, despite all evidence regarding direct, high-frequency stimulation of the hippocampus leading to worsened memory function, a very recent study showed that this deterioration of memory may actually be task dependent [105]. In this study, the authors implemented an associative memory task instead of the commonly used recognition memory task (participants were required to remember the association between two words instead of trying to remember the words themselves). They found that delivering high-frequency stimulation directly to the hippocampus in an open-loop manner during the encoding phase can actually improve associative memory, contrary to the existing body of evidence. This suggests that the choice of the memory task for testing a particular stimulation paradigm may be a critical variable, along with the parameters of the stimulation paradigm themselves.

2.3 Closed-Loop Stimulation

Although conditional open-loop approaches address some of the concerns of continuous open-loop stimulation, they still are unable to respond to the dynamically changing underlying brain activity. Furthermore, conditional open-loop stimulation approaches require testing in a controlled experimental environment, which significantly deters the translatability of such neuroprostheses. To develop an intelligent, dynamic neuroprosthesis that can eventually be translated into the real world, closed-loop systems will need to be developed that can respond to the brain as it navigates through a changing environment. Here, we discuss in detail two specific examples of closed-loop neuroprostheses that have led to improvement in memory formation based on systematic detection and delivery of an optimal stimulation.

2.3.1 Encoding State-Specific Stimulation

See Fig. 6.

It has been shown that the ongoing frequency of brain activity can be predictive of memory formation. Specifically, it has been shown that a decrease in theta power

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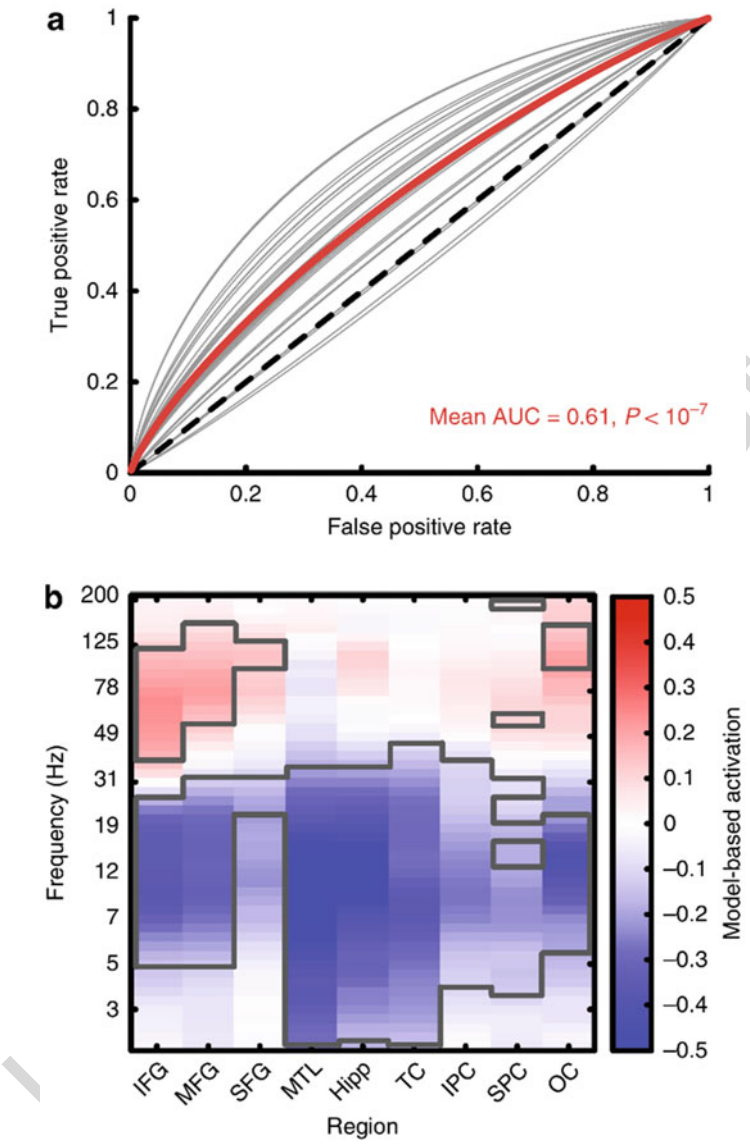

Fig. 6 This figure shows decreased low-frequency (i.e., theta band) activity and increased high-frequency (i.e., gamma band) activity in the mesial temporal lobe structures are predictive of improved memory performance. (**a**) The area under the curve for a classifier that can determine whether a brain state is conducive to accurate memory encoding or not. (**b**) A plot depicting the activation (or deactivation) of various brain regions commonly involved in memory encoding, during successful memory encoding. Note that activity in the lower-frequency band decreases in the mesial temporal lobe structures and increases in the higher-frequency band in the frontal gyrus. This type of online classifier can be used to classify current memory states and deliver stimulation to perturb bad memory states into good ones. (Reproduced from [122] under Creative Commons Attribution 4.0 International License; https://creativecommons.org/licenses/by/4.0/legalcode)

and a simultaneous increase in gamma power prior to stimulus onset represent a better "brain state" for encoding [123–128]. Increases in broadband gamma activity, with concomitant decrease in low-frequency power as observed in these studies, reflect an increase in asynchronous neuronal spiking and are thus reflective of increased cortical excitability [129–131].

With this in mind, Ezzyat and colleagues first collected iEEG data from 102 participants who performed a free word recall task and developed a classifier from spectrally decomposed iEEG signals in order to predict whether a particular word would be later remembered [98]. They demonstrated that the classifier could predict memory performance at an above chance level (mean area under the curve $= 0.63 \pm 0.07$). It is also interesting to note that, in line with the previously reported literature, this classifier primarily relied on widespread decreases in low-frequency power along with increases in high-frequency power across the frontal, temporal, and occipital cortex, as well as in the hippocampus. In a subset of these participants, the authors also delivered high-frequency stimulation to MTL structures in an open-loop manner during the encoding phase. While such open-loop stimulation consistently degraded memory performance (in line with current evidence [97, 132]), post hoc analysis showed that stimulation, when delivered on trials where their classifier predicted successful memory encoding (high encoding state), degraded memory but stimulation delivered on trials where their classifier predicted unsuccessful memory encoding improved memory. These data provide clear evidence that the memory effect of stimulation is brain state dependent. A subsequent study by the same group attempted to optimize the anatomical location of the stimulation [101]. They found that stimulation of the lateral temporal cortex, and not of the prefrontal, parahippocampal, or hippocampal region, increased gamma activity in poor encoding trials and improved performance on a verbal memory task.

Having established when and where to deliver stimulation, they developed an online version of their classifier, in order to determine the appropriate encoding states to stimulate in real time. The study reporting this closed-loop implementation was published in 2018, where Ezzyat and colleagues demonstrated the efficacy of such a closed loop, brain state-dependent neuroprosthesis for improving memory in 25 patients (see Fig. 7) [122]. They showed that stimulation of the lateral temporal cortex in their closed-loop fashion significantly increased the chances of remembering an item by about 15%, whereas stimulation elsewhere decreased chances of remembering an item, albeit nonsignificantly [122].

