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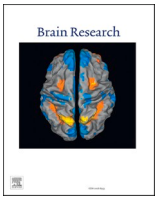

Review

Artificial sharp-wave-ripples to support memory and counter neurodegeneration

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ABSTRACT

Information processed in our sensory neocortical areas is transported to the hippocampus during memory encoding, and between hippocampus and neocortex during memory consolidation, and retrieval. Short bursts of high-frequency oscillations, so called sharp-wave-ripples, have been proposed as a potential mechanism for this information transfer: They can synchronize neural activity to support the formation of local neural networks to store information, and between distant cortical sites to act as a bridge to transfer information between sensory cortical areas and hippocampus. In neurodegenerative diseases like Alzheimer's Disease, different neuropathological processes impair normal neural functioning and neural synchronization as well as sharp-wave-ripples, which impairs consolidation and retrieval of information, and compromises memory. Here, we formulate a new hypothesis, that artificially inducing sharp-wave-ripples with noninvasive high-frequency visual stimulation could potentially support memory functioning, as well as target the neuropathological processes underlying neurodegenerative diseases. We also outline key challenges for empirical tests of the hypothesis.

1. Introduction

Imagine sitting in a lecture, watching the lecturer in the front, and listening to the constant stream of information she provides. You are focused, trying to absorb all the relevant bits and pieces. For this, the information arriving through your visual and auditory receptors is first processed in the sensory cortical areas (VanRullen, 2016). To gain more time to process the constant information stream, chunks of incoming information are buffered in sensory memory (e.g., the echoic, or the iconic memory), before passing selected parts onto higher-order association areas (Wutz and Melcher, 2013). Passing along the information from sensory memory to higher order-association stages involves a selection process (Luck and Vogel, 2013). This is often associated with attention, and only information that is in the focus of effortfully directed attention will be passed on from the initial processing stage (Awh et al., 2006; Hillyard et al., 1998; Vogel et al., 2005). In our example, the color of the shirt of the person sitting in front of you might not be relevant for the lecture and thus not attended to, resulting in this information being processed no further. Lasting access to these internal representations of sensory information likely requires encoding by long-lasting physical changes in neural networks in the hippocampus, the so-called memory traces or engrams (Hasselmo, 1999; Josselyn and Frankland, 2018). In the following, we argue that neural oscillations, especially short bursts of high-frequency oscillations above 100 Hz, so called sharp-wave-ripples (SWRs), play a crucial part in the information transmission and memory formation (Dickey et al., 2022b). Invasive stimulation approaches such as electrical or optogenetic stimulation can evoke SWRs (Behrens et al., 2005; Schlingloff et al., 2014). To overcome the limitations of invasive stimulation approaches, we propose using high-frequency visual stimulation to induce artificial SWRs. As a conclusion, we summarize how these artificial SWRs could potentially influence neurophysiological processes, improve different forms of memory, and alleviate neurodegenerative diseases.

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1.1. The temporal dimension of memory

To differentiate different forms of memory in time, Atkinson and Shiffrin (1968) proposed that information is first kept in the sensory register for a few hundred milliseconds before attended information is passed onto short-term memory, and then encoded in long-term memory. However, this theoretical concept of the short-term memory is disputed (Cowan, 2008; Öğmen and Herzog, 2016), as the function Atkinson and Shiffrin associated with this stage — the temporal storage of a few items for a very short time — can also be associated with working memory, namely the temporal storage and processing of information. Short-term memory can also denote the storage of information in the hippocampus before its consolidation to a lasting memory (Kragel and Voss, 2022; Voss et al., 2011). Regarding the former, Baddeley and Hitch (1974) proposed a model which largely overlaps with the first two stages of the model proposed by Atkinson and Shiffrin, but distinguishes itself by breaking the register and storage stages down to different sensory components and a central executive (Baddeley, 2010). On a neural level, primary sensory and association areas in the neocortex are at the core of the sensory memory (Teeuwen et al., 2021), whereas parietal and frontal cortical areas are key structures of the central executive (Smith, 2000). However, more recent findings point towards a network model of working memory, which involves communication across a brain-wide network (Christophel et al., 2017). Regardless of the specific neural mechanisms or details of names and labels, consensus exists that information is passed along multiple stages, from transient and fragile to durable and stable forms of memory.

1.2. The content dimension of memory

With respect to different subfields of memory, declarative and non-declarative memories, i.e., explicit information we can describe and implicit abilities and skills, can be differentiated (Werning and Cheng, 2017; Willingham and Goedert, 2001). Non-declarative abilities and skills can be learned and practiced, and it often involves refinement of motor sequences and patterns along a gradual trajectory, in which the cerebellum plays an important role (Schacter et al., 1993). Within declarative memory, and following our example above, we can distinguish episodic memory (i.e., the memory of the event of the lecture), and semantic memory (i.e., the memory of the facts presented in the lecture) (Tulving, 2002). For episodic and semantic memory, the hippocampus plays a central role (Squire and Zola-Morgan, 1988), and Buzsáki and Moser argue that both rely on the same neural processes, and that episodic memory can be transformed into semantic memory (Buzsáki and Moser, 2013). In short, similar to the consensus regarding the different temporal stages of memory processing, current theories on memory converge on the idea of distinct, yet partially correlated types of memory. For explicit memory, at least, the hippocampus and the interactions between hippocampus and neocortex play a central role.

