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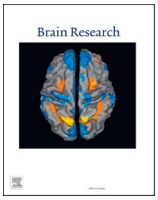

Review

Promising neurostimulation routes for targeting the hippocampus to improve episodic memory: A review

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ABSTRACT

This review aims to highlight modern neurostimulation approaches that are effectively activating the hippocampus and enhancing episodic memory performance. The hippocampus is a brain region known to play an essential role in episodic memory processes. However, as it is nestled deep within the brain, it has been a challenging target for traditional neurostimulation approaches, with studies reporting inconsistent memory effects. Recent studies suggest more than half of the electrical current from non-invasive transcranial electrical stimulation (tES) methods may be attenuated by the human scalp, skull, and cerebral spinal fluid. Thus, this review aims to highlight novel neurostimulation approaches that are showing promise as alternative routes for activating hippocampal circuitry. Early evidence suggests temporal interference, closed-loop and individualized protocols, sensory stimulation and peripheral nerve-targeted tES protocols warrant further investigation. These approaches each provide promising routes for activating the hippocampus by a) increasing its functional connectiveness to key brain regions, b) strengthening synaptic plasticity mechanisms, or c) enhancing neural entrainment specifically within and between theta and gamma frequencies in these regions. Importantly, these three functional mechanisms and the hippocampus' structural integrity are negatively impacted throughout the progression of Alzheimer's Disease, with episodic memory deficits likewise evident in early stages. Consequently, depending on further validation of the approaches reviewed here, these techniques could offer significant applied therapeutic value for patients suffering from memory deficits or neurodegenerative diseases including amnestic Mild Cognitive Impairment or Alzheimer's disease.

1. Introduction

The hippocampal circuitry within the brain has long been acknowledged as the 'hub of declarative memory' (Mankin & Fried, 2020), suggesting it as a potential therapeutic target for memory-focused neurostimulation approaches. However, its deep location within the brain challenges the effectiveness of traditional transcranial electrical stimulation (tES) approaches. Reviewing developments in modern neurostimulation approaches, several promising avenues for enhancing episodic memory processes are evident. Targeting the hippocampus indirectly or directly, these techniques offer alternative means of enhancing neural entrainment (specifically within and between theta and gamma frequencies), increasing functional connectivity between the hippocampus and key brain regions, and facilitating synaptic plasticity mechanisms. These notable methods include temporal interference; closed-loop and individualized protocols; sensory stimulation; and tDCS or tACS strategies that explore additional mechanisms. Importantly, the success of several of these protocols are especially relevant for patients suffering from memory deficits and neurodegenerative diseases including amnestic mild cognitive impairment (aMCI) or Alzheimer's Disease (AD).

2. The hippocampus and episodic memory consolidation

Memory consolidation refers to the "process by which short-term memories…become long-term memories" (Harrington et al., 2022). Long-term memory is typically classified as information which can be consciously recalled i.e. declarative or explicit memory; or unconscious memory information i.e. non-declarative or implicit (Camina & Güell, 2017). As shown in Fig. 1, non-declarative (implicit) memories are

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separated into four types; procedural, associative, non-associative and priming. Whereas declarative memories are categorized into episodic (relating to personal experiences) or semantic (referring to information about facts)(Camina & Güell, 2017). This review will focus on long-term episodic memory.

Humans rely daily on episodic memory to guide our sense of self and inform our decisions based on prior experience (Hebscher & Voss, 2020). As shown in Fig. 2, the hippocampus proper, located deep within the medial temporal lobe, consists of three major subfields (CA1-CA3) and forms part of the hippocampal formation i.e. "the dentate gyrus, hippocampus, subicular complex, and entorhinal cortex" (Schultz & Engelhardt, 2014, p. 6). Early evidence for the role of the hippocampus and hippocampal-formation in declarative memory stemmed from rodent and animal lesion experiments; human neuroimaging and neurophysiological studies; and from human case studies of memory impairments exhibited by patients with brain lesions (Squire, 1992). Although beyond the scope of this review, it's important to highlight that whilst the hippocampus has frequently been regarded as the seat of long-term memories, there remains debate about whether long-term memories are solely stored in this region or are also integrated within neocortical regions (Wiltgen et al., 2004; Yadav et al., 2022). Nevertheless, there is clear evidence that the encoding and consolidation of episodic memories critically depends on the hippocampus, the surrounding mesial temporal lobe structures and their interconnections to proximal and distributed brain circuits (Harrington et al., 2022; Hebscher & Voss, 2020; Mankin & Fried, 2020). Moreover, specific brain oscillatory activity has been associated with successful episodic memory processes.

3. Brain oscillations and memory

Brain oscillations refer to the synchronised rhythmic activity of neuronal populations within a given frequency band, which are linked with most cognitive processes including memory (Hanslmayr et al., 2019). Beginning with slower oscillations in the delta frequency (<4 Hz), these frequency bands increase in magnitude from theta, through to alpha, beta and gamma (>30 Hz) (Buzsáki & Draguhn, 2004; Byron et al., 2021). Due to neuronal network architecture, higher frequency oscillations are shown to be more locally-constrained, whilst slower oscillations can recruit wider neuronal circuits (Buzsáki & Draguhn, 2004). Thus different oscillatory frequencies provide a means of supporting synchronisation between either local and distant networks (Buzsáki & Draguhn, 2004).

With regards to successful declarative memory processes, numerous studies provide evidence for the roles of theta and gamma oscillations (Aktürk et al., 2022; Colgin et al., 2009; Jensen et al., 2007; Osipova et al., 2006). It's important to note that oscillations themselves don't serve specific cognitive functions, but rather their function is determined by a combination of their varying characteristics (i.e. amplitude, frequency, phase, power, cross-frequency coupling etc.) and the associated brain region(s) or networks (Aktürk et al., 2022; Hanslmayr et al., 2019). For example, this location and frequency specificity is evident from findings that theta oscillations in the fronto-parietal network (Aktürk et al., 2022), and right parietotemporal areas (Osipova et al., 2006) have been linked with memory processes. Adding to the complexity, the exact frequencies at which oscillatory bands can occur can vary not only across individuals, but also between brain regions themselves. For example, whilst temporal cortical regions exhibit theta oscillatory power changes in the classic 4–8 Hz frequency range, there is evidence suggesting hippocampal theta power changes occur at slower 3 Hz frequency, which in the literature is often considered delta frequency (Lega et al., 2012).

In relation to gamma frequency, from implanted electrodes in epileptic patients, it has been shown that gamma oscillations localised to the hippocampus, as well as the synchronous gamma oscillations between the hippocampus and rhinal cortex were associated with successful long-term memory encoding (Fell et al., 2001). Notably, also using implanted electrodes in epileptic adult patients, Griffiths et al. (2019) investigated the neural oscillatory patterns associated with, and preceding, different episodic memory processing stages. They found that alpha and beta (8 – 20 Hz) power decreases in the anterior temporal lobe preceded and predicted hippocampal fast gamma (60 – 80 Hz) power increases (by 100 – 200 ms) during successful memory formation (Griffiths et al., 2019). Additionally, they found that hippocampal slow gamma (40 – 50 Hz) power increases predicted and preceded anterior temporal lobe alpha/ beta power decreases (by 200 – 300 ms) during successful memory retrieval (Griffiths et al., 2019). Griffiths and colleagues (Griffiths et al., 2019) argue that these neural oscillations and connectivity are facilitated by the intrahippocampal pathway (a circuit with reciprocal connections between the anterior temporal lobe through

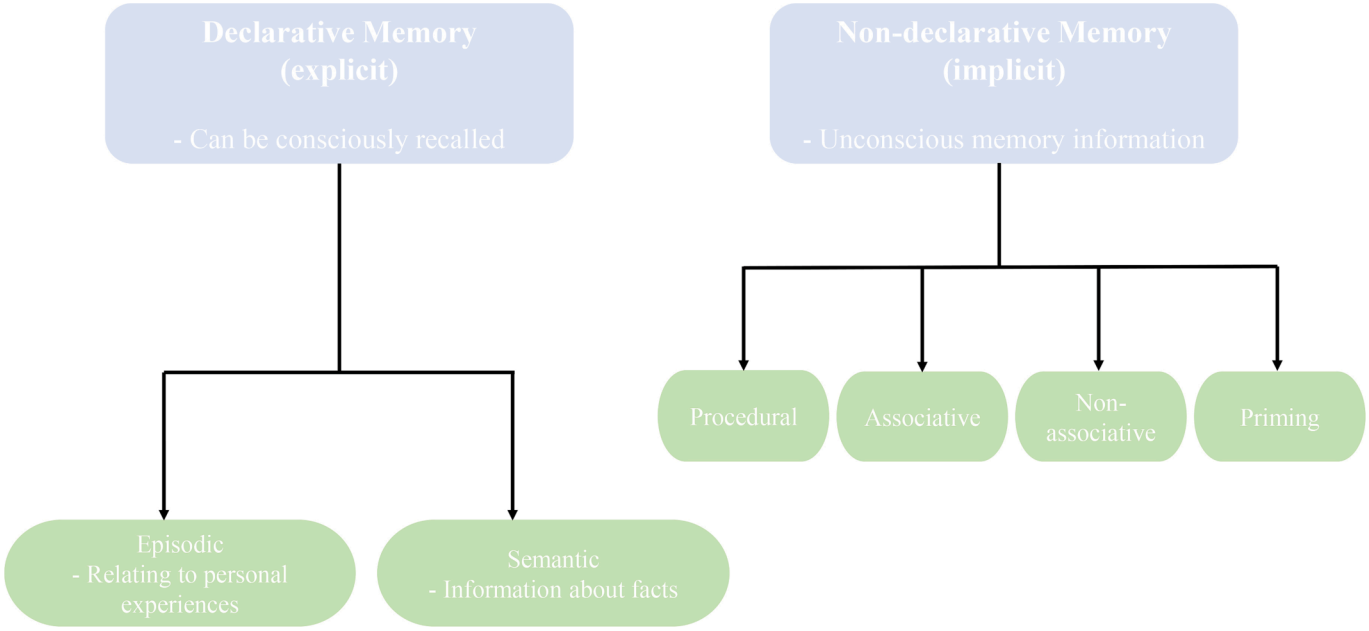

Fig. 1. Classification of Long-term Memory.