The process through which this closed-loop system was developed demonstrates the true power and importance that research can lend to developing a neuroprosthesis for memory. By starting with a working hypothesis, and using open-loop stimulation to customize timing of stimulation delivery, Ezzyat and colleagues were able to create an optimal classifier [98].

The optimized stimulation location reported in this work, i.e., the lateral temporal cortex, is significant because it is a brain region that has not previously been targeted for memory function. Furthermore, the lateral temporal cortex can actually be stimulated using noninvasive techniques (transcranial magnetic stimulation,

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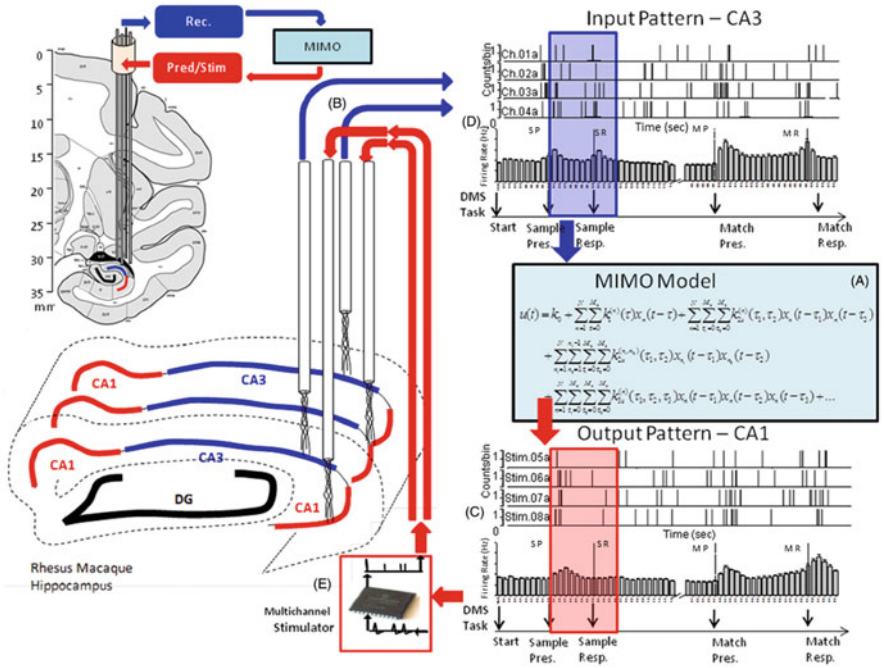

Fig. 7 Multi-input, multi-output (MIMO) nonlinear. Model in (**a**) spatiotemporal recording is calculated to (**b**) predict CA1 (red) firing (**c**) from CA3 (blue) recordings (**d**) and generate patterned stimulation (**e**) for feedback stimulation of the same CA1 areas. The anatomical diagrams show placement of CA3 and CA1 multicell recording tetrodes in their respective areas along the longitudinal axis of hippocampus. On stimulation trials, trains of electrical pulses mimicking the predicted strong code (when an item is correctly remembered) CA1 output were delivered to the same hippocampal electrode locations where the CA1 patterns were previously recorded. MIMO model stimulation patterns applied to the respective CA1 recording locations consisted of multichannel biphasic pulses of 10–50 μA, 1.0 ms duration with a minimum 50 ms between pulses, at ≤20 stimulation pulses per second per channel (obtained with permission from [136]; Copyright 2019; IOP Publishing)

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transcranial direct/alternating current stimulation), which may actually improve the feasibility of developing such a neuroprosthesis while minimizing potential surgical risks and complications [133, 134]. Thus lateral cortex stimulation may provide us with an alternate avenue to probe underlying memory networks in an attempt to develop an ideal memory neuroprosthesis which is consistent with other noninvasive approaches [135].

2.3.2 Multi-input Multi-output (MIMO) Model and Subject-Specific Patterns

The flow of information within model the various subfields of the hippocampus has been extensively studied. One of the fundamental operating principles of the brain is that information is represented in the spatiotemporal firing of neurons. As AU5

the information propagates from one structure to the next, it undergoes nonlinear transformations as a result of neuronal computations, generating a new spatiotemporal firing pattern. Thus, a potential neuroprosthesis for restoring hippocampal function may function to restore the physiological and efficient flow of information within various substructures of the hippocampus, by effectively predicting and stimulating output activity based on input activity. As discussed earlier, the hippocampus contains the distinct subfields of CA1 and CA3. Neuronal activity in CA1 is primarily driven by activity in CA3. Thus, it may be possible to predict the spatiotemporal activation patterns of CA1 neurons from the corresponding spatiotemporal activation patterns of CA3 neurons. This was first demonstrated by Song and colleagues, where they created a multi-input multi-output (MIMO) model of the CA3->CA1 transformation using a series of multi-input single-output (MISO) Laguerre-Volterra kernels [137, 138]. These models incorporated physiological variables such as the synaptic potential caused by the spatiotemporal firing patterns of CA3 neurons (calculated using a Laguerre-Volterra kernel expansion), the spike-triggered afterpotential within the CA1 (calculated using a feedback kernel), and the stochastic noise that models the intrinsic noise of the output neurons and the noise of the unobserved inputs. The efficacy of this MIMO model at predicting output firing patterns in CA1 using input firing patterns from CA3 was established in rats performing a spatial memory task almost a decade ago [137, 138].

Following this, Berger and colleagues developed a closed-loop implementation of this system, in which they were able to extract "weak codes" and "strong codes" from the MIMO model which corresponded the animal either forgetting a spatial memory or remembering it, respectively [139]. In trials where the model predicted a weak code from the MIMO model, a corresponding strong code stimulation was delivered in an attempt to facilitate efficient information transfer between the CA1 and CA3. The authors showed that this type of stimulation significantly improved spatial memory performance even in healthy animals. Furthermore, they demonstrated that delivering pseudorandom stimulation (by scrambling the coefficients of the Laguerre-Volterra kernels) was ineffective at improving memory function. Furthermore, they also demonstrated that this MIMO-based strong code stimulation was able to rescue memory performance in animals chronically treated with a glutamatergic antagonist (MK801) that impairs LTP.

These findings were later replicated in nonhuman primates (NHPs) using a spatial and recognition memory tasks [140] and most recently in humans [141]. Human testing was conducted on patients with medically refractory epilepsy who were implanted with macro- and microelectrodes for the presurgical evaluation of their epilepsy. A patient-specific MIMO model was developed for each individual patient, and MIMO-based stimulation was delivered on a short-term (delayed-match to sample) and long-term (delayed recognition) memory task. Memory performance was significantly higher in both of these memory tasks for the MIMO stimulation conditions, when compared to random stimulation and no stimulation. Thus, the authors demonstrated that facilitating the flow of information between the CA3 and CA1 subregions of the hippocampus using nonlinear estimation techniques

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can indeed improve memory performance, not only in animal models but also in humans.