2. Neural models of memory

On a smaller scale, the neural processes of memory involve the strengthening of synaptic connections between neurons, thereby forming engrams (Josselyn and Frankland, 2018). The engram formation depends in large part on NMDA-receptor based long-term potentiation (Tonegawa et al., 2015), is likely initiated by neural oscillations (Jutras and Buffalo, 2010), and is regulated by different neuromodulators such as noradrenaline and acetylcholine (Shine, 2019).

The classical model for memory formation is long-term potentiation (LTP) and long-term depression (LTD) of synaptic connections between pyramidal cells. Depending on the timing and strength of neural input to presynaptic cells, and the amount of calcium influx to the postsynaptic cell, the receptor density at the postsynaptic cell can be dynamically adjusted to increase or decrease the synaptic connection strength between neurons (Bear and Malenka, 1994). The latter can be imagined as a weight of a connection where a larger weight corresponds to a stronger connection. Multiple neighboring cells can then form sparse neural networks with connections of variable weights between cells, incoming information can be stored in specific patterns of synaptic weights, and different information can be stored in different patterns of synaptic weights within the same network (Izhikevich, 2006; Jensen and Lisman, 2005). Retrieving information from this network then only requires the activation of part of the network: A cue can activate one node or part of the network and activity can spread according to the pattern of synaptic weights.

Both the formation and the retrieval of information from such an engram requires temporally fine-tuned (i.e., synchronous) activity of neurons in the network, as famously stated by Donald Hebb (Hebb, 1949). Transient synchronization in the activity allows transferring information between cell groups (Fries, 2015), and the retrieval of information from a network requires the synchronous activation of all cells within the network (Joo and Frank, 2018). In summary, synchronous neural activity is hypothesized to be at the heart of memory formation, and theoretical models and empirical data suggest that neural oscillations are an economical way to synchronize neural cell networks (Buzsáki and Draguhn, 2004).

2.1. Neural oscillations and memory

As we described above, neural synchrony is central to the formation and retrieval of memories on the cellular level, and neural oscillations are one proposed way of synchronizing large cellular networks (Dickey et al., 2022b). Neural oscillations recorded by electrophysiological methods, such as local field potential (LFP) recordings, electroencephalography (EEG), or magnetoencephalography (MEG), can be regarded as the synchronous increase and decrease of summed postsynaptic activity of large cell populations (Cohen, 2017). Although some researchers regard oscillations as epiphenomena, merely reflecting the summed activity of large numbers of neurons, it is nonetheless striking that the population activity of these cell groups exhibit functions that go beyond the capabilities of single neurons (Engel and Gerloff, 2022). For example, episodes of fast oscillations can indicate states of high arousal, such as attentive stimulus processing, while states of low arousal, such as sleep, are primarily characterized by slow oscillations (Lendner et al., 2020; Steriade et al., 1993), although high-frequency SWRs also occur during rest and sleep (Buzsáki, 2015). On shorter time scales, the phase of slow oscillations likely reflects fluctuations in cortical excitability, and several findings suggest that low-frequency oscillations provide temporal windows for sensory processing and integration (Mizuseki et al., 2009; Ronconi et al., 2017). Oscillations in different frequency bands might also enable interactions between distant neural populations, with theta and gamma frequency bands for bottom-up and the beta band for top-down communication (Bastos et al., 2015; Vezoli et al., 2021). Similarly, the phase of slow oscillations can modulate the amplitude of faster oscillations in a hierarchical manner via cross-frequency coupling (Engel et al., 2013). Overall, neural oscillations are a ubiquitous mechanism to organize neural activity across large cell populations (Wang, 2010). Importantly, neural oscillations not only reflect ongoing processes, but they can be evoked with invasive and non-invasive brain stimulation methods to causally influence perception and cognition (Dayan et al., 2013) (Box 1).

2.1.1. Theta and gamma

Many studies have observed synchronization of theta and gamma oscillations between the hippocampus and neocortex during memory tasks, suggesting that both frequencies play a role in memory formation (Jensen and Lisman, 2005; Vivekananda et al., 2021). Indeed, the cross-frequency coupling — or neural code — of theta and gamma oscillations has long been suggested as a mechanism facilitating information encoding and retrieval (Lisman and Idiart, 1995). This theta-gamma neural code was initially proposed as a timing mechanism which

allows sequences of multiple short-term memories to be stored separately, hence activity patterns associated with multiple memories can be stored in a single neural network. Specifically, Lisman and Idiart (1995) posited that each item in memory is represented by a distinct gamma frequency sub-cycle of a single theta oscillation cycle. Thus, while gamma oscillations store the content of specific memories, they are temporally organized by a slower theta rhythm in which they are nested. Indeed, the number of items that can be stored in short-term memory (and therefore behaviorally reported) corresponds to the limited number of gamma oscillations which can occur within a given theta cycle (Lisman and Idiart, 1995). Subsequent developments of this theory have emphasized that the precise timing of gamma oscillations relative to theta cycles is crucial for memory formation: gamma oscillations must be phase-locked to the theta rhythm with each gamma cycle occurring at a particular phase of the theta cycle (Jensen and Lisman, 2005).