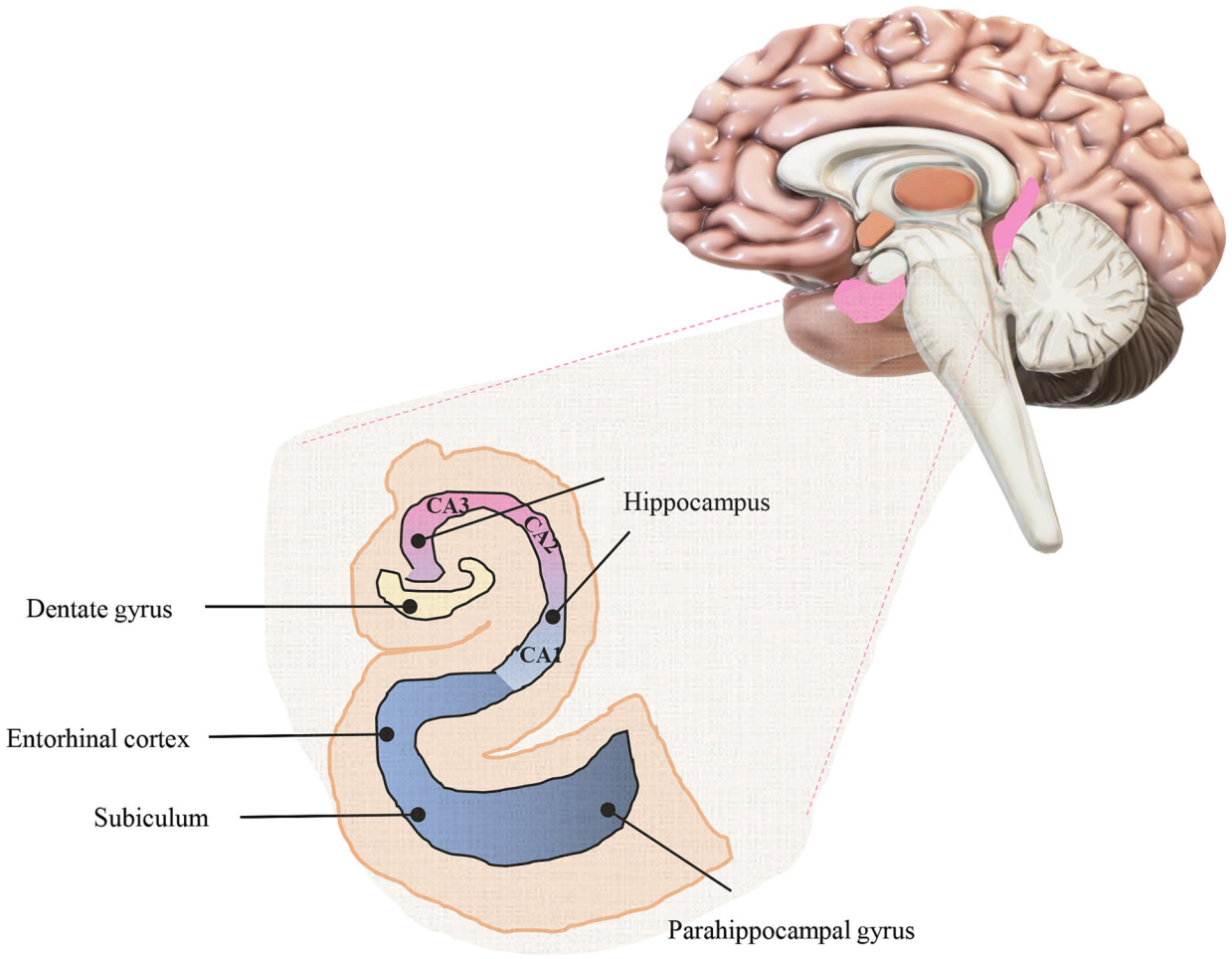

Fig. 2. The Hippocampus and Hippocampal Formation. The hippocampus proper consists of three major subfields (CA1-CA3). The hippocampal formation includes the hippocampus, dentate gyrus, subicular complex and entorhinal cortex.

the entorhinal cortex to the hippocampus), and that their results generalise earlier rodent findings to humans. In a similar vein, an interesting theory which also explores the role of neocortical desynchronized alpha and beta activity (i.e. power decreases) and hippocampal synchronized theta and gamma oscillations (i.e. power increases) during memory tasks is the complementary learning systems (CLS) theory. In a recent opinion piece, Hanslmayr and colleagues (Hanslmayr et al., 2016) put forth evidence to suggest the distinct roles these two processes play within episodic memory formation. However there remains several outstanding questions with this framework and thus future research is required to fully elucidate the extent and nature of these synchronized and desynchronized oscillatory activity in memory processes (as discussed later in this review).

On the other hand, increasing research has confirmed the facilitatory and causal role of theta and gamma oscillations in successful episodic memory processes (Colgin et al., 2009; Jensen & Colgin, 2007; Jensen et al., 2007; Köster et al., 2014; Lisman & Jensen, 2013; Osipova et al., 2006). Moreover, there is evidence pointing to theta-gamma coupling as a communication mechanism between memory circuits in the brain during human episodic memory (Hebscher & Voss, 2020). According to the theta-gamma coupling framework, theta frequency oscillations are proposed to facilitate coordination between the medial temporal lobe and distributed neocortical regions (Hebscher & Voss, 2020). In line with this, recent theoretical models propose that the number of gamma cycles nested in a single theta cycle are functionally relevant for memory processes (Aktürk et al., 2022). Several correlational findings support this "relationship between memory performance and theta-gamma cross-frequency coupling" (Aktürk et al., 2022). Moreover, recent research is demonstrating the functional role of theta-gamma oscillations and coupling patterns in individuals with memory difficulties such as those with aMCI (Vanneste et al., 2021). See the 'Memory Impairment: Alzheimer's Disease' section for more detail on this.

Additionally, the functional relevance of specific oscillatory patterns can be determined by modulating naturally occurring oscillations to determine if there's any behavioural effect on memory. This process of modulating endogenous oscillations is referred to as oscillatory entrainment (Hanslmayr et al., 2019). In humans, oscillatory entrainment can be achieved via various stimulation protocols including non-invasive transcranial electromagnetic stimulation (TMS), non-invasive transcranial electrical stimulation (tES), sensory stimulation and deep brain stimulation (DBS) techniques. Current theories argue that neural entrainment underlies 'online' or 'immediate' effects, whilst synaptic plasticity mechanisms are posited to facilitate longer-term 'offline' effects of stimulation (Adaikkan & Tsai, 2020; Kricheldorff et al., 2022; Vossen et al., 2015; Yavari et al., 2018). Nevertheless, additional mechanisms (such as the role of peripheral nerves) cannot be excluded (Luckey et al., 2020; van Boekholdt et al., 2021; Vanneste et al., 2020). Looking at episodic memory outcomes of neurostimulation studies specifically, results are relatively inconsistent. However, when focusing on the hippocampus and its distributed network, and neural entrainment within theta and gamma ranges specifically, there are several notable techniques which show promise. As this paper will later discuss, these findings are of critical importance in relation to memory impairment conditions such as AD.

4. Modern developments of traditional stimulation approaches

4.1. Traditional DBS, vs temporal interference (a modern non-invasive technique)

Deep brain stimulation (DBS), a form of invasive stimulation, involves applying electrical current directly to brain tissue via implanted electrodes, which are connected via subcutaneous wires to a pulse generator inserted below the collar bone (Chang et al., 2018). See Fig. 3 for a visual presentation of this. Although it is a standard tool for management of motor difficulties associated with Parkinson's Disease (as well as for seizure onset for epileptic patients), for memory improvement, initial DBS studies have seen inconsistent effects (Chang et al., 2018). Interestingly, a recent approach applying 100 Hz DBS (i.e. gamma frequency) to the posterior cingulate cortex (PCC) found that hippocampal activity could be modulated by targeting functionally connected brain regions (Natu et al., 2019). In this study of adult epileptic patients, DBS of the PCC decreased hippocampal theta power and increased hippocampal gamma-band power (Natu et al., 2019). Critically, this increase in hippocampal gamma power in fact predicted subsequent memory impairment (Natu et al., 2019). This suggests the causal role of gamma oscillations in the hippocampus for successful episodic memory processes.

However DBS has several known adverse effects and risks (Luo et al., 2021). This alongside its invasive nature means that it is not an optimal first-line treatment for those with memory impairments. Moreover, it is difficult to distinguish neural entrainment from stimulation artifacts in electrical recordings, further limiting its use (Hanslmayr et al., 2019). A more promising recent approach is non-invasive DBS via temporal interference (TI). Using computational modelling and mouse models, Grossman et al. (2017) demonstrated how through temporal interference, neural activity in deep brain regions could be modulated without recruiting overlying cortical areas. This electromagnetic stimulation method involves non-invasively applying different high-frequency oscillatory electrical currents via multiple electrodes. The resulting stimulation frequency is the difference between these electrode frequencies (i.e. the difference frequency). Grossman and colleagues (Grossman et al., 2017) propose that a successful TI protocol requires that the applied currents must a) be of high frequency, b) fall outside of endogenous frequency ranges, and c) differ by a small amount (which falls within a frequency range that neurons can respond to). In doing so, a 'modulating envelope' is created, with its peak located centrally between electrode locations (Liu et al., 2018). Consequently, at this peak location, neurons are only driven at the difference frequency.

Previously, this technique has been applied to peripheral nerves and muscles in physical therapy-related settings (Goats, 1990; Liu et al., 2018). However, Grossman and co-workers (Grossman et al., 2017) in this recent paper critically demonstrate how the approach can be leveraged to selectively target deep brain regions which has clear relevance for episodic memory processes. Comparing their TI protocol (with a difference frequency of 10 Hz) to traditional 10 Hz transcranial stimulation in anesthetized mice, this study reported targeted activation of hippocampal neurons in the TI condition, whereas both cortical and hippocampal activation in the transcranial condition (Grossman et al., 2017). Moreover, the envelop peak can be adjusted to specifically target deeper brain structures by varying electrode location(s), although this does come at the cost of the locus' width and strength (Grossman et al., 2017). Conversely, if electrode locations are held constant, the envelope's focus field can be modulated away from the centroid point by adjusting the electrical current ratio between electrode pairs while keeping the current sum fixed. This was shown to result in the peak modulation moving closer to the electrode pair with the lower current. As Grossman and colleagues highlight, an advantage of this is 'live-steering' of stimulation location even deep within the brain, is that it does not require moving electrode locations (Grossman et al., 2017).

As Kricheldorff and co-workers (Kricheldorff et al., 2022) suggest, TI

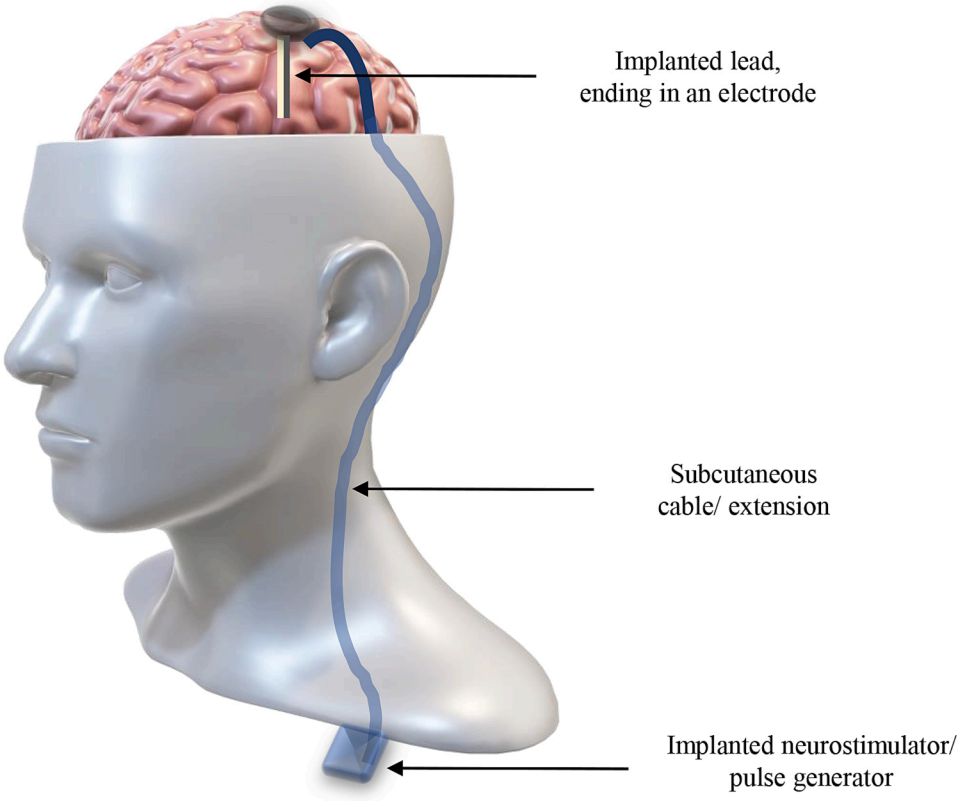

Fig. 3. Deep Brain Stimulation (DBS) Set Up. An invasive form of electrical stimulation. The electrode is surgically inserted under the scalp, with a lead reaching into deeper brain regions. The electrode cable connects subcutaneously to the stimulator device implanted below the clavicle.

could be a promising stimulation approach for reaching deeper brain structures such as the hippocampus and activating specific neuronal populations. This may combat related limitations associated with traditional tES methods. Although these findings were examined in mouse models, they show promise for translation into human studies. Additionally, Grossman and colleagues' (Grossman et al., 2017) study provided evidence for TI's ability to modulate motor movement, and highlight the potential for TI to be applied to memory-related circuits in the brain. This is an exciting area that requires further validation and investigation.