Although these findings are impressive, one major limitation persists – the stimulation is only delivered during the encoding phase, which means that the neuroprosthesis is dependent on the underlying experimental paradigm. This makes it difficult to translate such a neuroprosthesis into the real world, unless stimulation can be delivered in a continuous or pseudo-continuous fashion or time locked to some biomarker and still achieve memory improvements in real-world environments.

3 Conclusion and Future Directions

In this chapter, we've attempted to provide a comprehensive albeit not exhaustive overview of the current, state-of-art electrical neuromodulation technologies ranging from continuous and contingent open-loop systems to the recently developed closed-loop systems. We've identified the benefits and limitations of the currently available technologies and have provided detailed commentary on the various pieces of converging and diverging evidence in this field. It is important to note that relative to the overall field of neuromodulation, the field of neuromodulation for memory is still in its nascent stages. As such, there is a significant amount of variability and heterogeneity in the currently published literature, which makes it difficult to generalize the results and provide a universal consensus. This heterogeneity can be primarily broken down into the three categories below.

3.1 Stimulation Patterns and Parameters

A majority of the studies discussed here have attempted to use high-frequency stimulation to modulate the memory network, similar to what is currently used in Parkinson's disease as part of trials for AD [53, 66]. Others have attempted to use theta burst stimulation [95, 103, 104], and others have even attempted single pulse stimulation [88, 92]. Recent work with microstimulation instead of the more generally used macrostimulation has provided emerging evidence that the scale of stimulation may also play an important role in providing stimulation specificity and precision [99, 141]. The mechanisms through which these different types of stimulation affect the underlying nervous tissue can be dramatically different, and as a result, the outcomes from these varying stimulation protocols cannot be grouped together for a meta-level analysis.

3.2 Anatomical Locations

Although the hippocampus is thought to be the hub of the declarative memory network, the variety of anatomical structures that have been stimulated in the various

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studies discussed here has been immense. Some studies have attempted to directly stimulate the hippocampus and the neighboring entorhinal and parahippocampal regions, whereas others have attempted to modulate hippocampal activity by stimulating upstream structures that in turn project to the hippocampus. Since we know that electrical stimulation can affect cell bodies, myelinated and unmyelinated axons, in different ways, these results can also not be simply grouped together for meta-level analyses.

3.3 Experimental Environment and Memory Tasks

Perhaps the largest source of heterogeneity in this field arises from the wide array of memory tasks that have been used to investigate the effects of different neuroprostheses on specific types of memory. From our earlier discussion regarding the taxonomy of memory, there is a rich body of literature that supports anatomically and functionally distinct memory networks in the human brain, which means that different memory tasks will target specific mnemonic processes that may not actually be targeted by the particular stimulation paradigm implemented in that study. For instance, several studies have reported detrimental effects of hippocampal high-frequency stimulation on recognition memory; however, a recent study showed that similar hippocampal stimulation can actually have a beneficial effect on associative memory [105].

Despite this heterogeneity, however, a common underlying theme throughout this chapter has been the realization that the memory system is much more complicated than the almost mechanistic cortico-basal ganglia system that is pathological in Parkinson's disease. As a result, using blind, open-loop stimulation of brain structures involved in memory function does not seem to yield the same beneficial results that have been observed with other diseases. There is a pressing need to develop neuroprostheses for memory that account for and specifically target the dynamic nature of the brain and take a focused, hypothesis-driven approach to iterating on these technologies. Attempting to replicate the success of a particular stimulation paradigm from an entirely different disease model in order to modulate memory structures is akin to using a chainsaw to carve out an image on our wax memory tablet. Instead, it is necessary to understand the underlying pathology and develop targeted neuroprostheses that target the underlying mechanisms.

3.4 Moving Toward Real-World Implementations

Apart from the continuous open-loop stimulation neuroprostheses (most of which have failed to show robust improvements in memory function), none of the more advanced memory neuroprostheses discussed here have been tested outside of a well-controlled experimental environment. In fact, none of these more advanced approaches have even been tested outside the walls of a hospital room. Furthermore, all acute stimulation studies have utilized patients with medically refractory epilepsy

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with intracranial electrode implants to develop and test the varying neuroprosthetic designs. These factors make it difficult to generalize the results and predict whether such neuroprostheses will actually be feasible in real-world situations. In fact, there is emerging evidence that activity in the mesial temporal lobe structures may actually be substantially different in this patient population when the patients are allowed to walk instead of participating in tasks while sitting in their hospital beds [142].

Even the currently developed closed-loop technologies tend to rely on specific experimental paradigms in order to stimulate the brain. To make these technologies more translatable, it may be beneficial to use only the ongoing physiological or pathological brain activity as a contingency for delivering stimulation. For example, recently it has been shown that hippocampal ripples can be contingently stimulated with fornix stimulation [143]. Such sharp waves and ripples are believed to be involved in memory, planning, and influencing decisions and even can be a marker for pathological impact of disease [144]. Perhaps if we can find more naturally occurring biomarkers of memory, we can investigate stimulation on naturally occurring events.

A potential avenue for developing memory neuroprostheses that are more suitable for the real world is virtual reality. Using virtual reality, it may be possible to simulate realistic environments, making it possible to not only test the existing systems in a more naturalistic environment but also potentially identify biomarkers and physiological or pathological brain activity that may be used for contingent stimulation. In fact, virtual reality navigation has been shown to elicit theta oscillations in the human hippocampus analogous to those observed in moving rodents, which are not present in otherwise stationary humans [145]. However, it is important to point out that virtual reality may not be a substitute for physical movement as recent evidence suggests that virtual reality-induced hippocampal theta oscillations may not translate to real-world walking [142]. Thus, it may be necessary to create more immersive testing environments which facilitate movement while providing sufficient immersion to simulate the real world (Fig. 8).

There may also be other technological limitations that need to be addressed in order to facilitate real-world implementation of these neuroprostheses. For instance, in Berger's work with humans, they were limited by the number of neurons that they could record and the number of sites they could stimulate due to the limitations of the current neural interfaces [141]. It may be necessary to develop novel neural probes capable of high density recording and stimulation. To perform chronic single-unit recordings (which would be necessary for real-world implementations of the current closed-loop memory neuroprostheses), it may be necessary to control local tissue responses which may deteriorate the signal to noise ratio over time (see [146] for a review). Another major technical challenge to implementing chronic implants is battery life. Closed-loop stimulation approaches allow for battery conservation by only delivering stimulation when necessary; however, they also require the development of low-power chipsets that are capable of performing complex computations while drawing minimal power. The field of neuromodulation for seizure suppression provides some useful examples of