Researchers have also recognized the necessity of LTP in the hippocampus for memory formation to occur. Crucially, LTP induction critically depends on the relative timing between pre- and postsynaptic activity (Bi and Poo, 1998; Markram et al., 1997), and thus cells encoding sequences of items presented seconds apart, which are typically learned with ease, cannot be directly subject to immediate hippocampal processing. Theta and gamma oscillations have been argued to resolve this problem by operating a multi-item working memory buffer, where items presented over several seconds are retained in the neocortex before being fed to the hippocampus (Jensen and Lisman, 2005). In this conceptualization, items presented over several seconds remain represented in successive cortical gamma cycles, with each successive cycle representing a distinct sequential item. This proposed mechanism condenses items presented seconds apart into a sequence of cortical representations parsed by much shorter time periods (approx. 30 ms), which falls within the time constraint of hippocampal LTP. Thus, gamma oscillations can be thought to represent a parsing of items that is temporally appropriate for hippocampal processing, while theta oscillations act to relay these condensed representations from the cortical buffer to the hippocampus. Support for this theory comes from studies showing a phase-locking of theta and gamma band activity (Rasch and Born, 2013). Alternative accounts propose memory formation by potentiated synaptic input across longer intervals (Bittner et al., 2017).

The concept of representation by oscillatory phase is not new, however. Hippocampal place cells, as recorded in rats, have been known to fire reliably at a particular phase of theta oscillations (O'Keefe and Recce, 1993). Place cells are activated when the animal enters a specific place in its environment. The specific location in space which is represented by a particular place cell is known as the place field. Interestingly, as an animal moves from the periphery to the center of a place field, the firing of place cells shifts to earlier points of the theta cycle, specifically from the peak to the trough (at the center of the place field), a phenomenon known as phase precession (Buzsáki and Draguhn, 2004; Jensen and Lisman, 2005). Theta and gamma oscillations have been theorized to work in concert, to encode sequences of cortical representations and feed this information to the hippocampus. Interestingly, this theta-gamma code appears to underpin the encoding of semantic as well as spatial sequences of information, i.e., navigation in real and mental space (Buzsáki and Moser, 2013).

2.1.2. SWRs

SWRs are transient (40–100 ms) high-frequency oscillations occurring between 110 and 200 Hz in rodents (Buzsáki, 2015) and between 80 and 180 Hz in humans (Norman et al., 2019; Staresina et al., 2015). Such high frequency network oscillations are principally observed in the LFPs in the CA1 layer of the hippocampus, which is densely populated with pyramidal cells (Sullivan et al., 2011; Ylinen et al., 1995), and they are mainly induced by excitatory activity from the CA3 region (Buzsáki, 2015). SWRs are essential for memory consolidation in the hippocampus (Buzsáki et al., 1983), and orchestrate LTP at synapses between CA3 and CA1 (Sadowski et al., 2016).

Although a complete account of the cellular and network mechanisms responsible for the generation of SWRs remains elusive, converging evidence illuminates an intricate interplay between specific subgroups of excitatory and inhibitory hippocampal neurons (Stark et al., 2014). These authors showed in one experiment combining optogenetic stimulation, pharmacological blockades, and high-density extracellular recordings, that the activity of only a small number of CA1 pyramidal cells is sufficient to trigger SWRs, and pyramidal cell activity is necessary to maintain ripples. However, the same study demonstrated that such pyramidal cell activation can generate SWRs only in combination with fast synaptic inhibition. Although their activity is necessary, pyramidal cells are silenced by fast-spiking parvalbumin-positive interneurons. Optogenetic stimulation of these parvalbumin-positive interneurons can evoke SWRs (Schlingloff et al., 2014), and the periodic inhibition of pyramidal cells provides a mechanism for pacing SWRs (Stark et al., 2014).

Regardless of how such pyramidal cell - interneuron interactions are specifically realized, there is little doubt that the SWRs they underpin are crucial for memory formation. The temporal and spatial coordination of the spike content of SWRs is thought to represent a condensed replay of sequences of neural patterns formed while encoding new information (Buzsáki, 2015). When a SWR event occurs, it transfers this condensed hippocampal representation to various cortical regions, to consolidate the memory. Note that this echoes the mechanistic role proposed by theta-gamma code discussed above. Indeed, whereas the theta-gamma code describes how cortical representations are encoded in the hippocampus, SWRs facilitate consolidation of memories by transfer from the hippocampus to the neocortex (through replay of neural populations representing particular memories).

