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Direct electrical brain stimulation of human memory: lessons learnt and future perspectives

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Modulation of cognitive functions supporting human declarative memory is one of the grand challenges of neuroscience, and of vast importance for a variety of neuropsychiatric, neurodegenerative and neurodevelopmental diseases. Despite a recent surge of successful attempts at improving performance in a range of memory tasks, the optimal approaches and parameters for memory enhancement have yet to be determined. On a more fundamental level, it remains elusive as to how delivering electrical current in a given brain area leads to enhanced memory processing. Starting from the local and distal physiological effects on neural populations, the mechanisms of enhanced memory encoding, maintenance, consolidation or recall in response to direct electrical stimulation are only now being unravelled. With the advent of innovative neurotechnologies for concurrent recording and stimulation intracranially in the human brain, it becomes possible to study both acute and chronic effects of stimulation on memory performance and the underlying neural activities. In this review, we summarize the effects of various invasive stimulation approaches for modulating memory functions. We first outline the challenges that were faced in the initial studies of memory enhancement and the lessons learnt. Electrophysiological biomarkers are then reviewed as more objective measures of the stimulation effects than behavioural outcomes. Finally, we classify the various stimulation approaches into continuous and phasic modulation with an open or closed loop for responsive stimulation based on analysis of the recorded neural activities. Although the potential advantage of closed-loop responsive stimulation over the classic open-loop approaches is inconclusive, we foresee the emerging results from ongoing longitudinal studies and clinical trials will shed light on both the mechanisms and optimal strategies for improving declarative memory. Adaptive stimulation based on the biomarker analysis over extended periods of time is proposed as a future direction for obtaining lasting effects on memory functions. Chronic tracking and modulation of neural activities intracranially through adaptive stimulation opens tantalizing new avenues to continually monitor and treat memory and cognitive deficits in a range of brain disorders. Brain co-processors created with machine-learning tools and wireless bi-directional connectivity to seamlessly integrate implanted devices with smartphones and cloud computing are poised to enable real-time automated analysis of large data volumes and adaptively tune electrical stimulation based on electrophysiological biomarkers of behavioural states. Next-generation implantable devices for high-density recording and stimulation of electrophysiological activities, and technologies for distributed brain–computer interfaces are presented as selected future perspectives for modulating human memory and associated mental processes.

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Challenges of probing declarative memory with direct brain stimulation

Our ability to form, store and recall declarative memories has been one of the most challenging functions to map and modulate in the human brain. Unlike the implicit types of memory for motor skills, habits or emotional responses, which can be localized and treated in specific cortical, thalamic and basal ganglia regions,[1] explicit memory functions are distributed across widespread sensorimotor, limbic and executive networks. Declarative memory involves multiple complex cognitive functions (Box 1) but minimally requires the encoding and conscious recollection of unique episodes or general facts, involving multisensory representations in specific contexts of time and space. This function requires engagement of complex physiological processes across several levels of brain organization—from single cells to local assemblies and large-scale distributed networks—in multiple cortical and subcortical brain regions. Intracranially implanted (i.e. invasive) electrodes provide a rare but powerful opportunity to probe the role of specific regions in declarative memory and other cognitive functions.[10–14] Direct electrical stimulation (DES) using these intracranial electrodes can test causative roles of distinct anatomical targets and physiological processes in modulating human declarative memory performance.

Mapping the brain regions involved in processing declarative memories sounds easier than it actually is. The classic reports of subjective recollection or 're-experiencing' specific episodes from the past during intra-operative DES,[15,16] identified sparsely distributed locations of the effective stimulation sites across associative cortical areas. A recent thorough investigation of cortical DES[17] showed that such complex subjective responses are less frequent and less consistent than simple sensory or motor responses that are commonly localized in the clinical setting of cortical mapping. This important study showed that memory-related phenomena could be elicited by stimulating cortical areas of the limbic and

Box 1 The complexity of memory functions

Which memory function should be targeted by DES? Traditionally, declarative memory processes have been separated into memory encoding, storage (or maintenance), consolidation and retrieval. These processes are likely to depend on very different and possibly even opposing neurophysiological processes,[2–4] which may lead to interference between encoding and retrieval.[5] Thus, a DES pattern that improves initial memory formation (encoding) may actually impair consolidation and/or retrieval. One possibility to overcome this problem is asking the patient to intentionally select whether they want to encode or retrieve information in a given setting. Alternatively, some external information may be used to select the memory 'mode' that is most likely relevant in a given situation (e.g. enhance encoding during explorative behaviour and movement, facilitate retrieval during rest and boost consolidation during sleep).