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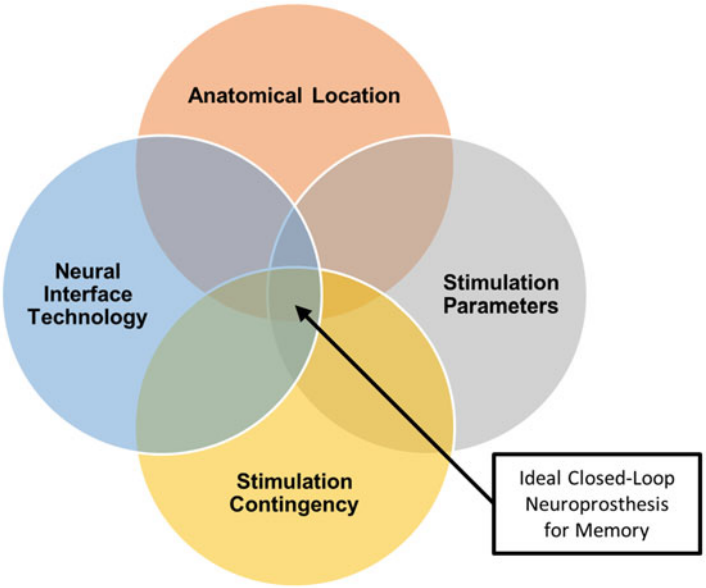

Fig. 8 Considerations for development of an ideal closed-loop neuroprosthesis for memory

such chipsets that are capable of recording and stimulating neural activity at a high density while performing complex operations with minimal power draw. An example of such a chip is the neural interface processor or NURIP, which is an application-specific integrated circuit capable of calculating many spectral features of a signal (phase locking value, cross frequency coupling, band energy, etc.) and passing these features to powerful nonlinear classifiers, all while maintaining minimal power consumption [147]. Adapting this existing technology for memory neuroprostheses or developing custom chipsets for the varying needs of memory neuromodulation may be necessary to facilitate translatability in this field.

Various chapters within this textbook illustrate novel neurotechnologies that facilitate high density recording and stimulation of the brain, others that demonstrate biocompatible composites that facilitate chronic neural implants, and yet others that describe small, low power electronics and communication technologies that allow for processing and transmission of high bandwidth neural activity. Together, these advances in neurotechnologies will certainly accelerate the development of future neuroprostheses for memory. However, it is certainly important to note that sufficiently advanced neurotechnologies are simply one of the many requirements for developing a real-world neuroprosthesis for memory.

With all this in mind, the requirements of the memory neuroprosthesis of the future are as follows:

1. Appropriate anatomical location: an in depth understanding of the memory target or anatomical location.

2. Appropriate stimulation parameters: an optimal selection of stimulation parameters to modulate memory networks in a spatiotemporally precise manner.
3. Appropriate stimulation contingency: Closed-loop stimulation should be based on biomarkers that can be robustly extracted in a real-world environment and should not be dependent on a particular experimental paradigm.
4. Appropriate neural interface technology: high density recording and stimulation capabilities, coupled with low power integrated circuits suitable for chronic implants.

References

1. Lowett, B.: Plato: Theaetetus. In: Proj. Gutenb (1883)
2. James, W.: Chapter 4: Habit. In: The Principles of Psychology (1890)
3. Gaugler, J., James, B., Johnson, T., et al.: 2016 Alzheimer's Disease Facts and Figures. Elsevier (2016)
4. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edn, Arlington (2013)
5. Plassman, B.L., Langa, K.M., Fisher, G.G., et al.: Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. **29**, 125–132 (2007). https://doi.org/10.1159/000109998
6. Prince, M., Comas-Herrera, A., Knapp, M., et al.: World Alzheimer Report 2016 Improving Healthcare for People Living with Dementia. Coverage, Quality and Costs Now and in the Future, London (2016)
7. Hescham, S., Lim, L.W., Jahanshahi, A., et al.: Deep brain stimulation in dementia-related disorders. Neurosci. Biobehav. Rev. **37**, 2666–2675 (2013)
8. Clark RE, Martin SJ (2018) Behavioral Neuroscience of Learning and Memory
9. Montejo, P., Montenegro, M., Fernández, M.A., Maestú, F.: Memory complaints in the elderly: quality of life and daily living activities. A population based study. Arch. Gerontol. Geriatr. **54**, 298–304 (2012). https://doi.org/10.1016/j.archger.2011.05.021
10. Tulving, E.: Episodic and semantic memory. In: Organization of Memory, pp. 381–403 (1972)
11. Tulving, E.: Episodic memory: from mind to brain. Annu. Rev. Psychol. **53**, 1–25 (2002). https://doi.org/0084-6570/02/0201-0001
12. Scoville, W.B., Milner, B.: Loss of recent memory after bilateral hippocampal lesions. J. Neuropsychiatr. Clin. Neurosci. **12**, 103–113 (2000)
13. Henke, K.: A model for memory systems based on processing modes rather than consciousness. Nat. Rev. Neurosci. **11**, 523–532 (2010). https://doi.org/10.1038/nrn2850
14. Universitaria, C.: Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N. Engl. J. Med. **345**, 956–963 (2002). https://doi.org/10.1056/nejmoa000827
15. Patterson, K., Nester, P.J., Rogers, T.T.: Where do you know what you know? The representation of semantic knowledge in the human brain. Nat. Rev. Neurosci. **8**, 976–988 (2007). https://doi.org/10.1038/nrn2277
16. Semah, F., Picot, M.C., Adam, C., et al.: Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology. **51**, 1256–1262 (1998). https://doi.org/10.1212/WNL.51.5.1256
17. Suthana, N., Fried, I.: Deep brain stimulation for enhancement of learning and memory. NeuroImage. **85**, 996–1002 (2014)
18. Eichenbaum, H.: Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron. **44**, 109–120 (2004). https://doi.org/10.1016/j.neuron.2004.08.028