Despite SWRs being prominently associated with offline processing, and thus the phase of memory processing associated with consolidation, SWRs have also been observed during encoding and recall phases of memory. By using intracranial recordings in human patients, Norman and colleagues (2019) found that the rate of hippocampal SWRs while encoding a sequence of images predicted the likelihood of their subsequent recollection. Moreover, the recollection of remembered images was accompanied by a higher ripple rate. Interestingly, in this experiment the SWRs observed during recall were coupled with a reinstatement of activity in those visual cortical sites active at encoding. Overall, it becomes increasingly clear that SWRs are one of the crucial elements in the formation and retrieval of explicit memory.

2.1.3. Synchronization between neocortex and hippocampus

Transient synchronization of neural oscillations has been proposed as a potential mechanism to transfer information between cell groups, and to bind different information to one coherent mental image (Fries, 2015). SWRs have been implicated in the formation, consolidation, and retrieval of memory, and they can synchronize different areas of the brain (Dickey et al., 2022b). A critical question is whether SWRs can act as drivers for information transfer based on the communication-through-coherence idea (Nitzan et al., 2020, 2022). As described in our example above, lasting access to internal representations of sensory information requires the encoding and consolidation of the information in sparse, distributed neural ensembles called memory traces or engrams (Hasselmo, 1999; Josselyn and Frankland, 2018). Varying levels of intrinsic neural excitability of cells within a network are one critical factor in determining which cells become part of an engram to encode a memory. Due to stochastic fluctuations in neural excitability, at any given time several neurons are in an excitable state which biases the formation of an engram (Josselyn and Frankland, 2018). Hippocampal-cortico-cortical co-ripples have been proposed as a potential mechanism to bind distant neocortical and deep-brain sites for the dynamic and rapid assembly of a neural network to encode specific information (Dickey et al., 2022b).

Box 1
Established and proposed methods to stimulate deep brain structures to improve cognitive performance

Established experimental methods exist to stimulate deep brain structures and artificially evoke SWRs in hippocampal slices or animals, such as tetanic electrical stimulation (Behrens et al., 2005), optogenetic manipulation (Stark et al., 2014), or dendritic application of KCl (Nimmrich et al., 2005). Importantly, artificial SWRs have been shown to improve memory performance, supporting the notion that artificial SWRs could mimic natural SWRs and be functionally relevant (Oliva et al., 2020). While it is possible to modulate cognitive performance in rodents using these methods (Fernández-Ruiz et al., 2019; Oliva et al., 2020), they are not suited for use in humans, due to the necessity of invasive stimulation. In humans, invasive deep-brain-stimulation of the Nucleus Basalis has been proposed as a possible treatment for memory dysfunctions, but some participants show cognitive improvement, while other show cognitive decline or no change in cognitive performance (Nazmuddin et al., 2021). Deep-brain-stimulation of the fornix, an output fiber tract of the hippocampus, shows more promising results with markedly improved cognitive performance (Ríos et al., 2022). Non-invasive electrical or magnetic stimulation has been proposed to remedy memory loss, but again with mixed results, as transcranial direct current stimulation showed no meaningful effects, and repetitive transcranial magnetic stimulation showed positive effects on general cognitive performance, but not on specific subtypes of cognition, such as memory (Gu et al., 2022). Recent experiments using transcranial ultrasound pulse stimulation indicated positive effects on cognition, but the very limited number of studies precludes strong conclusions on the efficacy of the method (Beisteiner et al., 2020; Dörl et al., 2022). 40 Hz repetitive visual stimulation has been reported to evoke synchronous oscillations in the neocortex and the hippocampus, with potentially positive effects on cognition (Manippa et al., 2022), but so far only one published study with 4 active versus 5 control AD participants showed improvement in cognitive performance (Chan et al., 2022). However, some doubt exists whether flicker induced 40 Hz oscillations can propagate beyond the visual cortex, as direct recordings from the thalamus, the primary visual cortex and the hippocampus of mice show neural entrainment to the 40 Hz stimulus on early stages of the visual pathway, but not in the hippocampus (Schneider et al., 2023; Soula et al., 2023). Recently, rapid invisible frequency tagging (RIFT) has been proposed as a new tool to influence or manipulate neural oscillations at higher frequencies (e.g., 68 Hz), which opens up the possibility to stimulate the brain at frequencies close to the frequency range of SWRs and beyond the frequency range of perceptual awareness (Seijdel et al., 2023). We recently showed that spatially organized high-frequency visual flicker can induce cortical responses in the same frequency as SWRs (Keil et al., 2023). In short, sequentially targeting neighboring retinal cones in rapid succession with a high-frequency flickering light and leaving a resting period in line with the refractory period (~10 ms) of the cones by occluding recently stimulated parts of the retina induces a steady-state visual evoked potential (SSVEP) at the frequency of the flickering light in the visual cortex (See Fig. 1). We propose that these stimulus-induced high-frequency oscillations can propagate beyond the visual cortex to mimic the functional role of natural SWRs.