A further level of complexity is that declarative memory is only very crudely conceptualized as a pure storage device but needs to enable flexible access to specific aspects of an episode (e.g. either its perceptual or its semantic aspects). Furthermore, memories need to be connected and integrated to usefully guide behaviour; a mere collection of disconnected individual episodes is not particularly helpful, but they should be organized into hierarchical knowledge structures. This also implies that memories should undergo transformations, in particular semanticization.[6,7] DES may attempt to support such memory transformation processes, e.g. by strengthening semantic representational formats in memory. A challenge is that this may come at the expense of reduced memory for perceptual details.

Not every event we encounter should be stored in memory. Not only do we want to filter out irrelevant details, but also be able to forget emotionally distressing events. The relevance of this 'positivity bias' for mental wellbeing—which may occur at the level of encoding, consolidation or retrieval—has often been described. And if unwanted information has been encoded, it is often still possible to purge it from our memories through deliberative and intentional forgetting.[8] Inhibitory control over memory is highly relevant for mental health,[9] but how it should be considered in DES for memory remains an open question. Modulation of the higher order executive brain functions is one possibility.

Finally, it is still an open question as to how we measure an improvement of memory outside of the laboratory, i.e. when stimuli are not experienced one after the other but in a continuous stream, and often actively sampled by our goal behaviour. Which events does a person in this natural environment even want to remember? An ecologically valid measure of memory and its impairment may be to use experience sampling methods such as mini-surveys or self-reports, and to inquire how often patients experienced subjective memory failure. This can be done concurrent with the new technologies for continuous recording and stimulation (see also the 'A new perspective for modulating memory and cognition' section) that are even capable of automatically inquiring cognitive states based on neural activity biomarkers (see also the 'Biomarkers of neuromodulation' section).

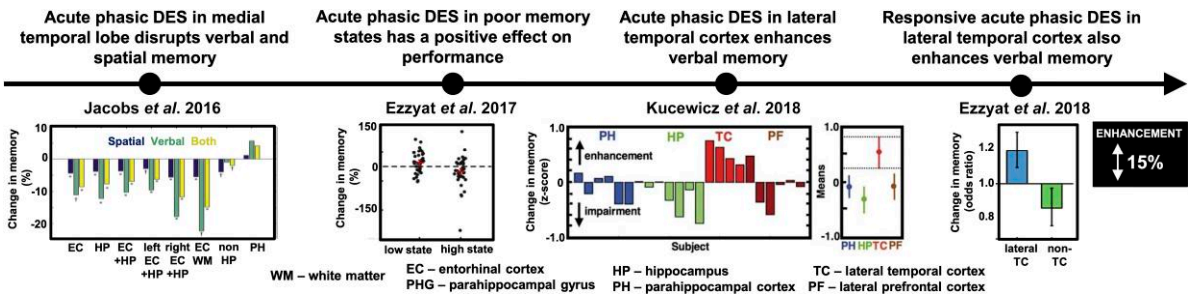

Figure 1 Summary of key findings from the Restoring Active Memory multi-site collaborative project (RAM). First of all, the project failed to replicate the positive effects of DES in mesial temporal lobe structures and found that stimulation in this region in many cases actually impairs verbal and spatial memory. Second, DES applied during predicted poor memory states had a beneficial effect on memory. The beneficial effect was selective to stimulation in the lateral temporal cortex. Third, responsive (closed-loop) DES in that brain region during poor memory states resulted in the same magnitude of memory enhancement (~15%) as non-responsive (open-loop) stimulation. Adapted from Jacobs *et al.*,[32] Ezzyat *et al.*[25,67] and Kucewicz *et al.*[24]

salience networks. Notably, hippocampal electrodes were not stimulated in this study.