4.2. Transcranial magnetic stimulation

As presented in Fig. 4, TMS is a non-invasive stimulation technique where a magnetic coil (in the shape of a Fig. 8) is placed over a participant's head (Kricheldorff et al., 2022). From this coil, a high-intensity magnetic field is generated from which an electrical current can either hyperpolarize or depolarize neuronal populations, influencing oscillatory entrainment (Hebscher & Voss, 2020; Kricheldorff et al., 2022). TMS is a well-established form of stimulation, having originally received FDA approval for treatment-resistant Major Depressive Disorder (Cohen et al., 2022). Since then, various TMS devices have subsequently received FDA approval for the treatment of different clinical conditions such as migraines, OCD, smoking cessation, and MDD-related anxiety (Cohen et al., 2022). Notably however, TMS devices have, as of yet, failed to receive approval for the treatment of Alzheimer's Disease or memory impairment conditions (Cohen et al., 2022). That being said, as outlined below, several TMS parameters and modern approaches continue to be investigated and warrant further investigation in the episodic memory field.

4.3. Modern TMS approaches: Network effects of 'chronic' rTMS and task-specific cTBS

In repetitive TMS (rTMS), stimulation at a given frequency is applied in repeated pulse sequences in order to modulate neuronal and oscillatory activity (Kricheldorff et al., 2022). Whilst there is evidence that rTMS is more optimal than standard TMS protocols due to the longer-lasting local and distant effects (Kricheldorff et al., 2022), there is debate about how rTMS exerts its influence on episodic memory performance (Hebscher & Voss, 2020). It was originally believed that rTMS' effects were solely via the creation of a temporary lesion in the locally stimulated brain region, however it has recently been highlighted that rTMS can induce more network-wide effects (Hebscher & Voss, 2020). Notably, rTMS approaches that are positively impacting episodic memory are not only those that take into consideration the larger network within which the hippocampus lies and is functionally connected to (Hebscher & Voss, 2020), but also those applying stimulation in a chronic fashion.

Chronic rTMS-beta applied to hippocampal-cortical networks. For example, in a study of healthy younger adults, it was found that rTMS-beta applied over 5 consecutive days to the left-parietal brain region, increased functional connectivity between the hippocampus and precuneus, retrosplenial cortex, fusiform and parahippocampal cortices, superior parietal cortex and left lateral parietal cortex, whilst improving associative memory tested 24 h later (Wang et al., 2014). Wang and Voss (2015) subsequently extended these findings and demonstrated that enhanced memory performance was maintained when tested 15 days later. Following this, Hermiller, Karp and co-workers (Hermiller et al., 2019a) similarly applied rTMS-beta over 5 consecutive days, targeting the hippocampal-cortical network and found improved episodic memory when tested 1 week post-stimulation. In their younger sample, they furthermore demonstrated that these episodic memory gains did not come at the cost of accelerated long-term forgetting. Thus, rTMS-beta targeting hippocampal-related brain structures have shown

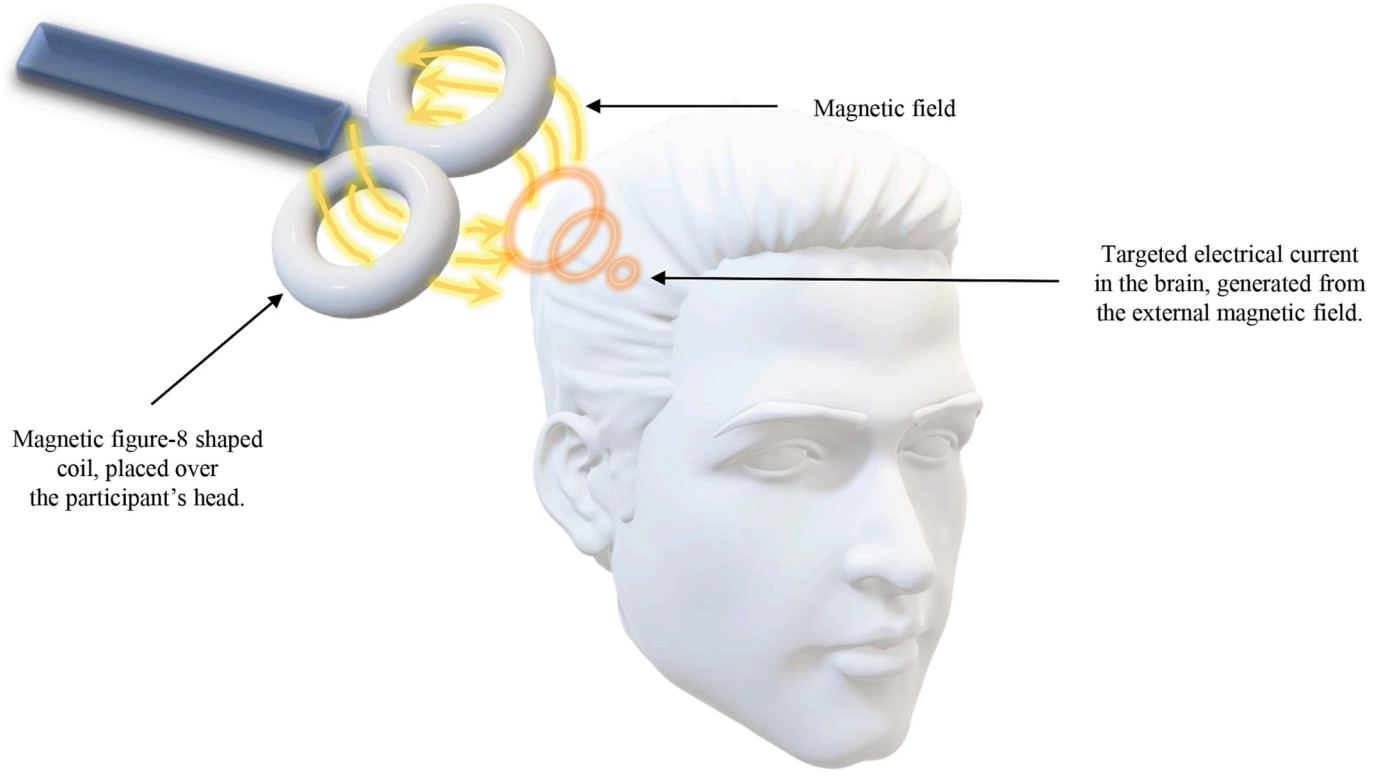

Fig. 4. Transcranial Magnetic Stimulation (TMS) Set Up. A non-invasive form of electromagnetic stimulation. A magnetic Fig. 8-shaped coil is placed over a subject's head. From this, a high-intensity magnetic field is generated, resulting in an electrical current that can permeate through to the targeted brain region.

demonstratable effects on functional connectivity and episodic memory processes. See Tables 1-4 for more details on study designs, stimulation parameters, the episodic memory task used and each study's main findings.

However, a distinct disadvantage of rTMS approaches, is the time-duration required to elicit desired effects, with protocols typically requiring at least 20 min over several consecutive days (Freedberg et al., 2019; Phipps et al., 2021). However, a more recent TMS variation involving reduced time commitment, which is being investigated in the memory domain, is continuous theta burst stimulation (cTBS). Specifically, those targeting hippocampal theta activity are seeing notable success in recent years. cTBS administers electromagnetic pulses in a theta-nested gamma pattern, and is proposed to influence endogenous episodic network activation and function (Kricheldorff et al., 2022).

cTBS applied to hippocampal-cortical networks. Hebscher and Voss (2020) summarise two recent studies that demonstrate how a single session of hippocampal cTBS can enhance episodic memory processes. Importantly, one of these studies highlights how cTBS and not beta-TMS had positive memory effects (Hermiller et al., 2019b). In this study, stimulation was applied between the learning and test phase of a memory task. Moreover, it critically demonstrates how functional connectivity between the hippocampus and hippocampal-cortical networks are causally relevant for episodic memory processes and responsive to cTBS (Hermiller et al., 2019b). By targeting a similar hippocampal-circuitry, a second study likewise showed how cTBS compared to control TMS conditions effectively enhanced memory processes (Tambini et al., 2018)(see Tables 1-4). Moreover, their results highlighted how functional connectivity between the hippocampus and related brain regions predicted these cTBS memory effects (Tambini et al., 2018).

Interestingly, these findings that chronic (or offline) externally-induced beta synchrony successfully enhanced memory performance are not addressed by the earlier mentioned Complex Learning Systems (CLS) theory. In their synchronization and desynchronization framework, Hanslmayr and colleagues (Hanslmayr et al., 2016) propose that alpha or beta neocortical stimulation-induced synchrony during learning tasks should impair memory performance, and theta or gamma hippocampal stimulation-induced synchrony during learning tasks should enhance memory performance. However, whilst the paper highlights several outstanding questions that remain to be investigated, one question not addressed is how beta or alpha stimulation or theta or gamma stimulation applied separate to task stages might contribute to or hinder memory processes. This is especially important, as from the studies referenced here, initial evidence does suggest that chronic rTMS-beta can have a faciliatory effect on subsequent memory processes.

On a related note, as evident from these groups of studies, when stimulating hippocampal-cortical networks, whether rTMS-beta is applied in a chronic fashion, or whether cTBS is applied between the learning and test phase of a memory task, both induced positive memory effects. One explanation for this could be how online TMS' memory effects appear to be driven by modulation or interference of neural activity in a specific brain region, whilst memory processes are facilitated or inhibited via long-term potentiation or depression mechanisms from offline TMS protocols (as discussed in earlier reviews by Bergmann and colleagues, and Phipps and colleagues) (Bergmann et al., 2016; Phipps et al., 2021). Applying this to the above studies, this would suggest theta stimulation between learning and test phases modulates oscillatory activity in hippocampal-cortical networks supporting memory consolidation, whilst chronic offline beta induces LTP to subsequently facilitate memory formation. More research is needed into identifying the memory-specific mechanisms of action behind different oscillatory frequencies and how these might differ at task or non-task related stages.

In review of TMS protocols for memory-focused research, an obvious advantage are their location and temporal specificity (Yavari et al., 2018). However, rTMS protocols are less advantageous (than cTBS for example) due to the time-duration required to elicit desired memory effects. Thirdly, when applying stimulation to hippocampal-cortical networks during memory tasks, as a means of activating the hippocampus, it is important to consider how the synchrony of different frequency ranges are proposed to differentially contribute to or impair memory processes. Fourthly, whether stimulation is applied in a continuous (chronic) fashion, or at task-related stages will also determine the preferred stimulation frequency, and efficacy of the protocol at enhancing episodic memory performance. Finally, a point worth mentioning here is, in relation to theta-targeting stimulation protocols (such as cTBS), their efficacy may be challenged due to difficulties associated with identifying optimal endogenous theta frequency ranges, as this can vary both within and between individuals. However, as mentioned earlier in this review, this challenge is relevant to other stimulation modalities which also target theta frequencies, and is not unique to cTBS. In comparison to TMS approaches however, there are several factors which support tES as a more scalable, accessible, and cost-effective treatment option should the optimal stimulation parameters be determined (also summarised in Table 1).

4.4. Transcranial electrical stimulation

Traditional Approaches. Two of the most common forms of tES applied in memory-focused studies are tDCS and tACS. The main difference between these two approaches is the modality of electricity applied (either direct or alternating, respectively). As shown in Fig. 5, in both tDCS and tACS protocols, low intensity current (between 1 and 2 mA) is applied via two electrodes (typically enclosed in saline-soaked sponges) which are placed on the scalp, with the intention of modulating brain activity (van Boekholdt et al., 2021; Woods et al., 2016; Živanović et al., 2022). However, because the current waveform in tACS and tDCS differs, there are different proposed mechanisms of action (Živanović et al., 2022). In tDCS, typically one electrode is positively charged (i.e. anode) whilst the other is negatively charged (i.e. cathode). Thus, a constant electrical current passes through these electrodes, either depolarizing or hyperpolarizing the resting membrane potential of neurons located beneath the respective electrodes. If sufficient, this de or hyperpolarization, either increases or decreases their likelihood of firing an action potential (Kricheldorff et al., 2022). As such, the proposed mechanism of action is this bias towards neuronal excitation or inhibition, and subsequent behavioural consequences for cognitive functions such as memory (Galli et al., 2019; Majdi et al., 2022; Živanović et al., 2022).