3. Artificial SWRs as a mechanism to influence neurophysiology and support memory

Human studies have suggested that SWRs play a crucial role in the transfer of information between neocortex and hippocampus (Dickey et al., 2022b; Norman et al., 2021). Moreover, it can be speculated that the functional role of cortical ripples is not restricted to memory, because they co-occur and phase-lock with other cortical sites more than with hippocampus (Dickey et al., 2022a; Dickey et al., 2022b). Direct stimulation of the hippocampus in animals can reliably evoke SWRs, but indirect stimulation in humans has received limited experimental support (Box 1). We therefore propose a novel stimulation protocol involving high-frequency visual stimulation of the neocortex and the hippocampus in the frequency range of natural SWRs (80–180 Hz; (Norman et al., 2019; Staresina et al., 2015) to induce high-frequency oscillation, i.e., artificial SWRs, that mimic physiological events (Keil et al., 2023). Our proposed method employs flicker frequencies beyond the threshold of perceptual awareness, which should reduce the stimulus load for the participant, even with prolonged use. It allows influencing the neocortex in the frequency range of cortical ripples, which provides a direct route to the functional mechanisms of cortical ripples. Importantly, SWRs synchronize neocortex and hippocampus, and using a stimulation in the SWR frequency range promises to allow the signal propagation of artificial SWRs along the same neural routes as naturally occurring SWRs (See Fig. 1).

3.1. Propagation of artificial SWRs

Following the example from the introduction, chunks of information that the lecturer has just presented are kept in sensory memory. To pass this quickly decaying information on to more stable representations, neural networks in sensory cortical areas need to be synchronized with higher-order brain areas (e.g., the hippocampus), either by structural or by functional connectivity (Dalton et al., 2022; Fries, 2015). The hippocampus is structurally connected to a number of different brain areas. While the entorhinal cortex is the main interface to and from the hippocampus, other areas in its vicinity also have direct anatomical connections with the hippocampus, such as the perirhinal cortex or the parahippocampal cortex (Dalton et al., 2022). In addition, a fiber-tracking study in humans revealed connections between the hippocampus, temporal, occipital, parietal and frontal areas, including primary visual areas (Maller et al., 2019). Especially important in the context of visual stimulation to influence the hippocampus are direct connections between the visual and temporal lobes, such as the inferior longitudinal fasciculus (Catani, 2003; Herbet et al., 2018). A recent study also identified prominent direct connections between the primary visual cortex and the dorsal hippocampus (Dalton et al., 2022). In light of the potential functional gradient along the long axis of the hippocampus, which associates the dorsal hippocampus with memory (Strange, 2022; Strange et al., 2014), this structural connection between visual areas and the dorsal hippocampus could provide a direct route to synchronize the visual cortex and the hippocampus to transfer information and influence memory-related processes.

Aside from structural connection, it is also possible to dynamically coordinate information flow within brain networks (Singer, 1999). The basis of this functional connectivity is the synchronization of fluctuations of neural activity in different local neural ensembles, which facilitates the flow of information between these ensembles (Womelsdorf et al., 2007). Importantly, different frequencies have been associated with information flow in different directions, with lower frequencies subserving top-down influences, and higher frequencies subserving bottom-up information flow (Bastos et al., 2015; Vezoli et al., 2021). In light of the potential influence of high-frequency visual stimulation on hippocampal activity, artificially evoked cortical ripples in the primary visual cortex could act as a high-frequency bottom-up driver for hippocampal ripples or could also induce hippocampal-cortico-cortical co-ripples for the dynamic formation of neural networks for memory formation.

Future studies employing simultaneous recordings from the visual cortex and the hippocampus are needed to elucidate the way of transmission. One hypothesis is the direct entrainment of hippocampal activity by the evoked ripples in visual cortex. This would likely manifest

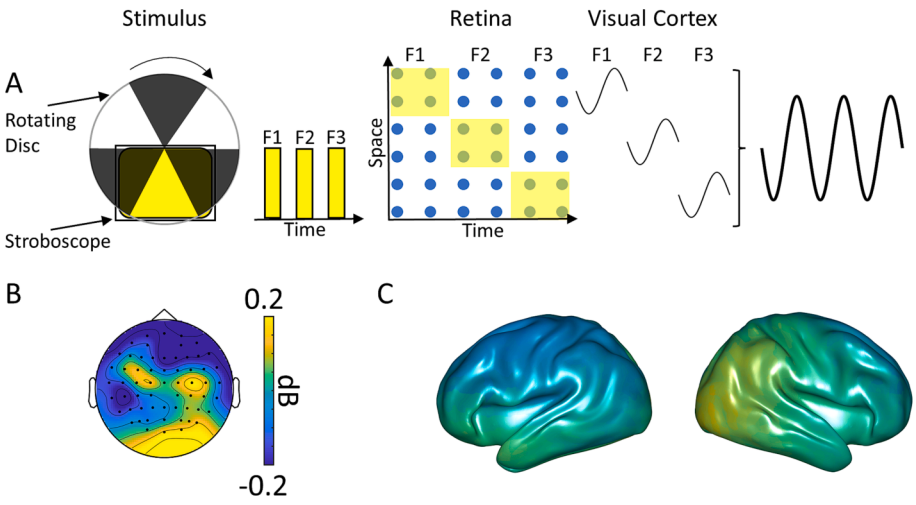

Fig. 1. Overview of the proposed method to induce high-frequency oscillations: (A) High-frequency visual stimulation with a stroboscope creates a flickering visual stimulus (F1, F2, F3). Combining the high-frequency visual stimulation with a rotating disk allows sequentially targeting neighboring retinal cells, which results in a temporal sequence of evoked potentials in adjacent parts of the visual cortex. Summed across the visual cortex, this results in a steady-state visual evoked potential (SSVEP). (B) Stimulation at 165 Hz results in an SSVEP with an occipital topography. (C) Source analysis reveals the right-lateralized source of the 165 Hz SSVEP in visual cortex. Adapted from Keil et al. (2023).