While this study shows that higher cognitive functions such as declarative memory rely on distributed networks rather than individual brain regions, DES is not confined to focal effects either but is thought to elicit widespread brain responses. In fact, even microstimulation preferentially activates widely distributed neuronal assemblies more than local cell populations in the immediate vicinity of the stimulating electrode.[18] The electrophysiological responses to DES have recently been more systematically studied in the human brain,[19–22] confirming both local and distal effects of macro-electrode stimulation. DES-induced changes in the spectral activities were observed both close to the stimulation site on the neighbouring electrode contacts (4–10 mm) and away in remote cortical areas (>10 cm away). Still, even these recent studies that used the same experimental dataset found various and often opposite effects in neural activities of particular frequencies of the human intracranial EEG (iEEG) spectrum, revealing challenges for consistent signal processing and data analysis. The effects of the frequency or amplitude of the stimulation current or the proximity to the white matter tracts[23] are also subjects of pending debate. Eliciting consistent neural responses in particular iEEG frequency bands, for instance theta or gamma, would be pivotal for predicting the effects on memory processing. The recent studies prove how challenging it is even to determine the most effective parameters of current frequency or amplitude to obtain a desired effect on the iEEG activities underlying successful memory performance.[21,22,24,25]

One would imagine that electrical stimulation of a given patch of the cortex consistently elicits the same neurophysiological and behavioural responses every time it is applied. In practice, however, DES evokes a complex response of the underlying neural networks that is reflected in heterogeneity of the neural, cognitive and behavioural effects,[26] even in the case of simple sensory or motor functions. This variability may derive from a number of different factors. First, the excitability of the stimulated brain region may undergo substantial fluctuations,[27,28] which was found to be reflected by the phase of ongoing low-frequency oscillations (in particular, in the theta frequency range[29]). These local excitability fluctuations may, however, be driven in remote areas that process variable degrees of attentiveness, drowsiness or task engagement. Second, physiological activity patterns in single brain regions may reflect different variables depending on current goals, an effect known as 'mixed selectivity'.[30] Finally, effects of repetition suppression (or repetition enhancement) may lead to sparser (or more pronounced, respectively) responses due to changes in the tuning functions of individual neurons or neural assemblies.

If predicting the electrophysiological responses to DES is challenging enough, then how much more unpredictable are the cognitive and behavioural outcomes? This was clearly demonstrated in the case of mesial temporal lobe stimulation to modulate spatial memory performance. Positive effects that were originally reported in a pioneering study with six epilepsy patients[31] failed to be reproduced in a similar behavioural paradigm with a larger group of patients,[32] despite an overall match of the anatomical location as well as the parameters of stimulation. Precise anatomical location, including proximity to white matter tracts, were proposed as a key factor for predicting the effects on memory performance[23,33,34] along with others that may account for inconsistencies observed across the early studies.[34–36]

Most of the early studies reported the behavioural effects either in individual cases[37–39] or small groups of patients,[31,40–50] where significant effects of DES were found only in some individual patients or on a group level—often inconsistent across studies. The need for more robust and reproducible results can be addressed with larger multicentre studies. One of the first such studies yielded breakthrough data (Fig. 1) showing a robust positive effect of DES in the lateral temporal cortex on verbal memory performance observed both on the level of single patients and the group.[24] This effect was confirmed in the same project using a closed-loop stimulation approach with another group of patients.[25] Thus, two studies with ~50 patients altogether showed consistent effects of DES in the lateral temporal cortex but not the other brain regions, including the hippocampus. Surprisingly, however, a positive effect in a similar paradigm was subsequently reported with analogous stimulation in the hippocampus.[51] Hence, even though increasing the study size makes the results more robust and reproducible across large studies, it may not necessarily generalize to other smaller studies.

More studies have been conducted with non-invasive brain stimulation methods (Box 2) to modulate memory functions. These, however, were also challenged by the issues of mixed effects, lack of consistency and heterogeneity of the study designs and stimulation paradigms.[36,57–59] A systematic review of the studies confirmed moderate effects limited to working, episodic and procedural memory.[60] One recent study showed a 10–20% enhancement in verbal memory,[61,62] which was in the same range of magnitude as the DES studies.[24,25] Duration of the stimulation-induced performance in these was limited to only acute immediate effects. A more recent study has shown promising

Box 2 Overview of non-invasive brain stimulation approaches

The most prominent non-invasive brain stimulation methods that could be applied in humans are transcranial magnetic stimulation (TMS), transcranial electric stimulation and, more recently, focused ultrasound. In addition, vagus nerve stimulation is a semi-invasive method that has been applied in several psychiatric diseases as well as in pharmacorefractory epilepsy patients with contraindications for resective surgery (e.g. because of bilateral hippocampal lesions).