Conversely, whilst a constant current is applied in tDCS, in tACS a sinusoidal current is applied (Woods et al., 2016). Essentially, in tACS, the positive/ negative charge flowing through each electrode alternates for each half cycle (Woods et al., 2016). As such, tACS applies a current that rhythmically oscillates around a specific frequency, leading to rhythmical hyperpolarization and depolarization of the membrane potential, which can modulate brain activity via entrained neural oscillations (Živanović et al., 2022). Thus whilst tDCS' effects were traditionally proposed to result from exciting or inhibiting neuronal activity, tACS was applied with the intention of modulating brain oscillations (Woods et al., 2016). In the literature, tACS has been applied more effectively to cognition and perception than memory (Booth et al., 2022). However, in relation to memory, both the specific frequency and targeted location of tACS protocols is of importance. For example, Grover and colleagues (Grover et al., 2022) compared the effect of r-tACS at gamma or theta frequencies in both the dorsolateral prefrontal cortex or inferior parietal lobule regions for 4 consecutive days at improving episodic memory. In their sample of healthy older adults, whilst IPL-theta (i.e. low frequency stimulation) improved working memory (measured by the recency effect), DLPFC-gamma (i.e. high frequency stimulation) improved long-term memory (measured by the primacy effect)(Grover et al., 2022). Moreover, they demonstrated that the inverse stimulation parameters (i.e. IPL-gamma or DLPFC-theta) showed no positive memory effects, confirming the importance of location and frequency specificity of stimulation. Importantly, in their

Table 1
Alternative Neurostimulation Approaches: Study Designs[a.]

Neurostimulation Approach	Authors (year)	No. of Experiments	Blinding	Participants	Study Design	Groups/ Conditions	Randomized
Chronic beta-rTMS	Wang et al (2014)	2	NR	E1: 16 YA E2: 8 YA	Parallel and Cross-over [C1]	E1: Active and sham conditions E2: Control condition only	N
Chronic beta-rTMS	Wang & Voss (2015)	1	NR	16 YA	Parallel and Cross-over [C2]	2 conditions: Active and sham	Y
Chronic beta-rTMS	Hermiller, Karp et al (2019)	1	NR	16 YA	Cross-over [C3]	2 conditions: Active and sham	N
cTBS of cortico-hippocampal networks	Hermiller, VanHaerents, et al (2019)	1	NR	24 YA	Cross-over [C4]	4 conditions: 3 active, and 1 sham	N
cTBS of cortico-hippocampal networks	Tambini et al (2018)	2	NR	E1: 57 YA E2: 22 YA	Cross-over [C5]	E2: Active and control	N
tACS and intracranial EEG	Huang et al (2017)	1	UB	10 epileptic patients	n/a	1 group	N
Transcutaneous Auricular Vagal Nerve Stimulation (aVNS)	Jacobs et al (2015)	1	SB	30 OA	Crossover	2 conditions: Active and sham	Y
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)	Luckey et al (2020)	1	DB	30 OA	Parallel	2 conditions: Active and sham	Y
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)*	Vanneste et al (2020)	9	DB	~20 to 45 YA per experiment	Parallel	2–4 conditions per experiment	Y
Theta-modulated Oscillatory tDCS (otDCS)	Vulić et al., 2021	1	SB	18 YA	Cross-over [C6]	3 conditions: Active, active-control, and sham	N
Theta-synchronized visual and auditory stimuli	Clouter et al (2017)	4	SB	~ 9 to 24 YA per experiment	Parallel and Cross-over	4 Experiments • Exp 1: 4 conditions • Exp 2: 5 conditions • Exp 3: 6 conditions • Exp 4 - control: 4 conditions	N
Bimodal theta stimulation during consolidation	Roberts et al (2018)	2	NR	1: 50 YA 2: 40 YA	Parallel	Each experiment had 2 groups (active and control)	NR
Gamma Entrainment Using Sensory (GENUS) Stimulation	Chan et al (2022)	2	Phase 1: UBPhase 2: SB	Phase 1: 13 YA 12 OA 16 mild-AD patients 2 epileptic patients Phase 2: 15 mild AD patients	Phase 2: Parallel	Phase 1: 1 group Phase 2: 2 groups (active and sham)	Phase 1: N Phase 2: Y
Gamma Entrainment Using Sensory (GENUS) Stimulation	Khachatryan et al (2022)	1	NR	15 YA 1 epileptic patient	Cross-over	6 conditions	Y
Visual stimulation, at individualised theta frequency	Köster et al (2019)	1	NR	20 YA	Cross-over	3 conditions: Active, active-control, and sham	N
Cross-frequency tACS (gamma-burst tACS coupled to theta-peak or trough)	de Lara et al. (2018)	3	DB	72 YA	Parallel	2 conditions: Active and active-sham	Y
Individualised EEG-tACS at ITF-1	Aktürk et al. (2022)	1	SB	46 YA	Parallel	3 conditions: Active, active-control, and sham	Y

Notes. This table includes alternative neurostimulation approaches that are seeing initial success with activating the hippocampus and enhancing episodic memory processes. However, as research into the respective approaches are still relatively nascent, further investigation into these protocols is warranted in order to determine or confirm optimal parameters. To aid with this, this table summarises the main study design element. Abbreviations include: Unblinded (UB); Single-blind (SB); Double-blind (DB); Young-adult (YA); Older-adult (OA); Alzheimer's Disease (AD); Not Recorded (NR).

[C1] Cross-over delay of 1–4 weeks between 2 conditions.
[C2] Cross-over delay of 6–26 days between 2 conditions.
[C3] Cross over delay of 4–30 weeks between the 2 conditions.
[C4] Cross-over delay of 2–5.8 days between 4 conditions.
[C5] Cross-over delay of 1 week between 3 conditions.
[C6] Cross-over delay of 7 – 10 days between the 2 sessions.
[a] Incl. 9 human experiments and 1 rodent experiment.

Table 2
Alternative Neurostimulation Approaches: Stimulation Parameters.

Neurostimulation Approach	Authors (year)	Stimulation Montage	Hz	Intensity (mA)	Ramp up/ Ramp Down (s)	Stimulation Timing (mins)	Stimulation Administration
Chronic beta-rTMS	Wang et al (2014)	Lateral Parietal Network*	20 Hz pulses	n/a	n/a	20	Chronic, for 5 consecutive days.
Chronic beta-rTMS	Wang & Voss (2015)	Lateral Parietal Network*	20 Hz pulses	n/a	n/a	20	Chronic, for 5 consecutive days.
Chronic beta-rTMS	Hermiller, Karp et al (2019)	Lateral Parietal Network*	20 Hz pulses	n/a	n/a	20	Chronic, for 5 consecutive days.
cTBS of cortico-hippocampal networks	Hermiller, VanHaerents, et al (2019)	Individual Parietal Cortical Locations	Theta-burst: 50 Hz triple pulses, repeated at 5 Hz frequency for 600 pulses. Intermittent theta-burst: Bursts delivered in an on/ off cycle. Beta-stim: 1,600 pulses at 20 Hz, in an on/ off cycle.	n/a	n/a	20	During consolidation
cTBS of cortico-hippocampal networks	Tambini et al (2018)	pIPC	50 Hz triple pulses, repeated at 5 Hz frequency for 600 pulses	n/a	n/a	20	Immediately before encoding
tACS and intracranial EEG	Huang et al (2017)	FPz/ Oz [1]	1	~0.25 to 1 (zero-to-peak)	NR	NR	During waking resting-state (eyes closed) and afternoon sleep.
Transcutaneous Auricular Vagal Nerve Stimulation (aVNS)	Jacobs et al (2015)	Ear clip in the left external acoustic meatus on the inner side of the tragus (and right arm)	8 (with 200 μs pulse width)	5.0		17	During encoding and consolidation
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)	Luckey et al (2020)	Left and right C2 dermatomes	n/a	1.5	30/10	12.5	During encoding phases (250 s × 3)
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)[a]	Vanneste et al (2020)	Left and right C2 dermatomes	n/a	1.5	5/5 [b]	25[c]	Exp 1: Between 2 tasks Exp 2/3: Non-task specific Exp 4: During encoding and consolidation Exp 5,6,8: During encoding Exp 7: Varied depending on condition Exp 9: During test retrieval phases 7 days after encoding.
Theta-modulated Oscillatory tDCS (otDCS)	Vulić et al., 2021	Left posterior parietal cortex (P3 / CC)**	5	1.5 (±0.1 mA)	30/30	20	Before encoding
Theta-synchronized Visual and Auditory Stimulation	Clouter et al (2017)	n/a	Audiovisual stimulation at 4 Hz	n/a	n/a	NR	Luminance and amplitude of movies were flickered at experimental or control frequencies and different phase-offset.
Bimodal Theta Stimulation During Consolidation	Roberts et al (2018)	n/a	5.5 Hz	n/a	n/a	36	During consolidation
Gamma Entrainment Using Sensory (GENUS) Stimulation	Chan et al (2022)	n/a	40	n/a	n/a	60	Phase 1: Single session Phase 2A: Chronic (60 min) daily GENUS for 3 months
Gamma Entrainment Using Sensory (GENUS) Stimulation	Khachatryan et al (2022)	n/a	40	n/a	n/a	15	During the session (5 min × 3 regular flicker conditions)
Visual Stimulation, at Individualised Theta Frequency	Köster et al (2019)	n/a	Individual-theta (between 3 and 8 Hz)	n/a	n/a	15	Stimuli were flickered at the individualized frequency or static (non-flickering).
Cross-frequency tACS (gamma-burst tACS	de Lara et al. (2018)	Left temporal lobe (T7, FPz/T8)**	Experiment 1: 5 (slow-theta) Experiment 2: 8	Exp 1: 0.75 mA (peak-to baseline) Exp 2: 0.5 mA	30/10	10	During encoding

(*continued on next page*)

Table 2 (*continued*)

Neurostimulation Approach	Authors (year)	Stimulation Montage	Hz	Intensity (mA)	Ramp up/ Ramp Down (s)	Stimulation Timing (mins)	Stimulation Administration
coupled to theta-peak or trough)			(fast-gamma) Experiment 3: Merged theta-gamma	(peak-to baseline) Exp 3: 1 mA (peak-to-baseline)			
EEG-tACS at Individualised Theta Frequency (ITF) minus 1 Hz	Aktürk et al. (2022)	Left fronto-parietal network: (F3 / P3)**	ITF (4–7 Hz) – 1	1.5	3/3	20	One session which occurred: After encoding/ retrieval of one set of the tasks. Before encoding/ retrieval of a second set of the tasks.

Notes. This table includes alternative neurostimulation approaches that are seeing initial success with activating the hippocampus and enhancing episodic memory processes. However, as research into the respective approaches are still relatively nascent, further investigation into these protocols is warranted in order to determine or confirm optimal parameters. Adding to Table A1, this table summarises the main experimental stimulation parameters. Abbreviations include: Not Reported (NR); Posterior inferior parietal cortex (pIPC); Contralateral Cheek (CC).

* Nearest hippocampal structure to MNI coordinate × = -24, y = -18, z = -18.

** Stimulation electrode locations according to the International 10–20 system of EEG electrode placement.

[1] except for 1 patient whose electrode placement was different.

[a] Incl. 9 human experiments, and 1 rodent.

[b] for all except Exp. 6 which was 30/5.

[c] except for Exp 1 which was 20.

sample, participants with lower baseline cognitive function benefited from stimulation the most with greater memory improvements 1-month post-stimulation (Grover et al., 2022).

In support of the role of gamma-tACS, a recent systematic review looking at the effectiveness of tACS protocols on working memory or long-term memory processes, summarises how anterior-targeted tACS at gamma frequency had significant modulatory effects on long-term memory storage (Booth et al., 2022). However, it is not as straightforward as suggesting that gamma-focused stimulation provides the only potential therapeutic avenue for stimulation. There is evidence that factors such as endogenous oscillatory patterns, and theta-gamma coupling may underlie the subsequent success of various stimulation protocols.