in a strong phase-locking of activity in visual cortex and hippocampus with a minimal delay in the ripple onset between both areas. An alternative hypothesis is the change of the excitation-inhibition balance in the hippocampus due to strong bottom-up input. This would likely manifest in an increase in the number of SWRs, and potentially also changes in amplitude and/or duration of SWRs after the onset of ripples in V1 without phase-locking and with a variable delay in the activity in both areas.

3.2. Memory formation

Increased SWR rate supports successful memory encoding (Norman et al., 2019), and inducing artificial SWRs during or immediately after information processing could act as a direct synchronization between sensory and higher order areas, to bind information to a coherent memory representation (Dickey et al., 2022b). In short, the combination of stimulus processing in sensory cortices, sensory memory as an ultra-short-term information storage, and artificial SWRs to synchronize different brain areas could represent a potential mechanism for information transfer. Entrainment of cortical oscillations could thus act as a carrier of information from neocortex to hippocampus by transiently binding neocortical and deep brain structures. Crucial aspects in this information transfer are the timing, density, and frequency of SWRs. As mentioned above, varying levels of intrinsic neural excitability of cells within a network determine which cells become part of an engram to encode a memory, and several neurons are simultaneously in an excitable state, which biases these neurons to form an engram (Josselyn and Frankland, 2018). Depending on the way of transmission of artificial SWRs to the hippocampus, different hypotheses are conceivable for the potential mechanism. If the hypothesis of a direct entrainment of hippocampal activity by the evoked ripples in visual cortex is correct, it would be possible to precisely establish transient synchronous neural networks comprising sensory areas and hippocampus to form an engram. If the hypothesis of a change in excitation-inhibition balance in the hippocampus due to strong bottom-up input, which increases the rate of SWRs, is correct, it could be possible to boost the processes associated with successful memory encoding, albeit without precise control of the timing of activation of the involved neural networks. Future work will need to establish the optimal timing and frequency of the synchronized neural activity relative to the onset of the to-be-remembered item to form an engram, and whether activation of different areas of the visual cortex activates different areas of the hippocampus. With respect to the timing and density of SWRs, intracranial recordings in humans have indicated that an increased ripple rate after the offset of the to-be-remembered item correlates with increased memory recall (Norman et al., 2019).

3.3. Aging

As we age, sensory processing and cognitive abilities decline. It has been hypothesized that reduced synaptic plasticity and neural degeneration characterize the physiological aging process of the brain (Rossini et al., 2007). With increasing age, neural oscillations show a general slowing, i.e., a decrease of peak frequencies, and a deterioration of functional connectivity between neocortical areas (Jafari et al., 2020; Scally et al., 2018). Whether reduced synaptic plasticity could be the underlying cause of changes in neural oscillations, especially SWRs, or whether a disruption of SWRs leads to an impairment in LTP generation, which leads to synaptic dysfunction, or whether both processes occur in parallel with potentially snowballing effects is not entirely clear, but experimental evidence points towards a critical role of SWRs for tuning synaptic plasticity (Sadowski et al., 2016). Inducing artificial SWRs with sensory stimulation could potentially increase synaptic plasticity and counter the deterioration of neural networks by artificially increasing LTP. Future EEG or MEG studies focusing on cognitive abilities are needed to determine if targeting physiological degeneration by artificially inducing SWRs will prevent age-related change in neural oscillations and thus counter age-related functional decline.

3.4. Neurodegenerative diseases

Neurodegenerative diseases such as Alzheimer's disease (AD) are characterized by accumulation of neurofibrillary Tau protein tangles and Amyloid-β (Aβ) plaques, and their neurotoxic effect leads to further cell death (Hardy and Higgins, 1992). Severe cognitive decline results, and patients suffer from progressive dementia marked by impaired spatial orientation and memory loss. While the Aβ cascade hypothesis was one of the first ideas on the physiological mechanism of AD, Aβ plaques may not play a prominent role in the degenerative process after disease initiation (Spires-Jones and Hyman, 2014). Synaptic loss is also an early sign of AD (Ishii et al., 2017). The role of synaptic loss in AD pathophysiology may be equally important, and may occur