TMS and transcranial electric stimulation can be either used to excite or to inhibit brain regions, depending on stimulation parameters. Both of them have relatively limited penetration depth, i.e. they are limited in their abilities to target deep brain regions such as the hippocampus. However, some attempts in this direction have been made, and it is possible to non-invasively enhance cortical-hippocampal networks and memory performance, as shown in a study using TMS to parietal regions to exert indirect influences on hippocampal activity and function.[52]

While it has been argued that TMS effects are relatively artificial because of the large magnetic fields that are induced, transcranial electric stimulation may be more physiological. This is particularly the case for transcranial electric stimulation with alternating (oscillatory) currents, i.e. transcranial alternating current stimulation. Transcranial alternating current stimulation may be selectively effective by increasing endogenous subthreshold oscillations, a mechanism known as 'entrainment' (for a review, see Hanslmayr *et al.*[53]).

In addition to these relatively established methods, a more recent approach consists in the delivery of ultrasonic stimulation via focused ultrasound; for a recent review, see Sarica *et al.*[54]). Again, depending on stimulation parameters, focused ultrasound may be both excitatory and inhibitory; in addition to its application at high intensity for resective surgery, low-intensity focused ultrasound can be safely used to exert reverse effects on brain functioning[55] and may be a potential treatment option for memory dysfunction in Alzheimer's disease.[56]

results of chronic effects with a non-invasive stimulation[63] (see also the next section, 'Biomarkers of neuromodulation').

Biomarkers of neuromodulation

To reliably predict the behavioural effects of DES, one would first need validated biomarkers of cognitive processes that may be targeted via neuromodulation. The large study on memory DES described before correlated the effects of stimulation on memory performance and on iEEG activities in the gamma frequency range induced by memory encoding at specific sensory and associative cortical locations.[64] Positive modulation of gamma power with DES in the lateral temporal cortex, i.e. more power when stimulated, was associated with improved memory performance, whereas negative modulation with DES in the mesial temporal lobe, i.e. less power when stimulated, correlated with memory impairment. These results were congruent with the opposite effects of DES in the two structures,[24,25,32,65,66] revealing a positive and a negative neuromodulation, respectively (Fig. 1). It should, therefore, be possible to predict the behavioural outcomes of DES based on its effect on iEEG activities (i.e. gamma power). On the other hand, it may be possible to deliver stimulation during less beneficial states and thereby modify these brain states into more beneficial states. This approach was taken in several previous studies, which first used pattern classification analyses to identify biomarkers of memory formation and then stimulated in trials showing poor-functioning states.[25,67,68] In these studies, DES (charge-balanced, square-wave stimulation at 50–200 Hz, 0.3 ms pulse width and 1.0–3.0 mA amplitude) applied when stimuli were presented for encoding during identified poor states improved recall performance in the task. Even though the behavioural effects were only moderate, these pioneering studies set a new standard for using machine-learning tools to validate iEEG biomarkers and identify optimal time points for DES.

Previous smaller studies described particular electrophysiological activities that were modulated by DES without validating a possible biomarker. For instance, enhanced performance in a spatial memory task observed with DES in the entorhinal cortex was associated with resetting of the iEEG theta rhythm in the hippocampus.[31] Hippocampal stimulation that enhanced performance in a verbal memory task was found to modulate iEEG power of the hippocampal theta rhythm.[51,69] Amygdala stimulation, which led to improved memory for images, modulated theta and gamma iEEG coherence and phase-amplitude coupling between the mesial temporal lobe structures.[70] Other studies showed evoked responses, which may correspond to low-frequency power increases and/or phase resetting, or general activation of a distinct brain region in response to effective DES.[38,40,43,44] None of these studies, however, demonstrated a causal relationship between a neural activity and modulation of behaviour, e.g. through an intervention that would specifically target the activity and cause either an enhancement or an impairment in memory performance, which would be needed to validate an electrophysiological biomarker predictive of both positive and negative effects of DES.