Combining Closed Loop and Individualised Protocols. Recently, tACS protocols which investigate more individualised stimulation parameters are seeing positive results on episodic memory enhancement. In fact, a review of tES effects on brain oscillations, plasticity, cognitive functions and clinical group outcomes highlights how tACS protocols in conjunction with neuroimaging (EEG or fMRI) are likely to be of significance in future research (Yavari et al., 2018). Supporting this, in a study of healthy younger adults, individualised theta frequency (EEG-tACS) was applied to the left fronto-parietal network at either an endogenous range (i.e. individualised theta frequency 'ITF') or a slightly slower frequency (ITF-1) and episodic memory was assessed (Aktürk et al., 2022). Using a closed-loop strategy, this paper highlighted that whilst tACS applied at peak endogenous theta phase led to increased rs-oscillatory power, it did not enhance memory (Aktürk et al., 2022). In fact EEG-tACS delivered at a frequency slightly below the endogenous peak range (ITF-1) was preferential for effective memory enhancement (Aktürk et al., 2022) (See Tables 1-4 for more details on the study design and results). The finding that increased gamma power didn't correlate with enhanced memory supports an earlier-discussed study (Natu et al., 2019) which found that increased hippocampal gamma-power post-DBS in fact resulted in impaired memory processes.

In Aktürk and co-workers' (Aktürk et al., 2022) study, the ITF-1 group with increased left fronto-parietal rs-theta connectivity after tACS had better memory performance. Moreover, functional connectivity between the PCC and hippocampus predicted the effect size of stimulation on memory performance (Aktürk et al., 2022). Consequently, Aktürk and colleagues (Aktürk et al., 2022) argue for the potential for regions exterior to the temporal lobe as a target for modulating hippocampal circuitry activity and memory performance. Supporting this, Mankin and Fried (2020) note that direct DBS of the hippocampus has been found to disrupt memory processes, whereas stimulating regions such as the entorhinal cortex (which projects to the hippocampus) is potentially more effective for memory improvement. As well as highlighting that stimulating regions functionally connected to the hippocampus may lead to greater hippocampal-activation and memory benefits (than direct hippocampal stimulation), what these studies also critically suggest is that the effectiveness of stimulation protocols on memory performance potentially hinge upon one's individual endogenous oscillatory frequencies. Thus, closed-loop strategies offer an intuitive way for stimulation to be applied at optimal endogenous frequency range, phase, or cycle timings. Moreover, these findings suggest that memory can be enhanced by slowing theta cycles to accommodate a greater number of nested gamma cycles (Aktürk et al., 2022).

This supports the earlier discussed theta-gamma coupling framework, and provides an example for how a closed-loop strategy is of particular importance. Further evidence of this can be seen in de Lara and colleagues' (de Lara et al., 2018) study which applied tACS to the temporal lobe in healthy adults. In their study, gamma-tACS applied to the trough phase of a theta-tACS cycle, significantly impaired verbal episodic memory. Interestingly, continuous gamma-tACS or gamma-tACS coupled with the peak phase of theta-tACS cycle, induced no significant memory effects in this study (de Lara et al., 2018) (study details listed in Tables 1-4). This confirms the causal role of theta-gamma coupling in episodic memory processes. With regards to neural entrainment protocols, this is often referred to as cross-frequency phase-amplitude coupling (PAC). PAC refers to how the phase of a slow oscillation (e.g. theta) can entrain the amplitude of a faster oscillation (e.g. gamma), in what is known as a phase-locked manner (de Lara et al., 2018). In PAC, the nested frequency (in this case, gamma cycles) can have different phase offsets (at for example, the peak or trough of theta cycles) (as shown in Fig. 6).

Importantly, a recent human study has shown how gamma oscillations nestled at theta trough phase (as opposed to theta-peak) are functionally relevant for hippocampal PAC and subsequent memory performance (Lega et al., 2014). This finding was specifically related to slow-theta activity (between 2.5 and 5 Hz), which as mentioned earlier in this review, has previously been considered within the delta range. Thus closed-loop strategies that accurately identify optimal endogenous

Table 3
Alternative Neurostimulation Approaches: Memory Task Details and Neurophysiological Measures Recorded.

Neurostimulation Approach	Authors (year)	Memory Task Type	Memory Task Stimuli	Memory Tested	Neuropsych Battery Included	Neurophysiological Measures Recorded
Chronic beta-rTMS	Wang et al (2014)	Recall: Face-word association task	20 pairs	Baseline (1 day prior to stim) Midpoint (Immediately after 3rd stim session) Endpoint (1 day after final stim)	Y	Structural MRI Rs-fMRI
Chronic beta-rTMS	Wang & Voss (2015)	Recall: Face-word association task	20 pairs	Baseline (1 day prior to stim) Midpoint (Immediately after 3rd stim session) Endpoint (1 day and 15 days after final stim)	Y	Rs-fMRI
Chronic beta-rTMS	Hermiller, Karp et al (2019)	Recall: Face-word association task and Verbal word association task	20 face-word pairs 28 word pairs	Pre-stim baseline: 1 hr before stim Post-stim: 1 day after final stim session	Y	N
cTBS of cortico-hippocampal networks	Hermiller, VanHaerents, et al (2019)	Recognition: Word items	104 words 96 distractors	Same day: 1 hr after stimulation/ consolidation	N	Rs-fMRI
cTBS of cortico-hippocampal networks	Tambini et al (2018)	Recognition: Object items	780 objects divided between 3 sessions	Same day: 2.5 hrs after encoding.	N	Rs-fMRI
tACS and intracranial EEG	Huang et al (2017)	n/a	n/a	n/a	n/a	Intracranial EEG
Transcutaneous Auricular Vagal Nerve Stimulation (aVNS)	Jacobs et al (2015)	Recognition and Recall: Face-name association task	60 pairs 60 distractors	Same day: Immediately after consolidation (i.e. 10 min after encoding).	Y	Pulse Rate (via a Finger Pulse Oxymeter)
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)	Luckey et al (2020)	Recall and Delayed Recall: Swahili-English word association task	50 pairs	7 and 28 days after encoding.	Y	Salivary α-Amylase and cortisol
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)[a]	Vanneste et al (2020)	Exp 1: Attentional auditory oddball task Exp 2/3: n/a Exp. 4: Recognition: Face-name association task Exp 5–9: Recall and Delayed Recall: Swahili-English word association task	Exp 1–3: n/a Exp 4: 60 pairs and 60 distractors Exp 5–9: 75 pairs	Exp 1–3: n/a Exp 4: Same day Exp 5–9: Same day, and 7 days later	N	P3b ERP Salivary sAA and cortisol Pupil Diameter Rs-EEG
Theta-modulatedOscillatory tDCS (otDCS)	Vulić et al., 2021	Recall: Face-word association task	20 pairs 30 distractors	1 and 5 days after encoding.	N	N
Theta-synchronized Visual and Auditory Stimulation	Clouter et al (2017)	Associative Memory: 3 s movie video and sound clips were paired together.	Exp 1, 2 and 4: 96 pairs Exp 3: 192 pairs	Same day: After encoding and a distractor task.	N	EEG
Bimodal Theta Stimulation During Consolidation	Roberts et al (2018)	Recognition: Word items	200 words 100 distractors	Same day: After stimulation.	N	EEG
Gamma Entrainment Using Sensory (GENUS) Stimulation	Chan et al (2022)	Delayed Recall: -name association task	NR	Same day: Immediately after encoding (at Month 1, and again at Month 3).	Y	Functional and structural MRI Scalp EEG and intracranial EEG Bloods for APOE status Actigraphy
Gamma Entrainment Using Sensory (GENUS) Stimulation	Khachatryan et al (2022)	n/aattention (visual oddball or counting) tasks	n/a	n/a	N	Scalp EEG Intracranial EEG Eyetracking
Visual Stimulation, at Individualised Theta Frequency	Köster et al (2019)	Recognition: Object items	450 objects 150 distractors	Same day: Post encoding, after a filler task that took 15 mins	N	EEG
Cross-frequency tACS (gamma-burst tACS coupled to theta-peak or trough)	de Lara et al. (2018)	Recall and Delayed Recall: Paired-associative word learning task	54 pairs	Same day (10 mins after encoding) and 1 day later.	N	N
Individualised EEG-tACS at ITF-1	Aktürk et al. (2022)	Visual MemoryBoston Naming Test Auditory MemoryOkten Verbal Memory Test	50 (25 stimuli in each task)	Same day: Immediately after encoding (for tasks pre-stimulation) and immediately after encoding (for tasks post-stimulation)	Y	Pre-stim: rs-EEG and during encoding phase Post-stim: rs-EEG, and during encoding phase

Notes. This table includes alternative neurostimulation approaches that are seeing initial success with activating the hippocampus and enhancing episodic memory processes. However, as research into the respective approaches are still relatively nascent, further investigation into these protocols is warranted in order to determine or confirm optimal parameters. Adding to Tables 1 and 2, this table summarises the various episodic memory task elements. Abbreviations include Not Reported (NR);
[a] Incl. 9 human experiments, and 1 rodent.

theta oscillatory frequencies and target specific theta-phases, should preferentially enhance stimulation outcomes, as opposed to open-loop strategies such as de Lara and colleagues (de Lara et al., 2018) which attempt to mimic theta-gamma PAC but without consideration for variation between individual or function-specific endogenous frequencies.

Another recent finding which closed-loop paradigms should consider moving forward, is cross regional PAC (xPAC). Whilst it is generally accepted in light of rodent and human research that greater hippocampal PAC is significantly associated with increased memory recall (Tort et al., 2009) and successful episodic memory performance (Lega et al., 2014), what is less well investigated is the role of xPAC in mnemonic processes. Recently, however, when measuring hippocampal activity during episodic processes via intracranial electrodes in 40 human subjects, Wang and colleagues (Wang et al., 2021) specifically found significant and functionally-relevant xPAC between hippocampal theta oscillations, and entorhinal and parahippocampal cortical gamma oscillations, with posterior hippocampal connections (compared to anterior) showing preferential xPAC also. The authors discuss how xPAC in humans extends earlier rodent findings and supports the proposition that item integration across cortical regions is supported by xPAC, and consequently facilitates successful episodic memory processes (Wang et al., 2021). Thus, future closed-loop neurostimulation approaches could seek to investigate these xPAC patterns further and examine whether xPAC modulation can enhance episodic memory performance.

4.5. A novel combined approach.

In relation to tDCS approaches, whilst there are substantially more papers investigating this as a neurostimulation means of memory enhancement, these have historically seen mixed effects in improving episodic memory performance in humans. For example, a *meta*-analysis by Galli and colleagues (Galli et al., 2019) found that whilst several individual papers report significant results, after conducting a *meta*-analysis of these, overall, tDCS protocols showed non-significant effects on episodic memory enhancement. Moreover, Galli and colleagues (Galli et al., 2019) note that the effectiveness of tDCS protocols on memory are yet to be fully determined.

As outlined earlier, traditional tDCS is applied with the intention of modulating cortical excitability. However, recent studies have investigated the effects of an adapted protocol of frequency-modulated tDCS (termed 'otDCS')(Vulić et al., 2021; Živanović et al., 2022). The aim behind this approach is to rhythmically modulate the current intensity (without the polarity shifts of tACS) and consequently entrain endogenous oscillatory patterns, whilst also influencing cortical excitability (Vulić et al., 2021). Interestingly, Vulić and co-workers (Vulić et al., 2021) demonstrated the beneficial effects of both traditional constant anodal tDCS and anodal theta-modulated tDCS protocols applied to the posterior parietal cortex in improving associative memory in healthy younger adults. (See Table 2 for otDCS stimulation parameters). Associative memory refers to the binding together of multiple bits of information which enables episodic memory formation and retrieval (Vulić et al., 2021). Compared to sham conditions, these two active stimulation groups showed improved memory 1 and 5 days later, although with slight deterioration in memory performance over time. Vulić and colleagues (Vulić et al., 2021) proposed that the effects of stimulation on activating these regions and enhancing memory processes was likely via their 'convergent pathways to the hippocampus'.