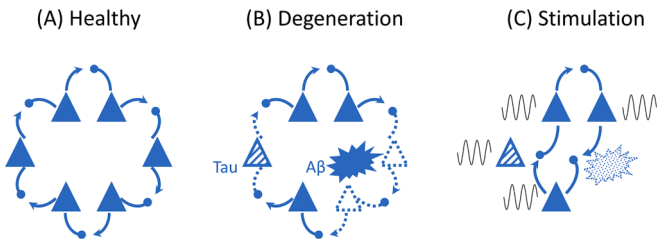

Fig. 2. Hypothesized relationship between neural network activity, neuropathology, and the potential therapeutic effect of noninvasive high-frequency visual stimulation. (A) In healthy neural networks, neurons form synaptic connections and memory can be stored in the patterns of connections between neurons. (B) In neurodegenerative diseases, various pathological mechanisms interrupt normal neural activity, for example the formation of Tau protein tangles impairs cell functioning, the formation of Aβ plaques causes cell death, and the synaptic connections degenerate. (C) Artificially inducing SWRs could potentially counter the neurodegeneration or slow the disease progression by activating the glymphatic system to clear Aβ plaques, activating glial cells, and supporting the formation of new synaptic connections.

simultaneous to or even precede Aβ deposition (Tzioras et al., 2023), and SWRs may play a central role in the impaired synaptic function (Caccavano et al., 2020; Sanchez-Aguilera and Quintanilla, 2021). With respect to glial cells, one line of research points towards a specific role of oligodendrocytes and the loss of the axonal myelin sheaths in AD and the improvement of memory and SWRs with increased myelination (Chen et al., 2021). Across different hypotheses on the pathophysiological mechanisms of AD, impaired SWRs appear to play a central role. Therefore, it is reasonable to speculate that directly targeting the impaired SWR generation via brain stimulation could alleviate the symptoms of AD (Fig. 2).

3.4.1. *Amyloid-β plaques and activation of the glymphatic system*

Aβ is a neuropeptide derived from the amyloid-beta precursor protein (APP), which is evolutionary conserved across vertebrates, indicating its critical physiological importance (Tharp and Sarkar, 2013). However, its functional role is controversial (Hiltunen et al., 2009). Accumulation of Aβ appears to be one of the earliest biomarkers of AD, disrupting SWRs and impairing memory formation (Hampel et al., 2021; Nicole et al., 2016). In terms of a potential cause of Aβ plaque formation, an imbalance between Aβ synthesis and clearance has been proposed. For the latter, the glymphatic system is important, as this pathway possibly drains excessive Aβ from the brain to the cerebrospinal fluid (CSF) (Iliff et al., 2012). Importantly, this mostly occurs during slow-wave-sleep (SWS), when SWRs also occur for memory consolidation (Branger et al., 2016). In AD, the observed increase of SWS might be a compensatory mechanism to counter the reduced SWR density, and the overall SWR impairment may cause impaired encoding, consolidation, and retrieval of memory (Cushing et al., 2020). Interestingly, recent work in humans indicates that visual stimulation can drive CSF flow (Williams et al., 2023). Linking artificial SWRs induced by noninvasive visual stimulation, CSF flow, and memory impairment, it is plausible that targeting the impaired SWR generation with artificial SWRs could restore glymphatic system function, thus facilitating greater Aβ clearance, while at the same time increasing the overall SWR density, which could alleviate the AD memory pathology.

3.4.2. *Activation of glia cells*

In addition to a degeneration of neural tissue, white matter impairment, namely the alteration of the myelination of central nervous axons, has been identified in AD (Chen et al., 2021). While myelination is usually implicated in supporting the axonal structure and increasing the conduction speed of action potentials along the axon, recent research points to experience-related changes in myelination, which indicate that myelination may play an important role in neural plasticity and memory (Xin and Chan, 2020). Chen and colleagues showed in a mouse model of AD that stimulating myelin renewal can improve memory performance and increase SWR density and frequency (Chen et al., 2021). Moreover, myelin is needed to facilitate the coupling of hippocampal SWRs to cortical spindles after learning, (Steadman et al., 2020). Increased myelination could therefore lead to the improvement of memory and SWR functionality, thereby countering the AD pathology. Similar to targeting the activation of the glymphatic system with artificial SWRs to alleviate the AD pathology, we can speculate that artificially increasing the SWR density could promote glia cell activity and the axonal remyelination, which could improve neural network functionality and memory formation.

3.4.3. *Countering synapse loss in hippocampus and neocortex*

Molecular changes and cellular degeneration are at the core of current AD models. Aβ and tau can cause synapse loss, which can then lead to neuroplastic deficits and cognitive decline (Tzioras et al., 2023). Importantly, synaptic dysfunction may be detectable before clinically relevant Aβ deposition (Hampel et al., 2021). Whereas it is usually thought that molecular changes and cellular degeneration cause changes in synaptic activity, the inverse is also possible with synaptic activity altering molecular structure and function (Iaccarino et al., 2016). In light of early changes in synaptic activity in AD and synaptic loss being an AD hallmark, synaptic dysfunction seems to be the critical link between neuropathology and cognitive symptoms (Jackson et al., 2019), and experimental evidence points towards a critical role of SWRs in tuning synaptic plasticity (Sadowski et al., 2016). Therefore, and as we have described above with respect to the effects of general aging on cognition and the role of synaptic loss therein, artificially inducing synaptic plasticity by inducing artificial SWRs could counter early pathological synapse loss in AD, which could either prolong normal functioning or even prevent the neurodegenerative progression.