More direct evidence for the causal relationship is provided by targeting a neural activity pattern with DES and predicting behavioural outcomes. One of the first such studies tested the effect of synchronous stimulation of two connected mesial temporal lobe structures on memory performance in an attempt to enhance a previously observed connectivity marker of successful memory formation.[42,71] The study found a trend for better memory performance with in-phase stimulation between the structures than with sham or anti-phase stimulation. Although there was no significant memory enhancement, the study pioneered a heuristic approach to testing the effects of DES. A similar approach to synchronous stimulation of the prefrontal and parietal cortical regions was associated with memory enhancement.[72]

These studies suggest that targeting a specific iEEG biomarker of memory processing may be more effective than trying to enhance memory functions only at a level of the observed behavioural change. Physiologically induced activities during memory encoding were specifically used as a target for DES timing and parameter settings to mimic or boost endogenous iEEG activities.[37,64,73–75] On the other hand, responding to a biomarker may also result in a neural effect without any observable behavioural counterpart, in particular if the biomarker is not highly specific for memory functions. In

fact, a recent study showed a modulation of event-related potentials in a specific subregion of the hippocampus without an effect on task performance.[76] Thus, the therapeutic potential of targeted amplification or entrainment remains to be clearly demonstrated in case of intracranial studies.[53]

Another way to test the causal relationship between ongoing brain states and DES effects could be to trigger presentation of the encoded stimuli to the phase of an ongoing neural oscillation.[77] Although electrical stimulation is not involved, this biomarker approach has been repeatedly adopted in targeted memory reactivation studies during sleep, i.e. presenting cues that had been paired with stimuli during previous learning stages during specific phases of slow waves.[78] However, this approach may be less feasible during memory formation or retrieval in real-world settings, where the exact timing of stimuli to be encoded or the occurrence of retrieval cues is typically difficult or impossible to control.

While the timing of stimuli may be difficult to control in ecological settings, a more feasible strategy may be to trigger the timing of DES to specific biomarkers; we now have the tools to trigger and test DES in response to neural activities, which can be analysed in real-time and in a closed loop of sensing and stimulation. This is one example of 'responsive' DES, in which a response in the form of stimulation at particular parameters is controlled by feedback from real-time biomarker analysis. Closed-loop responsive stimulation can be a powerful tool for validating an iEEG biomarker and testing the putative physiological mechanisms of DES modulation of memory processing. The biomarker first needs to be reliably detected together with particular memory processes, then it has to be robustly induced by DES at specific parameters; finally, it should ideally be consistently modulated together with memory performance.[79] This principled approach assumes that DES-mediated modulation of memory functions works by inducing the physiological iEEG activities underlying memory processing.[37,80] However, recent studies of iEEG activities induced by various parameters or patterns of passive DES outside of any cognitive task[19–22,81] reveal a more complex picture. DES applied at particular frequencies and amplitudes may either induce or suppress neural activities across a range of iEEG frequencies and anatomical locations. For instance, DES at gamma frequencies can actually decrease the power of iEEG activities in the gamma range and at the same time increase the power in the theta range.[22] There is variability in these passive responses between studies, not to mention the variability between specific cases, as discussed before. Lack of a reliable biomarker may be part of the reason for only moderate effects of biomarker-driven stimulation compared to a non-responsive open-loop DES approach,[24,25] which does not use feedback from the neural activities. Closed-loop, biomarker-driven, real-time responsive DES that would outperform simple open-loop stimulation remains yet to be clearly demonstrated. Without validated biomarkers, responsive DES is challenging and difficult to interpret or optimize.

So far, neither the mechanisms of stimulation nor the neurophysiological basis of biomarkers have been fully elucidated, even for the classic clinical application of deep stimulation in the basal ganglia for movement disorders.[82–85] Given the complexity of the immediate acute responses that often cannot be expressed with the conventional concepts of neural excitation or inhibition, the term 'neuro-modulation' was proposed to express lasting network effects of stimulation.[86] There is a growing body of literature about the effects of stimulation on the molecular, cellular and behavioural levels.[87] Still, we are only beginning to understand the physiological mechanisms of stimulation and of the biomarkers that should ideally be used to evaluate the effect of stimulation on the level of neural networks. Further research on these questions will be key to understanding and developing new applications for treating specific brain functions. Arguably, even classic deep stimulation in basal ganglia could then be more effective in treating movement disorders, not to mention cognitive deep brain stimulation (DBS) approaches such as those used to enhance memory functions.[88,89]