Interestingly, in the two active conditions, some participants responded to constant tDCS whilst others benefited from theta-tDCS, thus it is proposed that theta-otDCS could be an effective protocol for those who don't respond to traditional constant-tDCS (Vulić et al., 2021). Moreover, the fact that some participants responded to one stimulation protocol whilst others responded to the other, potentially suggests the different modes of mechanism of each stimulation protocol (Vulić et al., 2021). Specifically, Vulić and colleagues (Vulić et al., 2021) posit that otDCS could be preferential to traditional tACS, given otDCS' potential to simultaneously entrain oscillations whilst inducing synaptic plasticity via cortical excitability, whereas tACS is not known to induce synaptic plasticity changes. However future research on this topic including neurophysiological data is needed to confirm or refute this hypothesis.

4.6. Alternative mechanisms: The transcutaneous approach.

Interestingly, some studies highlight that the inconsistent results in this area likely stem from insufficient mechanistic understanding behind tES protocols (van Boekholdt et al., 2021; Vanneste et al., 2020). One recent alternative explanation that has been proposed and explored is the 'dual' transcranial and transcutaneous mechanism behind tES (Asamoah et al., 2019; Majdi et al., 2022; van Boekholdt et al., 2021; Vanneste et al., 2020). This alternative mechanism has been gathering increasing momentum in the literature. For example, van Boekholdt and colleagues (van Boekholdt et al., 2021) argue that the electrical field generated from tDCS may be weakened by the scalp, skull and cerebral spinal fluid. This means only a small proportion likely reaches targeted brain regions, suggesting that the transcranial mechanism of tDCS is consequently less effective than originally believed (van Boekholdt et al., 2021). Conversely, nerves located just below the skin are proposed to be exposed to greater electrical currents sufficient to generate action potentials in the nerves (van Boekholdt et al., 2021). Three such nerves include the vagus nerve, and peripheral nerves such as the trigeminal nerve and greater occipital nerve, which have recently been suggested for their indirect route of modulating brain activation via neurotransmitter-facilitated synaptic plasticity mechanisms (Luckey et al., 2023).

Whilst these three nerves are anatomically distinct, there is evidence suggesting their pathways similarly synapse at the nucleus tractus solitarius (NTS) (Luckey et al., 2023). This is important because subsequent projections from the NTS, transverse various brainstem nuclei such as the locus coeruleus, nucleus basalis, or dorsal raphe nucleus influencing release of their respective neurotransmitters (i.e. noradrenaline, acetylcholine or serotonin) (Luckey et al., 2023). Indeed, the projections of several brainstem nuclei can influence the concentrations of neurotransmitters such as noradrenaline, acetylcholine, and serotonin, which in turn have been shown to influence specific brainwave activity (Jee, 2021). Moreover, the stimulation of these nerves has not only been shown to influence neurotransmitter levels, but that these are fundamental for synaptic plasticity processes and likely underlie the cognitive and behavioural effects of the transcutaneous element of tES protocols.

Initially, this evidence stemmed from vagus nerve research. As a stimulation target, the vagus nerve has received more attention in the literature than the trigeminal or greater occipital nerve (Luckey et al., 2023). Vagus nerve stimulation (VNS) originally received FDA-approval for the treatment of depression and epilepsy (Yap et al., 2020). However, due to the risks associated with the invasive nature of this procedure, transcutaneous vagus nerve stimulation (tVNS) protocols began to be investigated (Yap et al., 2020). These typically target the auricular branch of the vagus nerve (ABVN) or the neck's cervical branch (Yap et al., 2020). Summarising the VNS and tVNS research thus far, Luckey and colleagues (Luckey et al., 2023) highlight how certain vagus nerve stimulation protocols can effectively modulate cortical serotonin,

Table 4
Alternative Neurostimulation Approaches: Summary of Results.

Neurostimulation Approach	Authors (year)	Main Results Summary
Chronic beta-rTMS	Wang et al (2014)	• Beta-rTMS delivered chronically for 5 days enhanced episodic memory, increased functional connectivity and synaptic plasticity across cortico-hippocampal networks. • The enhanced memory effect was evident when tested 24 h later.
Chronic beta-rTMS	Wang & Voss (2015)	• Replicating and extending Wang and colleagues' (2014) findings, this paper demonstrated that rTMS-beta led to long-lasting effects. • When tested 15 days later, memory was significantly enhancement post-stimulation compared to sham.
Chronic beta-rTMS	Hermiller,Karp et al (2019)	• When a second memory recall task was administered, there was no interference effect in the active stimulation condition.
cTBS of cortico-hippocampal networks	Hermiller, VanHaerents, et al (2019)	• cTBS and not beta-frequency stimulation had positive memory effects • their findings conform the causal role of hippocampal-cortical functional connectivity in episodic memory processes
cTBS of cortico-hippocampal networks	Tambini et al (2018)	• Adding **to** Hermiller, VanHaerents, et al (2019) finding above, this paper similarly demonstrated cTBS's positive memory effects. • Moreover it highlights how the degree of functional connectivity between these brain regions in fact predicted the size of the memory effects.
tACS and intracranial EEG	Huang et al (2017)	• When standard 2 mA of tACS is applied, only low intensities reach cortical/ deeper brain structures
Transcutaneous Auricular Vagal Nerve Stimulation (aVNS)	Jacobs et al (2015)	• The number of hits was significantly greater for the active condition compared to sham. • There was no difference in encoding/ cognitive assessments. Thus, the effect was specific to the task.
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)	Luckey et al (2020)	• The active stimulation group recalled significantly more words on day 7 and 28. • There was no significant difference in learning (encoding) on day 1, or on processing speed. • Salivary α-Amylase levels increased significantly immediately after active-stimulation, and 7 and 28 days later.
Non-Invasive Transcutaneous Stimulation of the Greater Occipital Nerve (NITESGON)	Vanneste et al (2020)	• In a series of 9 human experiments and 1 rodent experiment, greater occipital nerve stimulation was found to increase several proxies of LC-NA activation (sAA levels, pupil diameter and P3b ERP response, theta-gamma neural oscillations in the medial temporal cortex), increased functional connectivity between the LC and hippocampal-cortical networks, and improved associative memory, memory recall and delayed recall. • The memory effect was further found to be due to the transcutaneous mechanism, specific to the greater occipital nerve, and due to enhanced consolidation (not encoding or retrieval) processes.
Theta-modulated Oscillatory tDCS (otDCS)	Vulić et al., 2021	• otDCS and traditional tDCS applied to the left PPC, both improved associative memory 1 & 5 days later, compared to sham (although with a slight deterioration by day 5). • However, at the individual level, participants responded differently to each stimulation type, suggesting different physiological mechanisms.
Theta-synchronized Visual and Auditory Stimulation	Clouter et al (2017)	• When audiovisual stimuli were presented at synchronously (i.e. 0-degree phase offset, and not 90, 180 or 270) and flickered at theta frequency (and not delta or alpha), episodic memory performance was enhanced.
Bimodal Theta Stimulation During Consolidation	Roberts et al (2018)	• Audiovisual stimulation at theta (5 Hz) frequency, applied during consolidation, led to enhanced theta power during stimulation and retrieval, and improved episodic memory performance.
Gamma Entrainment Using Sensory (GENUS) Stimulation	Chan et al (2022)	• Phase 1: A single session of GENUS effectively led to gamma entrainment. • Phase 2A: Daily GENUS over 3 months led to reduced hippocampal atrophy and ventricular dilation, increased functional connectivity between AD and memory-related brain circuits, and enhanced delayed memory recall.
Gamma Entrainment Using Sensory (GENUS) Stimulation	Khachatryan et al (2022)	• Combining GENUS stimulation with cognitive tasks enhanced entrainment in deeper brain regions incl. the hippocampus,

(*continued on next page*)

Table 4 (*continued*)

Neurostimulation Approach	Authors (year)	Main Results Summary
		compared to no-task conditions.
Visual Stimulation, at Individualised Theta Frequency	Köster et al (2019)	• Visual stimulation at individual theta frequency enhanced memory performance, in comparison to individual theta or sham condition. • Not only this, but theta visual stimulation led to enhanced theta-gamma cross-frequency PAC for stimuli that were remembered versus those forgotten. • Theta-gamma PAC was significantly higher across all electrodes, but especially so for those located at left-temporal and centro-frontal sites. • Notably, stimulation had no effect on theta or gamma power.
Cross-frequency tACS (gamma-burst tACS coupled to theta-peak or trough)	de Lara et al. (2018)	• Theta-gamma PAC is functionally relevant for episodic memory processes. Gamma bursts when coupled to theta-trough of tACS phase, impaired memory. However when coupled with theta-tACS peak, or continuously to theta-tACS it had no memory effect. • Note, the impairment effect could be due to the fact that the stimulation protocol didn't take into consideration individualized oscillations.
Individualised Protocol (EEG-tACS at ITF-1)	Aktürk et al. (2022)	Slowing endogenous theta oscillations enhanced memory recall. Specifically, • ITF tACS induced entrainment effects (i.e. increased theta power) but had no memory effect. • Whilst no entrainment was observed in the ITF-1 group, this group had significantly enhanced memory performance.

Notes. This table includes alternative neurostimulation approaches that are seeing initial success with activating the hippocampus and enhancing episodic memory processes. However, as research into the respective approaches are still relatively nascent, further investigation into these protocols is warranted in order to determine or confirm optimal parameters. Adding to Tables 1,2 and 3, this table summarises the main findings of each study. Abbreviations include: Locus Coeruleus (LC); Noradrenaline (NA); Nucleus Tractus Solitarius (NTS); Posterior Parietal Cortex (PPC).

acetylcholine and dopamine levels, with these neurotransmitters being essential for neural plasticity processes and inducing desired behavioural outcomes (Luckey et al., 2023). In fact, several studies suggest and implicate the mediating role of the locus coeruleus (LC) in tVNS protocols, including those assessing memory outcomes (Hulsey et al., 2016; Hulsey et al., 2017; Jacobs et al., 2015).

Despite the small size of the locus coeruleus, it is the Central Nervous System (CNS)'s main source of noradrenaline (Sharma et al., 2010). Not only do its projections extend to numerous brain regions, but the majority of these axons terminate in the hippocampus and neocortical regions (Feinstein & Heneka, 2017). In fact, given the dense projections from the LC to the hippocampus, it is particularly subject to noradrenaline (NA) modulation by the LC (Hansen, 2017). In relation to episodic memory formation, rodent evidence and the behavioural tagging hypothesis highlight how these processes depend upon the "corelease of noradrenaline and dopamine via locus coeruleus terminals in the hippocampus" (Hansen, 2017, p. 3; Moncada, 2017). Moreover, with regards to neural oscillations, LC activation and its subsequent NA release has been shown as a key moderator of EEG activity in neocortical and hippocampal regions (Berridge & Foote, 1991; Berridge et al., 1993). In a series of motor cortex-related experiments in rats and humans, Asamoah and colleagues (Asamoah et al., 2019) critically validated how tACS entrained neural oscillations, and influenced motor behaviour via both transcranial and transcutaneous mechanisms. Importantly, this study demonstrated that when the transcutaneous mechanism (i.e. stimulation of peripheral nerves) was blocked via application of a topical anaesthetic under electrodes on the scalp, entrainment effects were significantly reduced (Asamoah et al., 2019).

Indeed, supporting this, recent greater occipital nerve stimulation studies further validate a transcutaneous mechanism behind tES protocols and spotlight the LC's key role within these memory and synaptic plasticity processes (Luckey et al., 2022a; Luckey et al., 2022b; Luckey et al., 2020; van Boekholdt et al., 2021; Vanneste et al., 2020). The greater occipital nerve and trigeminal nerve (cranial nerve V) originate in the spine and brain respectively, with the former branching off to the posterior of the scalp vertex, and the latter across the face and forehead (Luckey et al., 2023). As referenced earlier, it is these projections that offer a means of transcutaneously activating the brain via their afferent connections to the NTS and the brainstem nuclei.