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19. Manns, J.R., Eichenbaum, H.: Evolution of declarative memory. Hippocampus. **16**, 795–808 (2006). https://doi.org/10.1002/hipo
20. Cappaert, N.L.M., Van Strien, N.M., Witter, M.P.: Hippocampal Formation, 4th edn. Elsevier (2014)
21. Treves, A., Rolls, E.T.: Computational analysis of the role of hippocampus in memory. **4**, 374–391 (1994)
AU9
22. Martin, S.J., Grimwood, P.D., Morris, R.G.M.: Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. **23**, 649–711 (2000)
23. Giovanello, K.S., Verfaellie, M., Keane, M.M.: Disproportionate deficit in associative recognition relative to item recognition in global amnesia. Cogn. Affect. Behav. Neurosci. **3**, 186–194 (2003). https://doi.org/10.3758/CABN.3.3.186
24. Mayes, A.R., Holdstock, J.S., Isaac, C.L., et al.: Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. Hippocampus. **14**, 763–784 (2004). https://doi.org/10.1002/hipo.10211
25. Suthana, N.A., Ekstrom, A.D., Moshirvaziri, S., et al.: Human hippocampal CA1 involvement during allocentric encoding of spatial information. J. Neurosci. **29**, 10512–10519 (2009). https://doi.org/10.1523/JNEUROSCI.0621-09.2009
26. Pilly, P.K., Grossberg, S.: How do spatial learning and memory occur in the brain? Coordinated learning of entorhinal grid cells and hippocampal place cells. J. Cogn. Neurosci. 1031–1054 (2012)
AU10
27. Burgess, N., Maguire, E.A., O'Keefe, J.: The human hippocampus and spatial and episodic memory. Neuron. **35**, 625–641 (2002). https://doi.org/10.1016/S0896-6273(02)00830-9
28. Chen, J., Olsen, R.K., Preston, A.R., et al.: Associative retrieval processes in the human medial temporal lobe: hippocampal retrieval success and CA1 mismatch detection. Learn. Mem. **18**, 523–528 (2011). https://doi.org/10.1101/lm.2135211
29. Squire, L.R., Alvarez, P.: Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. **5**, 169–177 (1995). https://doi.org/10.1016/0959-4388(95)80023-9
30. McNaughton, B., McClelland, J.: Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failure of connectionist models of learning and memory. Psychol. Rev. **102**, 419–457 (1995)
31. Mégevand, P., M Groppe, D., Bickel, S., et al.: The hippocampus and amygdala are integrators of neocortical influence: a cortico-cortical evoked potential study. Brain Connect. **2017**, 0527 (2017). https://doi.org/10.1089/brain.2017.0527. ahead of p:brain
32. Hasselmo, M.E., Wyble, B.P.: Free recall and recognition in a network model of the hippocampus: simulating effects of scopolamine on human memory function. Behav. Brain Res. **89**, 1–34 (1997). https://doi.org/10.1016/S0166-4328(97)00048-X
33. Kumaran, D., Maguire, E.A.: Match mismatch processes underlie human hippocampal responses to associative novelty. J. Neurosci. **27**, 8517–8524 (2007). https://doi.org/10.1523/JNEUROSCI.1677-07.2007
34. Hasselmo, M.E.: The role of hippocampal regions CA3 and CA1 in matching entorhinal input with retrieval of associations between objects and context: theoretical comment on Lee et al. (2005). Behav. Neurosci. **119**, 342–345 (2005). https://doi.org/10.1037/0735-7044.119.1.342
35. Kitamura, T., Ogawa, S.K., Roy, D.S., Okuyama, T.: Engrams and circuits crucial for systems consolidation of a memory. Science. **356**, 73–78 (2017). https://doi.org/10.1126/science.aam6808
36. O'Keefe, J., Dostrovsky, J.: The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. **34**, 171–175 (1971). https://doi.org/10.1016/0006-8993(71)90358-1
37. Eichenbaum, H.: Time cells in the hippocampus: a new dimension for mapping memories. Nat. Rev. Neurosci. **15**, 732–744 (2014)
38. Aronov, D., Nevers, R., Tank, D.W.: Mapping of a non-spatial dimension by the hippocampal/entorhinal circuit. Nature. **543**, 719–722 (2017). https://doi.org/10.1002/cncr.27633.Percutaneous

Uncorrected Proof

39. Kang, M., Byun, K., Ho, J., et al.: Proteogenomics of the human hippocampus: the road ahead. BBA - Proteins Proteomics. **1854**, 788–797 (2015). https://doi.org/10.1016/j.bbapap.2015.02.010
40. Aggleton, J.P., O'Mara, S.M., Vann, S.D., et al.: Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. Eur. J. Neurosci. **31**, 2292–2307 (2010). https://doi.org/10.1111/j.1460-9568.2010.07251.x
41. Saunders, R.C., Aggleton, J.P.: Origin and topography of fibers contributing to the fornix in macaque monkeys. Hippocampus. **17**, 396–411 (2007). https://doi.org/10.1002/hipo.20276
42. Kirk, I.J., Oddie, S.D., Konopacki, J., Bland, B.H.: Evidence for differential control of posterior hypothalamic, supramammillary, and medial mammillary theta-related cellular discharge by ascending and descending pathways. J. Neurosci. **16**, 5547–5554 (1996)
43. Skaggs, W.E., Mcnaughton, B.L., Wilson, M.A., Barnes, C.A.: Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. Hippocampus. **6**, 149–172 (1996)
44. Alonso, J.R., Hoi, S.U., Amaral, D.G.: Cholinergic innervation of the primate hippocampal formation: II. Effects of fimbria/fornix transection. J. Comp. Neurol. **375**, 527–551 (1996)
45. Schuurman, P.R., Bosch, A., Bossuyt, P., et al.: A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N. Engl. J. Med. **342**, 461–468 (2000)
46. Kupsch, A., Benecke, R., Müller, J., et al.: Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N. Engl. J. Med. **355**, 1978–1990 (2006). https://doi.org/10.1056/NEJMoa063618
47. The Deep-Brain Stimulaiton for Parkinson's Disease Study Group: Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in parkinson's disease. N. Engl. J. Med. **345**, 956–963 (2001)
48. Lozano, A.M., Lipsman, N.: Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron. **77**, 406–424 (2013). https://doi.org/10.1016/j.neuron.2013.01.020
49. Fernandez, G., Hufnagel, A., Helmstaedter, C., et al.: Memory function during low intensity hippocampal electrical stimulation in patients with temporal lobe epilepsy. Eur. J. Neurol. **3**, 335–344 (1996)
50. Velasco, A.L., Velasco, F., Velasco, M., et al.: Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia. **48**, 1895–1903 (2007). https://doi.org/10.1111/j.1528-1167.2007.01181.x
51. Hamani, C., McAndrews, M.P., Cohn, M., et al.: Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann. Neurol. **63**, 119–123 (2008). https://doi.org/10.1002/ana.21295
52. Freund, H.-J., Kuhn, J., Lenartz, D., et al.: Cognitive functions in a patient with parkinson-dementia syndrome undergoing deep-brain stimulation. ArchNeurol. **66**, 781–785 (2009)
53. Laxton, A.W., Tang-Wai, D.F., McAndrews, M.P., et al.: A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann. Neurol. **68**, 521–534 (2010). https://doi.org/10.1002/ana.22089
54. Sankar, T., Chakravarty, M.M., Bescos, A., et al.: Deep brain stimulation influences brain structure in Alzheimer's disease. Brain Stimul. **8**, 645–654 (2015). https://doi.org/10.1016/j.brs.2014.11.020
55. McLachlan, R.S., Pigott, S., Tellez-Zenteno, J.F., et al.: Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia. **51**, 304–307 (2010). https://doi.org/10.1111/j.1528-1167.2009.02332.x
56. Boëx, C., Seeck, M., Vulliémoz, S., et al.: Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure. **20**, 485–490 (2011). https://doi.org/10.1016/j.seizure.2011.03.001
57. Miatton, M., Van Roost, D., Thiery, E., et al.: The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy Behav. **22**, 759–764 (2011). https://doi.org/10.1016/j.yebeh.2011.09.016
58. Oh, Y.-S., Kim, H.J., Lee, K.J., et al.: Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure. **21**, 183–187 (2012). https://doi.org/10.1016/j.seizure.2011.12.003