Various approaches to neuromodulation

There are multiple approaches to modulate memory processing. Closed-loop stimulation triggered by online analysis of iEEG signals is but one example of responsive, i.e. biomarker-driven approaches. The non-responsive DES in an open loop, where the stimulation is applied at fixed times of cognitive processing or continuously, does not require online biomarker analysis. It can still take advantage of iEEG signal analysis such as in case of the multi centre study,[24] which determined the anatomical targets and parameters of stimulation before an experiment based on offline analysis during task performance without any stimulation. During the experiment, the location (a pair of electrodes in a brain region that showed memory-related spectral power changes) and the parameters of the electrical current (frequency, amplitude, pulse width and duration that induced the largest iEEG response) were fixed and DES was triggered at predefined times of memory encoding. These were changed, however, after each experiment based on offline biomarker analysis. Even though it was not a responsive closed-loop stimulation *per se*, the approach benefited from the offline biomarker analysis. In the end, the magnitude of the resultant positive effect of open-loop DES on memory performance was like the one obtained in the follow-up study with DES applied in a closed loop.[24,25] Therefore, the effect of brain stimulation may be robust to various stimulation approaches, where responsive DES is just one example in a range of effective approaches to modulate memory processing.

Most of the previous studies that reported a positive effect of DES on memory functions were not employing responsive stimulation (Table 1). Many of the initial reports applied electrical current in a particular brain target continuously in time and at fixed parameters.[38–40,42,44–47,93] This most basic type of stimulation can generally be classified as 'continuous', in which electrical current is delivered at fixed parameters continuously in time, in contrast to 'phasic' approaches with current delivered only at discrete times, i.e. phasically. The phasic approaches can use both open and closed loop of stimulation, where the former is non-responsive with no need for online signal recordings and the latter is responsive on the basis of feedback analysis of the recorded signals and biomarkers. Closed-loop analysis is typically performed in real-time to close the loop with minimal delays, but the feedback from the analysis can extend over longer periods of time. Extending the loop is especially needed for analysis of longer stretches in recorded data or when intensive computations are required. One good example is seizure prediction and forecasting[94,95] that uses a long history of, for example, circadian rhythms in the recorded signals to perform classification analyses for estimating the probability of seizure occurrence at a present time (prediction) or in future (forecasting).[96–98] All in all, it could still theoretically be categorized as a closed-loop responsive stimulation, since DES would ultimately be delivered in response to analysis of the recorded signals—just delayed in time. The various scenarios of closing the loop for a responsive stimulation are summarized in Fig. 2, together with

Table 1 Basic classification of DES approaches applied for modulation of memory and cognitive functions

Category	Mode	Responsive?	Example use	Example study
Continuous	Chronic	No	DES permanently switched ON	Hamani *et al.*[38] Laxton *et al.*[44] Troster *et al.*[90]
Phasic	Chronic	No	DES switched ON manually during active cognition	Fell *et al.*[42] Koubeissi *et al.*[40] Miller *et al.*[43]
Phasic	Chronic	Yes	DES switched ON by automated state detection	Bergey *et al.*[91] Nair *et al.*[92]
Phasic	Acute	No	Open-loop DES triggered by a cognitive event	Suthana *et al.*[31] Inman *et al.*[70] Kucewicz *et al.*[24]
Phasic	Acute	Yes	Closed-loop DES triggered by feedback from brain activities	Ezzyat *et al.*[25] Hampson *et al.*[74]

Adaptive stimulation is not classified separately here as it is more general and can use several of the listed stimulation approaches.