For example, exploring this transcutaneous mechanism, Vanneste and colleagues (Vanneste et al., 2020) applied tDCS to the Greater Occipital Nerve (GON) with the intention of stimulating the LC-NA pathway (to increase hippocampal functional connectivity and promote theta-gamma coupling) and strengthen episodic memory. In a series of experiments (summarised in Tables 1-4), this paper critically found that stimulation of the GON increased several proxies of LC-NA activation (sAA levels, pupil diameter and P3b ERP response, theta-gamma neural oscillations in medial temporal cortex), increased functional connectivity between the LC and right hippocampus, and left/right dorsolateral prefrontal cortex, left/right precuneus, and right angular cortex, and improved associative memory, memory recall and delayed recall (Vanneste et al., 2020). It confirmed these effects were a direct result of GON stimulation by testing stimulation of this nerve invasively in rats, as well as non-invasively in humans by comparatively testing trigeminal and cervical five and six nerves (Vanneste et al., 2020). Moreover, it demonstrated that stimulation of GON improved memory via consolidation processes by confirming that stimulation during learning had no effects on attention/ encoding, and similarly by confirming that stimulation during retrieval processes had no significant effects (Vanneste et al., 2020). Finally, to test whether memory effects were a product of the transcutaneous mechanism of stimulation (and not transcranial), an anaesthetic (such as lidocaine or prilocaine) was applied to the scalp under the electrodes before stimulation in a control group, and this group showed significantly poorer memory recall than the non-anaesthetic (i.e. active stimulation) group (Vanneste et al., 2020).

This alternative understanding of tACS and tDCS mechanisms is promising and warrants further validation, especially in clinical samples of those experiencing memory difficulties from conditions such as AD. See the 'Looking Forward' section for more details on this. Overall, these tES approaches have several advantages over TMS or DBS approaches (see Table 1). Namely they have a favourable safety profile, are more cost-effective, portable, easier applied and adapted for double-blind or sham-controlled conditions (Gonsalvez et al., 2017; Lefaucheur et al., 2017; Majdi et al., 2022; Yavari et al., 2018).

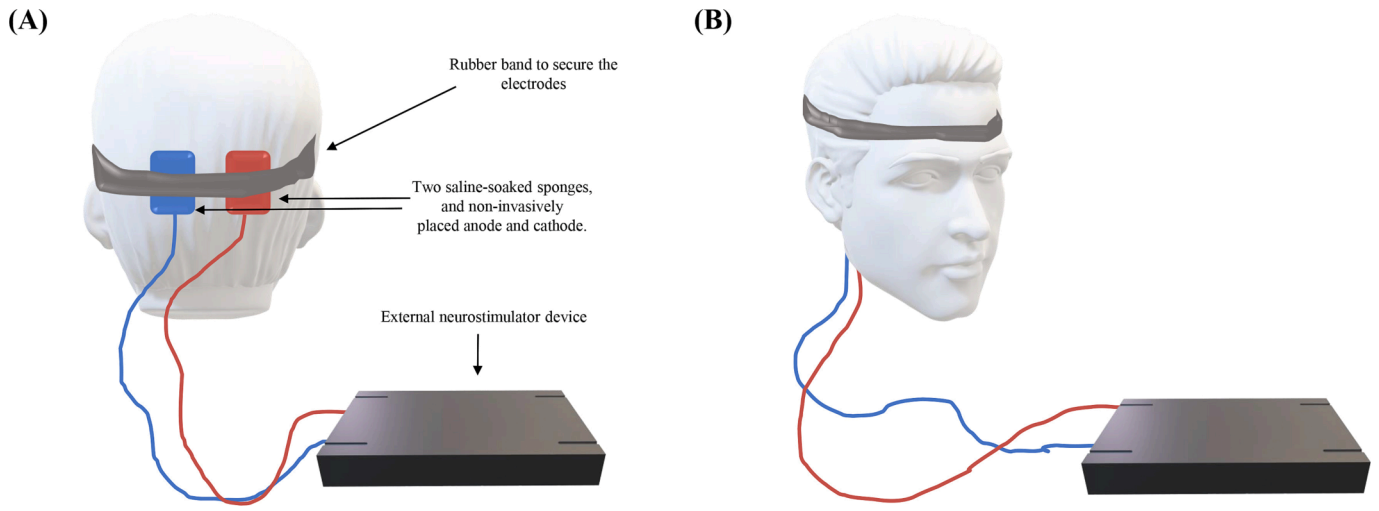

Fig. 5. Transcranial Alternating and Direct Current Stimulation ('tACS' and 'tDCS') Set Up. For both tDCS and tACS, two saline-soaked sponges (which each cover an electrode) are placed on the scalp, and held in place by a rubber band. These are connected to and controlled by an external stimulator device. (A) and (B) show an example set up of a participant, from a rear and front view, respectively.

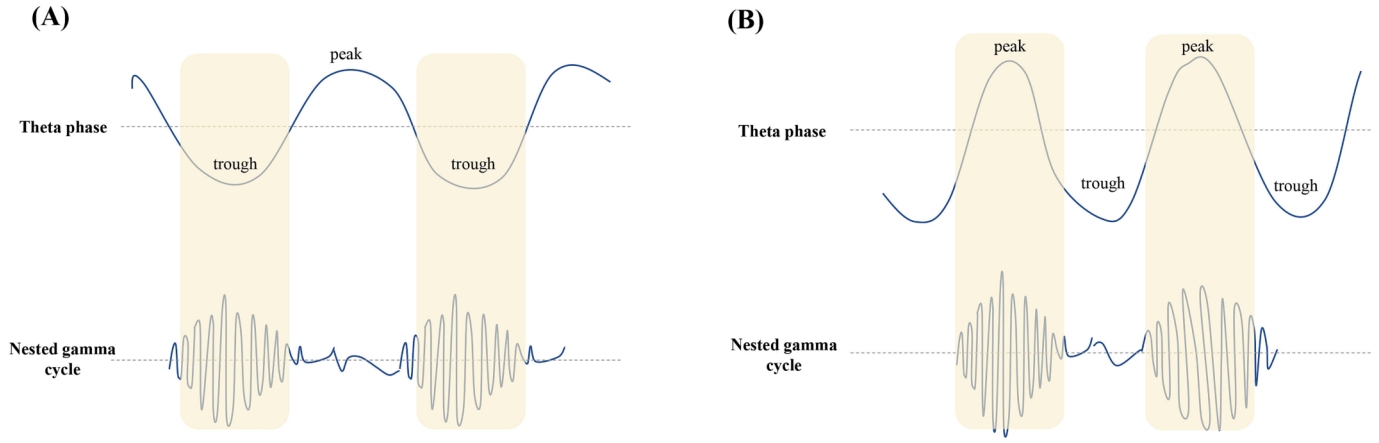

Fig. 6. Theta Gamma Cross Frequency Phase Amplitude Coupling. **(A)** Gamma oscillations nested in the trough of the theta phase. **(B)** Gamma oscillations nested in the peak of the theta phase. As shown above, the amplitude of gamma oscillations can be locked to different theta phases. Here, each gamma pattern has a different phase-offset, at either the theta-peak **(B)** or theta trough **(A)**. The causal role of theta-gamma coupling in episodic memory processes has been demonstrated, however further validation is needed to determine whether cross-frequency PAC can effectively modulate LTM performance.

4.7. Sensory stimulation

Alongside these TMS and tES approaches, other fruitful stimulation avenues aimed at entraining neural oscillations and modulating memory include sensory stimulation protocols targeting theta and gamma ranges. In recent years, various entrainment experiments have demonstrated that certain visual, auditory, or bimodal audio-visual sensory entrainment protocols can successfully enhance episodic memory performance. This next section will review the results of these papers, separated by their targeted frequencies.

As discussed earlier in this review, novel effective theta and gamma electromagnetic stimulation approaches are leveraging individualized protocols. Similarly, when investigating visual stimulation, the value of individualized theta-focused stimulation, and the role of theta-gamma phase amplitude coupling in memory performance has been demonstrated (Köster et al., 2019). In this study, the theta-power observed in response to rhythmic visual stimulation applied at individualized theta frequencies, indicated the effectiveness of the stimulation (Köster et al., 2019). However, it was the theta-gamma phase-amplitude coupling that predicted the degree of improved memory performance. Moreover, conversely, individualised alpha frequency visual stimulation had no memory effect (Köster et al., 2019).

Additionally, looking at bimodal sensory stimulation, in two experiments Roberts and colleagues (Roberts et al., 2018) found audio-visual stimulation applied at 5.5 Hz (theta frequency) resulted in enhanced episodic memory retrieval. Of note, EEG recordings during both stimulation and retrieval reported increased theta power during both stages. Secondly, these benefits were not found in two control conditions involving either white noise stimulation or beta frequency (14 Hz) sensory stimulation (Roberts et al., 2018). Interestingly, the sensory stimulation was applied between study and test phases for 36 min, likely supporting consolidation processes. Adding to this study, supporting the role of theta phase synchrony in episodic memory formation, Clouter and co-workers (Clouter et al., 2017) found that phase synchrony between audio and visual stimuli presented at theta frequency (4 Hz) enhanced episodic memory processes. Importantly, these results significantly compared to synchronous or asynchronous stimuli presented at slower (1.7 Hz) or faster frequencies (10.5 Hz) (Clouter et al., 2017). Summaries of these sensory stimulation protocols (and ones discussed later in this review) are included in Tables 1-4.

Whilst these results suggest the potential for sensory stimulation approaches to be applied effectively to older patients with memory

deficits or conditions such as Alzheimer's Disease, one potential limitation of auditory or visual stimulation paradigms for AD patients could be common age-related sensory processing impairment (Benussi et al., 2021). However, if this is considered and accounted for with adequate screening and baseline measures, this shouldn't confound the effectiveness of these stimulation protocols. In fact, sensory stimulation approaches focusing on gamma (40 Hz) frequencies are garnering greater support in the memory-focused literature and are demonstrating additional therapeutic benefits. These papers are importantly able to demonstrate how bimodal sensory gamma stimulation protocols can not only entrain oscillations within cortical and deeper subcortical regions such as the hippocampus, but that behavioural outcomes such as memory are subsequently enhanced. (Adaikkan & Tsai, 2020; Chen et al., 2022; Suk et al., 2020). These studies will be explored in greater detail in the subsequent AD sections.

4.8. Memory impairment: Alzheimer's disease

AD (the most common form of dementia), is one of the leading causes of death, and disproportionately affects the elderly population (Jellinger, 2022; Slater & Wang, 2021). In 2020, it was estimated that approximately 50 million people globally were affected by Alzheimer's Disease. Although the exact projection numbers vary, the literature agrees that by 2050 this number is expected to triple at least (Jellinger, 2022; Slater & Wang, 2021). Not only is this a concern at the individual level, but the burden this places on economies and health-care systems is substantial. Thus, finding an appropriate disease-modifying treatment is critical for both individuals and societies worldwide (Jellinger, 2022).

In terms of the pathology of Alzheimer's Disease, it is acknowledged that in the brain, AD has three key histopathological manifestations; neuronal cell death, extracellular amyloid plaque deposits and intracellular p-tau neurofibrillary tangles (NFTs) (Slater & Wang, 2021). Certain brain regions are more susceptible to these, including: the locus coeruleus, nucleus basalis, neocortex, entorhinal cortex and hippocampus (Slater & Wang, 2021). Additionally, hippocampal synaptic plasticity and synaptic and neuronal degeneration has been linked with declarative memory impairments associated with early Alzheimer's progression (Slater & Wang, 2021). Moreover, in mice with AD, there is recent rodent evidence for the link between AD pathology and altered brain activity (Byron et al., 2021). This study found that reduced amyloid precursor protein (APP) predicted attenuated theta-gamma coupling in the mouse hippocampus (Byron et al., 2021). Importantly, not only is there evidence highlighting how theta and gamma frequencies, and theta-gamma coupling play a facilitatory and causal role in episodic memory processes of healthy adults (Aktürk et al., 2022; Colgin et al., 2009; Hebscher & Voss, 2020; Jensen & Colgin, 2007; Jensen et al., 2007; Köster et al., 2014; Lisman & Jensen, 2013; Osipova et al., 2006), but there is also emerging evidence confirming their functional memory-related role in individuals with memory deficits and neurodegenerative conditions such as aMCI and Alzheimer's Disease.