Uncorrected Proof

59. Kuhn, J., Hardenacke, K., Lenartz, D., et al.: Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol. Psychiatry. **20**, 353–360 (2015). https://doi.org/10.1038/mp.2014.32
60. Kuhn, J., Hardenacke, K., Shubina, E., et al.: Deep brain stimulation of the nucleus basalis of Meynert in early stage of Alzheimer's dementia. Brain Stimul. (2015). https://doi.org/10.1016/j.brs.2015.04.002
61. Papez, J.W.: A proposed mechanism of emotion. Arch. Neurol. Psychiatr. **38**, 725–743 (1937)
62. Hescham, S., Lim, L.W., Jahanshahi, A., et al.: Deep brain stimulation of the forniceal area enhances memory functions in experimental dementia: the role of stimulation parameters. Brain Stimul. **6**, 72–77 (2013). https://doi.org/10.1016/j.brs.2012.01.008
63. Koubeissi, M.Z., Kahriman, E., Syed, T.U., et al.: Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. Ann. Neurol. **74**, 223–231 (2013). https://doi.org/10.1002/ana.23915
64. Maguire, E.A., Gadian, D.G., Johnsrude, I.S., et al.: Navigation-related structural change in the hippocampi of taxi drivers. Proc. Natl. Acad. Sci. USA. **97**, 4398 (2000)
65. Woollett, K., Maguire, E.A.: Report acquiring "the knowledge" of London's layout drives structural brain changes. Curr. Biol. **21**, 2109–2114 (2011). https://doi.org/10.1016/j.cub.2011.11.018
66. Lozano, A.M., Fosdick, L., Chakravarty, M.M., et al.: A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. J. Alzheimers Dis. **54**, 777–787 (2016). https://doi.org/10.3233/JAD-160017
67. Lee, D.J., Lozano, A.M.: Current status of deep brain stimulation for Alzheimer's disease: from chance observation to clinical trials. Cold Spring Harb Symp Quant Biol. **LXXXIII**, 037440 (2019). https://doi.org/10.1101/sqb.2018.83.037440
68. Whitehouse, P.J., Price, D.L., Struble, R.G., et al.: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science (80-). **215**, 1237–1239 (1982). https://doi.org/10.1086/275028
69. Turnbull, I.M., McGeer, P.L., Beattie, L., et al.: Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. Stereotact Funct Neurosurg. **48**, 216–221 (1985). https://doi.org/10.1159/000101130
70. Freund, H.J., Kuhn, J., Lenartz, D., et al.: Cognitive functions in a patient with parkinson-dementia syndrome undergoing deep brain stimulation. Arch. Neurol. (2009). https://doi.org/10.1001/archneurol.2009.102
71. Kueper, J.K., Speechley, M., Montero-Odasso, M.: The Alzheimer's disease assessment scale-cognitive subscale (ADAS-Cog): modifications and responsiveness in pre-dementia populations. A narrative review. J. Alzheimers Dis. **63**, 423–444 (2018). https://doi.org/10.3233/JAD-170991
72. Tuszynski, M.H., Thal, L., Pay, M., et al.: A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nat. Med. **11**, 551–555 (2005). https://doi.org/10.1038/nm1239
73. Liu, R., Crawford, J., Callahan, P., Blake, D.T.: Intermittent stimulation of the nucleus basalis of Meynert improves working memory in adult monkeys. Curr. Biol. **27**, 2640–2646 (2017). https://doi.org/10.1016/j.cub.2017.07.021.Intermittent
74. Jeong, D.U., Lee, J.E., Lee, S.E., et al.: Improvements in memory after medial septum stimulation are associated with changes in hippocampal cholinergic activity and neurogenesis. Biomed. Res. Int. **568587**, 2014 (2014). https://doi.org/10.1155/2014/568587
75. Gratwicke, J., Zrinzo, L., Kahan, J., et al.: Bilateral deep brain stimulation of the nucleus basalis of Meynert for Parkinson disease dementia a randomized clinical trial. JAMA Neurol. (2018). https://doi.org/10.1001/jamaneurol.2017.3762
76. Toda, H., Hamani, C., Fawcett, A.P., et al.: The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation. J. Neurosurg. **108**, 132–138 (2008). https://doi.org/10.3171/jns/2008/108/01/0132
77. Hamani, C., Stone, S.S., Garten, A., et al.: Memory rescue and enhanced neurogenesis following electrical stimulation of the anterior thalamus in rats treated with corticosterone. Exp. Neurol. **232**, 100–104 (2011). https://doi.org/10.1016/j.expneurol.2011.08.023

Uncorrected Proof

78. Hamani, C., Ewerton, F.I.S., Bonilha, S.M., et al.: Bilateral anterior thalamic nucleus lesions and high-frequency stimulation are protective against pilocarpine-induced seizures and status epilepticus. Neurosurgery. **54**, 191–197 (2004). https://doi.org/10.1227/01.NEU.0000097552.31763.AE
79. Lim, S.-N., Lee, S.-T., Tsai, Y.-T., et al.: Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. Epilepsia. **48**, 342–347 (2007). https://doi.org/10.1111/j.1528-1167.2006.00898.x
80. Fisher, R., Salanova, V., Witt, T., et al.: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. **51**, 899–908 (2010). https://doi.org/10.1111/j.1528-1167.2010.02536.x
81. Mullan, S., Vailati, G., Karasick, J., Mailis, M.: Thalamic lesions for the control of epilepsy. Arch. Neurol. **16**, 277–285 (1967)
82. Kerrigan, J.F., Litt, B., Fisher, R.S., et al.: Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy. Epilepsia. **45**, 346–354 (2004). https://doi.org/10.1111/j.0013-9580.2004.01304.x
83. Gao, F., Guo, Y., Zhang, H., et al.: Anterior thalamic nucleus stimulation modulates regional cerebral metabolism: an FDG-MicroPET study in rats. Neurobiol. Dis. **34**, 477–483 (2009). https://doi.org/10.1016/j.nbd.2009.03.001
84. Halgren, E., Wilson, C.L.: Recall deficits produced by afterdischarges in the human hippocampal formation and amygdala. Electroencephalogr. Clin. Neurophysiol. **61**, 375–380 (1985). https://doi.org/10.1016/0013-4694(85)91028-4
85. Stone, S.S.D., Teixeira, C.M., DeVito, L.M., et al.: Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J. Neurosci. **31**, 13469–13484 (2011). https://doi.org/10.1523/JNEUROSCI.3100-11.2011
86. Xia, F., Yiu, A., Stone, S.S.D., et al.: Entorhinal cortical deep brain stimulation rescues memory deficits in both young and old mice genetically engineered to model Alzheimer's disease. Neuropsychopharmacology. **42**, 2493–2503 (2017). https://doi.org/10.1038/npp.2017.100
87. Gondard, E., Teves, L., Wang, L., et al.: Deep brain stimulation rescues memory and synaptic activity in a rat model of global ischemia. J. Neurosci. **39**, 1222–1218 (2019). https://doi.org/10.1523/jneurosci.1222-18.2019
88. Halgren, E., Wilson, C.L., Stapleton, J.M.: Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories. Brain Cogn. **4**, 287–295 (1985). https://doi.org/10.1016/0278-2626(85)90022-3
89. Knowlton, R.C., Elgavish, R., Howell, J., et al.: Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. Ann. Neurol. **59**, 835–842 (2006). https://doi.org/10.1002/ana.20857
90. Elger, C.E., Helmstaedter, C., Kurthen, M.: Chronic epilepsy and cognition. Lancet Neurol. **3**, 663–672 (2004). https://doi.org/10.1016/S1474-4422(04)00906-8
91. Coleshill, S.G., Binnie, C.D., Morris, R.G., et al.: Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J. Neurosci. **24**, 1612–1616 (2004). https://doi.org/10.1523/JNEUROSCI.4352-03.2004
92. Lacruz, M.E., Valentín, A., Seoane, J.J.G., et al.: Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. Neuroscience. **170**, 623–632 (2010). https://doi.org/10.1016/j.neuroscience.2010.06.042
93. Suthana, N., Haneef, Z., Stern, J., et al.: Memory enhancement and deep-brain stimulation of the entorhinal area. N. Engl. J. Med. **366**, 1945–1946 (2012). https://doi.org/10.1056/NEJMc1203204; author reply 1946
94. Fell, J., Staresina, B.P., Do Lam, A.T.A., et al.: Memory modulation by weak synchronous deep brain stimulation: a pilot study. Brain Stimul. **6**, 270–273 (2013). https://doi.org/10.1016/j.brs.2012.08.001
95. Miller, J.P., Sweet, J.A., Bailey, C.M., et al.: Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain. **138**, 1833–1842 (2015). https://doi.org/10.1093/brain/awv095