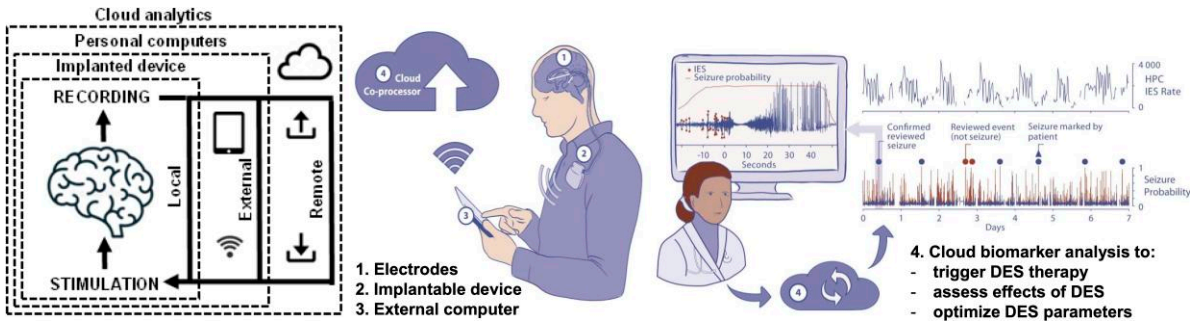

Figure 2 Example of adaptive DES based on continuous recording and data analysis distributed in closed loops of feedback response. Schematic diagram of possible scenarios for responsive stimulation in three closed loops of gradually more distributed and externalized brain–computer interface settings (left). An example of a closed-loop extension of data processing from an implanted device to distributed co-processing on external computer and cloud analytics of electrophysiological biomarkers (right). In this particular example, epileptic activities are automatically detected with machine-learning tools in the iEEG recordings streamed for cloud analytics. This provides biomarkers for adjusting the brain stimulation therapy for epilepsy and its comorbidities, including deficits in memory, cognition and mood. Adapted from Sladky *et al.*[112]

distribution of feedback analysis to local and remote computations. Hence, responsive stimulation can be implemented at a range of timescales and technical solutions for closing the loop.

Included in this basic proposal for categorization of the approaches is another distinction between acute and chronic modes of delivering electrical current. In the acute mode, which is typically applied in a laboratory or clinical environment, DES is only delivered on demand for a set period of time. This again can be very brief during a particular cognitive process such as memory encoding or recall of the open- or closed-loop stimulation (Table 1), which typically have short timescales even though they involve complex and even opposing interactions (see Box 1). Alternatively, stimulation can also extend over a wider time frame of intense vigilance and cognitive activity such as during office hours, regulated manually or adjusted automatically. An example would be switching the stimulation ON at work or at school and OFF during all the other periods of quiet wakefulness, resting and sleep or vice versa targeting a different consolidation process during sleep. In contrast, the chronic mode, which is typically applied outside of the laboratory or clinical environments, is defined as maintaining a given DES approach over extended time. Notice that both phasic and continuous categories of DES approach can be applied in the acute or chronic mode (Table 1). A responsive closed-loop DES (type of approach) can only be acutely switched on during active wakefulness or only at sleep to modulate sleep-dependent memory consolidation. It can also be chronically switched on—the category of stimulation is still phasic (not continuous) and the type is responsive but applied in a chronic mode. An example of this approach would be responsive stimulation triggered by seizure detection to improve patient's quality of life and general cognitive functioning as well (third row in Table 1).

Despite these versatile possible implementations of DES, clinical trials of safety and feasibility for improving memory and cognitive functioning have so far predominantly used continuous chronic stimulation. One study employed DES in the fornix of the hippocampus and tested the effect on various neuropsychological measures of declarative memory functions in Alzheimer's disease patients.[44,99,100] Another study targeted nucleus basalis of Meynert in Lewi body dementia,[101–104] Although these trials resulted in interesting observations such as DES-induced flashbacks[105] or even significant improvements in single cases,[106] there were no consistent long-term effects on memory performance with that type of stimulation. More consistent effects on cognitive functions were reported in other large longitudinal studies of responsive stimulation. For instance, a study of long-term responsive hippocampal stimulation for epilepsy treatment reported

improved cognitive functioning tested in neuropsychological assessments over multiple years of the DES therapy.[91,92] In this case, however, DES was targeted at the pathophysiological activities of epilepsy, hence the effects on memory and cognition could have been a secondary indirect effect such as in another large study of continuous DES of the anterior nucleus of the thalamus.[90,107] Safety and efficacy of phasic stimulation types targeted specifically at the cognitive functions remain to be demonstrated in pending clinical trials. Responsive DES driven by neural biomarkers of electrophysiological activities holds promise for more robust and reproducible results and more insight into the underlying neural mechanisms.

Even though it is possible to implement the various stimulation approaches into the non-invasive methods (see Box 2), including the responsive stimulation, it is more challenging to record and analyse the brain activities from the scalp EEG, magnetoencephalography or vagus nerve signals. The data quality of these signals in terms of the (i) signal-to-noise ratio; (ii) ability to record from deep brain regions and (iii) sensitivity to high-frequency signals is superior with direct techniques using invasive electrodes. Furthermore, invasive DES is more powerful than non-invasive transcranial alternating current stimulation/TMS, especially in case of the deep brain targets where amplitude of the non-invasive stimulation is strongly reduced with distance. There are also other, more practical issues to consider such as the recording equipment for sampling non-invasive signals, which is not easily wearable outside of the experimental setup. Compared to fully implantable invasive devices, the non-invasive scalp EEG electrodes or magnetoencephalography magnets are typically not adequate for applications beyond the laboratory setup. There are practical limitations to using the non-invasive recording and stimulation methods for studying the mechanisms and for modulation of memory functions acutely during experimentation and chronically in everyday life performance.