3.5. *Open questions and critical issues*

We have outlined our hypothesis, detailing how different invasive and non-invasive stimulation approaches can be used to artificially induce SWRs, or potentially entrain neural oscillations to mimic the properties of naturally occurring SWRs. We argue that these artificial SWRs could potentially influence neurophysiological processes, improve memory, and alleviate neurodegenerative diseases. However, several critical issues need to be carefully considered in future experimental and applied work.

3.5.1. *Direct experimental support*

Although different lines of experimental evidence support our hypothesis that SWRs can be artificially induced, this support is indirect. Indeed, several aspects of our argument need to be empirically tested. Whereas steady state visual stimulation is an established method to induce targeted frequencies in the visual cortex, and we could show that it is possible to induce neocortical responses in the frequency range of SWRs, it is unclear whether these oscillations propagate beyond sensory areas to the hippocampus (Schneider et al., 2023; Soula et al., 2023). Recordings from electrodes implanted in the hippocampus could show that SWRs can be artificially induced, and source reconstruction of MEG recordings could elucidate the signal propagation beyond the visual cortex. While it might not be necessary to directly target the hippocampus to alleviate aspects of AD pathology, for example the neocortical accumulation of Aβ in early stages of AD (Hampel et al., 2021), the hippocampus plays a central role in memory and hippocampal dysfunctions are at the heart of various cognitive impairments. Testing changes in learning and memory in the context of artificially induced SWRs could provide evidence for a positive effect of the noninvasive brain stimulation, even without providing a detailed view on the underlying mechanism of action.

3.5.2. Ethical considerations

While we hypothesize that noninvasive brain stimulation can either trigger natural SWRs or induce artificial SWRs, it is not clear whether these SWRs mimic the normal SWR functionality or could fill the gap of reduced SWRs due to neurodegeneration. As we have presented above, there are reasons to speculate that artificial SWRs could mimic the role of natural SWRs, but questions regarding the timing, density, and frequency need to be answered in carefully designed empirical studies. Similarly, questions regarding stimulation duration and intensity to achieve a safe and potentially clinically meaningful effect have to be carefully tested in clinical trials. Although artificial SWRs have been shown to improve memory performance in rodents (Fernández-Ruiz et al., 2019; Oliva et al., 2020), it remains possible that they could disrupt theta oscillations during encoding, consolidate irrelevant information, or interfere with normal memory processes. Similarly, it is possible that artificially induced SWRs lead to memory consolidation of irrelevant information or inhibits its forgetting. Unintended consequences of artificially induced SWRs therefore need to be carefully evaluated in cognitive tasks testing different forms of memory, before considering high-frequency visual stimulation to induce SWRs as a potential therapy for memory impairment or neurodegenerative diseases.

With respect to the direct influence of high-frequency visual stimulation on neural activity, the potential risk of overstimulation needs to be considered. In the progression of AD, neural hyperactivity is part of a neurotoxic vicious cycle of glutamate release and neural activation which leads to further glutamate release (Selkoe, 2019; Zott et al., 2019). Thus, it needs to be carefully monitored, whether high-frequency visual stimulation can lead to overstimulation of glutamatergic neurons, which could potentially worsen neurodegeneration. Moreover, high-frequency visual stimulation poses the risk of inducing epileptic seizures, which is increased in AD patients (Nicastro et al., 2016). Animal studies can be useful to determine the effect of high-frequency visual stimulation of different light intensities and across different durations to establish safety boundaries avoiding neural hyperactivity. Similarly, studies in human participants with implanted intracranial electrodes for diagnostic purposes as part of their evaluation for neurosurgical epilepsy treatment can help establish the safety boundaries to avoid inducing epileptic seizures, for example by using high frequencies of visual stimulation outside of the frequency range associated with photosensitive epileptic seizures (Mankowska et al., 2022; Parra et al., 2007).

4. Conclusion

In short, information must pass several stages from perception to a stable memory during memory formation. Whereas the different stages are associated with different local and network processes in the brain, neural synchrony between involved cell groups is important to transfer information and to form neural networks for information storage. SWRs have been implicated as a crucial mechanism to synchronize the hippocampus with the neocortex during memory encoding and retrieval. They also play a central role in various pathological processes in neurodegenerative diseases, such as AD. Therefore, we propose the hypothesis that artificially inducing SWRs could support memory processes and potentially alleviate the cognitive and physiological pathologies of neurodegenerative diseases.

CRediT authorship contribution statement

Julian Keil: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Hanni Kiiski:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Liam Doherty:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Victor Hernandez-Urbina:** Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Chrystalleni Vassiliou:** Validation, Writing – original draft, Writing – review & editing. **Camin Dean:** Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Markus Müschenich:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision. **Hamed Bahmani:** Conceptualization, Methodology, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ababax Health GmbH develops non-invasive stimulation techniques for digital health applications. We have filed a patent application for a device to deliver high-frequency spatially targeted visual stimulation.

Data availability

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

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