Uncorrected Proof

96. Merkow, M.B., Burke, J.F., Ramayya, A.G., et al.: Stimulation of the human medial temporal lobe between learning and recall selectively enhances forgetting. Brain Stimul. **10**, 645–650 (2017). https://doi.org/10.1016/j.brs.2016.12.011
97. Jacobs, J., Miller, J., Lee, S.A., et al.: Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron. **92**, 983–990 (2016). https://doi.org/10.1016/j.neuron.2016.10.062
98. Ezzyat, Y., Kragel, J.E., Burke, J.F., et al.: Direct brain stimulation modulates encoding states and memory performance in humans. Curr. Biol. **27**, 1251–1258 (2017). https://doi.org/10.1016/j.cub.2017.03.028
99. Titiz, A.S., Hill, M.R.H., Mankin, E.A., et al.: Theta-burst microstimulation in the human entorhinal area improves memory specificity. elife. **6** (2017). https://doi.org/10.7554/eLife.29515
100. Hansen, N., Chaieb, L., Derner, M., et al.: Memory encoding-related anterior hippocampal potentials are modulated by deep brain stimulation of the entorhinal area. Hippocampus. **28**, 12–17 (2018). https://doi.org/10.1002/hipo.22808
101. Kucewicz, M.T., Berry, B.M., Kremen, V., et al.: Electrical stimulation modulates high γ activity and human memory performance. eneuro. **5** (2018). https://doi.org/10.1523/eneuro.0369-17.2018
102. Kucewicz, M.T., Berry, B.M., Miller, L.R., et al.: Evidence for verbal memory enhancement with electrical brain stimulation in the lateral temporal cortex. Brain. **141**, 971–978 (2018). https://doi.org/10.1093/brain/awx373
103. Kim, K., Schedlbauer, A., Rollo, M., et al.: Network-based brain stimulation selectively impairs spatial retrieval. Brain Stimul. **11**, 213–221 (2018). https://doi.org/10.1016/j.brs.2017.09.016
104. Inman, C.S., Manns, J.R., Bijanki, K.R., et al.: Direct electrical stimulation of the amygdala enhances declarative memory in humans. Proc. Natl. Acad. Sci. **115**, 98–103 (2018). https://doi.org/10.1073/pnas.1714058114
105. Jun, S., Kim, J.S., Chung, C.K.: Direct stimulation of human hippocampus during verbal associative encoding enhances subsequent memory recollection. Front. Hum. Neurosci. **13**, 1–10 (2019). https://doi.org/10.3389/fnhum.2019.00023
106. Benabid, A.L., Pollak, P., Hoffmann, D., et al.: Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet. **337**, 403–406 (1991). https://doi.org/10.1016/0140-6736(91)91175-T
107. Lee, G.P., Loring, D.W., Flanigin, H.F., et al.: Electrical stimulation of the human hippocampus produces verbal intrusions during memory testing. Neuropsychologia. **26**, 623–627 (1988). https://doi.org/10.1016/0028-3932(88)90118-2
108. Haxby, J.V., Ungerleider, L.G., Horwitz, B., et al.: Face encoding and recognition in the human brain. Proc. Natl. Acad. Sci. **93**, 922–927 (2002). https://doi.org/10.1073/pnas.93.2.922
109. Larson, J., Wong, D., Lynch, G.: Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res. **368**, 347–350 (1986)
110. Sheridan, G., Moeendarbary, E., Pickering, M., et al.: Theta-burst stimulation of hippocampal slices induces network-level calcium oscillations and activates analogous gene transcription to spatial learning. PLoS One. **9**, e100546 (2014). https://doi.org/10.1371/journal.pone.0100546
111. Grover, L.M., Kim, E., Cooke, J.D., Holmes, W.R.: LTP in hippocampal area CA1 is induced by burst stimulation over a broad frequency range centered around delta. Learn. Mem. **16**, 69–81 (2009). https://doi.org/10.1101/lm.1179109
112. Hyman, J.M., Wyble, B.P., Goyal, V., et al.: Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough. J. Neurosci. **23**, 11725–11731 (2003)
113. Hölscher, C., Anwyl, R., Rowan, M.J.: Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo. J. Neurosci. **17**, 6470–6477 (1997)