Notably, leveraging resting-state EEG, the role of theta and gamma oscillations, and theta-gamma coupling in episodic memory processes of individuals diagnosed with aMCI, in comparison to controls, has been validated in a study by Vanneste and co-workers (Vanneste et al., 2021). In their study focusing on the posterior cingulate cortex (PCC) and parahippocampus, the aMCI group's impaired episodic memory performance was associated with reduced resting-state a) gamma power, b) theta coherence and c) altered theta-gamma coupling patterns, within-and-between these regions (Vanneste et al., 2021). Expanding on previous research, this paper critically demonstrates how in comparison to controls, altered theta and gamma patterns correlate with impaired episodic memory processes in those with memory deficits (Vanneste et al., 2021). Specifically, it highlights the potential for certain resting-state theta and gamma oscillatory characteristics and patterns to be used as a potential neurophysiological biomarker for early AD diagnosis (Vanneste et al., 2021). These findings also crucially highlight the potential for the hippocampus, theta-gamma coupling and gamma-band frequencies to serve as an effective target of neurostimulation therapies for those with AD.

As highlighted earlier in this review, in healthy adults, not only has the hippocampus' deep location hindered the effectiveness of electromagnetic stimulation protocols, but so too have open-loop strategies or insufficient mechanistic understandings played a role. These learnings are similarly relevant for studies focusing on AD groups. Specifically, traditional neurostimulation approaches are demonstrating inconsistent long-term memory effects within clinical AD samples. For example, some systematic reviews suggest that TMS can successfully enhance long-term memory (Birba et al., 2017), and is a more effective treatment option than tDCS (Holczer et al., 2020). Conversely, Majdi et al. (2022)'s *meta*-analysis found tDCS did have positive memory effects on those with Alzheimer's Disease in the six studies included. However the authors note that the effectiveness of tDCS protocols on memory are yet to be fully determined (Majdi et al., 2022).

Thus, building on the earlier-discussed studies applying alternative neurostimulation approaches to rodents or healthy adults, this next section will elaborate how these alternative approaches could have significant applied value at enhancing memory processes for those with memory deficits or neurodegenerative diseases such as aMCI or AD. Firstly, it will return to the TI technique and transcutaneous mechanistic approach, which have not yet been applied to clinical AD groups, to highlight the potential applied value of these protocols. Secondly, it will review successful modern neurostimulation approaches (including sensory, and individualized or closed-loop protocols) which are enhancing episodic memory in clinical AD groups, by targeting the hippocampus and gamma-oscillations. In doing so, several key elements for future clinical research will be highlighted.

4.9. Looking forward: Promising neurostimulation routes for AD research

As discussed earlier in this review, TI (temporal interference) is a novel means of non-invasively targeting deeper brain structures to modify behaviour. Only recently has this technique been explored as a brain stimulation approach (having originally been applied for peripheral nerve or muscular stimulation) (Goats, 1990; Liu et al., 2018). Specifically, of late, in mouse models and experiments, its feasibility and ability to activate hippocampal neurons and modulate motor movement was investigated and demonstrated (Grossman et al., 2017).

A clear advantage of this technique is how greater stimulation location specificity can be achieved (than with traditional tDCS approaches), as the depth of stimulation can be selectively controlled to recruit deeper neuronal populations such as those within the hippocampus (Grossman et al., 2017; Kricheldorff et al., 2022). Moreover, even within these deep brain regions, the focus point of stimulation can be 'live-steered' without needing to physically move electrode locations. These findings suggest the capacity for translation to humans and require further validation. This is especially important given how deeper brain regions are impacted in early-AD progression (Khachatryan et al., 2022). The potential applied value of this for memory deficits or neurodegenerative conditions cannot be underemphasised.

A second innovative approach worth validating in clinical AD samples, are those which leverage transcutaneous mechanisms of brain stimulation to target hippocampal regions by facilitating activation of neurotransmitter systems and oscillatory frequencies. Throughout the progression of Alzheimer's, degeneration of LC neurons has a consequential impact on the CNS' main source of NA, linking to increased rates of microglial inflammation, and resulting in further neuronal degeneration (Behl et al., 2022; Feinstein & Heneka, 2017; Takahashi et al., 2015; van Hooren et al., 2021). Supporting this, reduced NA levels are seen to impair clearance of amyloid-β by microglia, consequently increasing Aβ deposits in the cerebrum and hippocampus in AD brains (Ishii et al., 2015). Given NA's microglial anti-inflammatory properties, upregulation of this could further support AD treatment via its key anti-

inflammatory role clearing Aβ (Ishii et al., 2015). Thus, brain stimulation protocols that target the peripheral nerves to stimulate the LC-NA pathway could be an intuitive therapeutic route worth investigating. Given the success of Vanneste and colleagues (Vanneste et al., 2020) transcutaneous stimulation protocol at enhancing episodic memory processes in healthy older adults (via LC-NA activation, increased theta-gamma oscillations and functional connectivity between the hippocampus and key brain regions), this suggests the potential therapeutic value of this approach for those with neurodegenerative conditions such as AD. Thus, applying and validating this protocol in a clinical sample would be an exciting area for future studies and warrants further investigation.

A third promising non-invasive brain stimulation technique that is currently being applied to AD samples is sensory stimulation. Interestingly, whilst studies in healthy adults have demonstrated that sensory stimulation protocols focusing on theta frequency has positive memory-effects (Clouter et al., 2017; Roberts et al., 2018), in the AD literature, gamma (40 Hz) frequency sensory stimulation protocols in clinical samples are demonstrating greater therapeutic benefits. To begin, early mouse models demonstrated how monomodal (auditory or visual) 40 Hz stimuli induced gamma oscillations, enhanced glial responses, reduced amyloid plaque pathology, tau phosphorylation and neuronal and synapse loss characteristic of early stages of neurodegenerative diseases such as Alzheimer's (Adaikkan & Tsai, 2020; Chan et al., 2022; Chen et al., 2022; Martorell et al., 2019). Indeed, these sensory stimulation protocols not only a) entrained oscillations in neocortical and hippocampal regions, b) downregulated markers of AD neurodegeneration in deep-lying brain structures, and c) enhanced neuroprotective glial responses, but that critically enhanced cognitive and memory performance was observed post-stimulation. In fact, in a study of adults (including those with and without AD), 40 Hz bimodal sensory stimulation entrained deeper brain regions in both groups, as recorded by intracranial (iEEG) electrodes (Suk et al., 2020).

Subsequently, combined 40 Hz bimodal sensory stimulation protocols applied to human patients have demonstrated enhanced memory and pathophysiological benefits (Chan et al., 2022; Chen et al., 2022). In the literature, this protocol is frequently referred to as GENUS (Gamma ENtrainment Using Sensory stimulation) (Chan et al., 2022; Chen et al., 2022).

In Phase II of a GENUS study, daily 40 Hz light and sound stimulation was applied for 3 months to mild-AD patients (Chan et al., 2022). Post-stimulation, the experimental group demonstrated increased functional connectiveness between the default mode network and medial visual network, reduced hippocampal atrophy and better delayed memory performance. Moreover, whilst AD progression is normally associated with increased ventricular volume, the group receiving active stimulation showed no changes in ventricular volume or hippocampal atrophy suggesting GENUS' ability to slow the neurodegeneration process of AD (Chan et al., 2022).

Importantly, in these sensory stimulation protocols, the induced-gamma entrainment is observed not only in the sensory brain region specific to the stimulation modality, but also in other brain regions (incl. hippocampus, and other forebrain areas) by modulating neuronal spiking activity (Adaikkan & Tsai, 2020; Chen et al., 2022). This is especially relevant given how deeper brain regions are impacted in early-AD progression (Khachatryan et al., 2022) and implicated in episodic memory processes (Harrington et al., 2022; Hebscher & Voss, 2020; Mankin & Fried, 2020; Squire, 1992). Importantly, recent evidence suggests the strength of gamma entrainment in deeper brain regions such as the hippocampus could be strengthened further. Specifically, applying an extended-GENUS protocol, Khachatryan and colleagues (Khachatryan et al., 2022) investigated and demonstrated that the effectiveness of GENUS in humans could be increased by employing cognitive tasks with greater mental load during stimulation. In their study leveraging EEG recordings of 15 healthy subjects and 1 epileptic patient with intracranial recordings, they found that increasing the cognitive load of tasks during sensory stimulation increased the strength of gamma entrainment not only in the sensory cortex areas but also in deeper brain regions such as the hippocampus (Khachatryan et al., 2022). This finding that greater cognitive load during a task influences the degree of neural entrainment, is interesting in light of Grover and co-workers (Grover et al., 2022) discovery that tACS targeting DLPFC-gamma correlated with greater memory improvements 1 month post-stimulation for those with lower baseline cognitive levels. These two findings together suggest that greater cognitive load (whether due to increased task difficulty, or lower baseline measures), could recruit wider neuronal networks and enhanced entrainment, consequently leading to greater stimulation effects on memory. This is an area that also warrants further investigation. Additionally, there is evidence that bimodal (as opposed to monomodal) stimulation techniques likewise recruit more brain regions (Chan et al., 2022). Thus, sensory stimulation protocols being applied in clinical samples should consider these two factors when designing studies.

Furthermore, additional GENUS variations that may hold promise in future studies are those which incorporate closed-loop strategies, especially if the typical burst-like pattern of endogenous gamma activity is considered (Adaikkan & Tsai, 2020). There is already early evidence for the effectiveness of individualized sensory stimulation techniques specific to endogenous theta-frequencies (Köster et al., 2019). Given the comparative benefit of gamma-focused stimulation in AD studies, future studies should seek to examine if these benefits can be maximised by employing closed-loop and individualized strategies.

It is not only when applying sensory stimulation techniques that individualized protocols should be considered. As outlined earlier, in healthy adult samples, there is clear comparative trend towards greater positive effects in studies that employ electromagnetic stimulation that aligns with endogenous oscillatory frequencies and patterns (Aktürk et al., 2022). Thus, future clinical research must consider this factor, especially given how AD rodents and humans exhibit altered oscillatory patterns (Byron et al., 2021; Vanneste et al., 2021) which may inhibit the effectiveness of open-loop or standardized protocols. In a similar vein, protocols must be individualized to more than just endogenous oscillatory patterns. Specifically, a large scale study of AD patients noted an "inverted U-shape relationship between amyloid depositions and gamma power" such that early AD pathogenesis was associated with increased gamma power, whereas progressively decreased gamma power was associated with increased amyloid plaque levels during later AD progression/stages (Byron et al., 2021, p. 5). These findings bear consequence if brain stimulation approaches are being applied in clinical AD groups, as it suggests that the effectiveness of these protocols may vary for individual patients depending on how progressed their condition is. For example, given that gamma-frequency stimulation has been found to be more effective when administered at individualized frequencies (Aktürk et al., 2022), and in light of the finding that gamma oscillatory activity can vary depending on AD stage and amyloid burden (Byron et al., 2021), this suggests how one patient's optimal individualized gamma stimulation criteria may differ significantly at different timepoints. Adding to this, not only is it important to a) consider how a patient's current AD stage may inhibit or augment the effectiveness of stimulation protocols, and b) factor in how stimulation parameters may need to be amended both within-and-between participants, but c) it is also imperative for researchers to sufficiently report the participant breakdown for each AD phase, and for this variable to be considered in the analysis.

5. Conclusion

Overall, from reviewing the literature on promising alternative neurostimulation routes for targeting the hippocampus to improve episodic memory, several learnings are apparent. Due to the hippocampus' deep location within the brain, modern memory-modulating brain stimulation approaches that look promising are those which can

non-invasively either directly or indirectly activate this brain region. These include tES techniques that explore transcutaneous mechanisms, as well as bimodal sensory stimulation protocols such as GENUS. In sensory stimulation protocols, important factors which may contribute to memory enhancement are bimodal typologies, individualized gamma-frequency stimulation, and greater cognitive load during tasks. In addition, it would be exciting for future research to explore the feasibility of translating temporal interference research from mouse to human studies as the potential therapeutic value of this non-invasive DBS technique could be significant. Furthermore, clinical studies should consider Alzheimer's patients' disease progression stage when setting stimulation parameters, as well as when analyzing and reporting results. Notably, gamma-oscillations are receiving increasing support as a potential target frequency for stimulation protocols. However, individualized and closed-loop protocols based on endogenous oscillatory activities and AD stages are important parameters to consider.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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