Uncorrected Proof

114. Huerta, P.T., Lisman, J.E.: Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron. **15**, 1053–1063 (1995). https://doi.org/10.1016/0896-6273(95)90094-2
115. Kwag, J., Paulsen, O.: The timing of external input controls the sign of plasticity at local synapses. Nat. Neurosci. **12**, 1219–1221 (2009). https://doi.org/10.1038/nn.2388
116. Zeineh, M.M., Palomero-Gallagher, N., Axer, M., et al.: Direct visualization and mapping of the spatial course of fiber tracts at microscopic resolution in the human hippocampus. Cereb. Cortex. **27**, 1779–1794 (2017). https://doi.org/10.1093/cercor/bhw010
117. LaBar, K.S., Cabeza, R.: Cognitive neuroscience of emotional memory. Nat. Rev. Neurosci. **7**, 54–64 (2006). https://doi.org/10.1038/nrn1825
118. Hamann, S.B., Ely, T.D., Hoffman, J.M., Kilts, C.D.: Ecstasy and Agony: activation of the human amygdala in positive and negative emotion. Psychol. Sci. **13**, 135–141 (2002)
119. Paré, D.: Role of the basolateral amygdala in memory consolidation. Prog. Neurobiol. **70**, 409–420 (2003). https://doi.org/10.1016/S0301-0082(03)00104-7
120. Sweet, J.A., Eakin, K.C., Munyon, C.N., Miller, J.P.: Improved learning and memory with theta-burst stimulation of the fornix in rat model of traumatic brain injury. Hippocampus. **24**, 1592–1600 (2014). https://doi.org/10.1002/hipo.22338
121. Ung, H., Baldassano, S.N., Bink, H., et al.: Intracranial EEG fluctuates over months after implanting electrodes in human brain. J. Neural Eng. (2017). https://doi.org/10.1088/1741-2552/aa7f40
122. Ezzyat, Y., Wanda, P.A., Levy, D.F., et al.: Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. Nat. Commun. **9**, 1–8 (2018). https://doi.org/10.1038/s41467-017-02753-0
123. Long, N.M., Burke, J.F., Kahana, M.J.: Subsequent memory effect in intracranial and scalp EEG. NeuroImage. **84**, 488–494 (2014). https://doi.org/10.1016/j.neuroimage.2013.08.052 AU11
124. Sederberg, P.B., Kahana, M.J., Howard, M.W., et al.: Theta and gamma oscillations during encoding predict subsequent recall. J. Neurosci. **23**, 10809–10814 (2003)
125. Greenberg, J.A., Burke, J.F., Haque, R., et al.: Decreases in theta and increases in high frequency activity underlie associative memory encoding. NeuroImage. **114**, 257–263 (2015). https://doi.org/10.1016/j.neuroimage.2015.03.077
126. Guderian, S., Schott, B.H., Richardson-Klavehn, A., et al.: Medial temporal theta state before an event predicts episodic encoding success in humans. Proc. Natl. Acad. Sci. **106**, 5365–5370 (2009). https://doi.org/10.1073/pnas.0900289106
127. Fell, J., Ludowig, E., Staresina, B.P., et al.: Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG. J. Neurosci. **31**, 5392–5397 (2011). https://doi.org/10.1523/JNEUROSCI.3668-10.2011
128. Merkow, M.B., Burke, J.F., Stein, J.M., Kahana, M.J.: Prestimulus theta in the human hippocampus predicts subsequent recognition but not recall. Hippocampus. **24**, 1562–1569 (2014). https://doi.org/10.1002/hipo.22335
129. Crone, N.E., Korzeniewska, A., Franaszczuk, P.J.: Cortical gamma responses: searching high and low. Int. J. Psychophysiol. **79**, 9–15 (2011)
130. Miller, K.J., Leuthardt, E.C., Schalk, G., et al.: Spectral changes in cortical surface potentials during motor movement. J. Neurosci. **27**, 2424–2432 (2007). https://doi.org/10.1523/JNEUROSCI.3886-06.2007
131. Miller, K.J.: Broadband spectral change: evidence for a macroscale correlate of population firing rate? J. Neurosci. **30**, 6477–6479 (2010). https://doi.org/10.1523/jneurosci.6401-09.2010
132. Goyal, A., Miller, J., Watrous, A.J., et al.: Electrical stimulation in hippocampus and entorhinal cortex impairs spatial and temporal memory. J. Neurosci. **38**, 3049–3017 (2018). https://doi.org/10.1523/JNEUROSCI.3049-17.2018
133. Boggio, P.S., Khoury, L.P., Martins, D.C.S., et al.: Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease. J. Neurol. Neurosurg. Psychiatry. **80**, 444–447 (2009). https://doi.org/10.1136/jnnp.2007.141853
134. Boggio, P.S., Valasek, C.A., Campanhã, C., et al.: Non-invasive brain stimulation to assess and modulate neuroplasticity in Alzheimer's disease. Neuropsychol. Rehabil. **21**, 703–716

Uncorrected Proof

(2011). https://doi.org/10.1080/09602011.2011.617943
135. Reinhart, R.M.G., Nguyen, J.A.: Working memory revived in older adults by synchronizing rhythmic brain circuits. Nat. Neurosci. **22** (2019). https://doi.org/10.1038/s41593-019-0371-x
136. Hampson, R.E., Song, D., Opris, I., et al.: Facilitation of memory encoding in primate hippocampus by a neuroprosthesis that promotes task specific neural firing. J. Neural Eng. **10** (2013). https://doi.org/10.1016/j.freeradbiomed.2008.10.025.The
137. Song, D., Chan, R.H.M., Marmarelis, V.Z., et al.: Nonlinear dynamic modeling of spike train transformations for hippocampal-cortical prostheses. IEEE Trans. Biomed. Eng. **54**, 1053–1066 (2007). https://doi.org/10.1109/TBME.2007.891948
138. Song, D., Chan, R.H.M., Marmarelis, V.Z., et al.: Nonlinear modeling of neural population dynamics for hippocampal prostheses. Neural Netw. **22**, 1340–1351 (2009). https://doi.org/10.1016/j.neunet.2009.05.004
139. Berger, T.W., Hampson, R.E., Song, D., et al.: A cortical neural prosthesis for restoring and enhancing memory. J. Neural Eng. (2011)
140. Deadwyler, S.A., Hampson, R.E., Song, D., et al.: A cognitive prosthesis for memory facilitation by closed-loop functional ensemble stimulation of hippocampal neurons in primate brain. Exp. Neurol. **287**, 452–460 (2017). https://doi.org/10.1016/j.expneurol.2016.05.031
141. Marmarelis, V.Z., She, X., Popli, G., et al.: Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall. J. Neural Eng. **15**, 036014 (2018). https://doi.org/10.1088/1741-2552/aaaed7
142. Bohbot, V.D., Copara, M.S., Gotman, J., Ekstrom, A.D.: Low-frequency theta oscillations in the human hippocampus during real-world and virtual navigation. Nat. Commun. **8**, 1–7 (2017). https://doi.org/10.1038/ncomms14415
143. Talakoub, O., Gomez Palacio Schjetnan, A., Valiante, T.A., et al.: Closed-loop interruption of hippocampal ripples through fornix stimulation in the non-human primate. Brain Stimul. **9**, 911–918 (2016). https://doi.org/10.1016/j.brs.2016.07.010
144. Buzsáki, G.: Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus. **25**, 1073–1188 (2015). https://doi.org/10.1002/hipo.22488
145. Ekstrom, A.D., Caplan, J.B., Ho, E., et al.: Human hippocampal theta activity during virtual navigation. Hippocampus. **15**, 881–889 (2005). https://doi.org/10.1002/hipo.20109
146. Ghasemi, P., Sahraee, T., Mohammadi, A.: Closed- and open-loop deep brain stimulation: methods, challenges, current and future aspects. J Biomed Phys Eng. **8**, 209–216 (2018). https://doi.org/10.31661/jbpe.v8i2.898
147. O'Leary, G., Groppe, D.M., Valiante, T.A., et al.: NURIP: neural interface processor for brain-state classification and programmable-waveform neurostimulation. IEEE J. Solid State Circuits. **53**, 3150–3162 (2018). https://doi.org/10.1109/JSSC.2018.2869579
148. Squire, L.R.: Memory systems of the brain: a brief history and current perspective. Neurobiol. Learn. Mem. 171–177 (2004)

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