A new perspective for modulating memory and cognition

The responsive DES studies for epilepsy management revealed an important insight into a possible mechanism for improving memory and cognition. Patient performance in cognitive tasks was progressing together with the therapeutic effect of DES on epilepsy. Hence, the positive effects on cognition could be achieved by alleviating the pathophysiological activities of epilepsy and/or by modulation of physiological memory processes. Chronic recordings from a recent study with repeatedly taken memory tasks showed clear correlations between a gradually decreasing rate of seizures and a gradually improving task performance in response to optimizing therapeutic parameters of DES.[108]

These results suggest a strategy to DES that is alternative to entrainment or to the attempts to mimic a physiologically occurring activity pattern described before. Instead of improving or boosting relatively physiological activities underlying memory processing, it may be more promising to target pathological activities that interfere with cognitive functions or to modulate malfunctioning memory processing. Restoration of memory functions may, therefore, be due to alleviation in pathophysiology or due to stimulation-induced counteraction of a detrimental brain state unrelated to any brain disorder. This logic is congruent with an assumption that it is more feasible to restore a malfunctioning process than to enhance a properly functioning one. It was found that DES is more likely to have a positive effect when applied in a state of 'poor' than in a state of 'good' memory encoding as predicted by iEEG spectral activities.[64,67] In other words, DES can work more effectively by tuning or rescuing suboptimal states of memory processing than by modulating or stabilizing the ones that are already close to optimal. Either way, biomarkers of neural activities are required in both strategies to trigger the timing, adjust the parameters and/or change the pattern of DES by monitoring its immediate and long-lasting effects. A good example is provided with activities in the beta frequency range induced in the posterior brain regions by non-invasive stimulation in the anterior prefrontal areas.[62] The posterior beta activities served as a biomarker of the positive effect, despite not necessarily reflecting the activities underlying successful memory formation *per se*. Such biomarkers can be used over time to assess and adjust DES for optimal performance.

This leads us to the concept of adaptive stimulation. It can be generally defined as intelligent and flexible stimulation adjusted by biomarkers of neural activity. The main feature that makes it different from the classic stimulation approaches summarized in Table 1 is the ability to adapt over time, as the name implies, based on the history of biomarker analysis. It is different to a classic implementation of responsive stimulation, which is driven by biomarker analysis but is not adapted over time based on the history of outcomes. Therefore, it can be regarded as a special case of responsive stimulation with adaptation of parameters over time. One of its first applications was in the DBS therapy for Parkinson's disease.[109,110] In this particular example, pathological oscillations in the beta frequency range serve as the biomarker for modulating motor functions. Notice that here the stimulation is also not targeting the healthy physiological processes of movement generation to boost their underlying neural activities, but instead focuses on eliminating pathological beta oscillations that possibly interfere with the physiological processing of movement generation. In the original implementation of adaptive stimulation, the pathological beta oscillations are detected in the recorded signal to inform the location and timing of therapeutic DES. These can be adjusted online on the basis of immediate local analysis or offline based on long-term recordings streamed wirelessly from the implanted device. The former (i.e. immediate local analysis as in[111]) could be conceived as a special case of responsive stimulation, since the parameters are adjusted immediately on the implanted device; the latter (i.e. long-term offline analysis as in[108]) require integration to other computer devices or cloud environments for more intensive analysis[112,113] (Fig. 2), which enables adapting the parameters based on a long history of stimulation outcomes that is too large to be stored on the implanted device. Distributing data storage and analytics over to online resources opens limitless opportunities for dense tracking and modulation of neural activities and behaviour[114,115] as outcome measures to be compared across time. In Parkinson's patients[111] and more recently also in epilepsy,[116] this biomarker-based approach provides arguably the first 'proof-of-concept' evidence of successful application of adaptive brain stimulation.

In terms of memory and cognition, such technology now enables chronic, real-life tracking of a wide range of iEEG spectral activities that accompany memory processing and behaviour.[117–120] Compared to epilepsy or movement disorders, the target location and neural activities during memory processing are more difficult to determine as they are dynamic in time and distributed across the brain.[118,121–123] The spatiotemporal dynamics typically involve a wide spectral frequency range of neural activities sampled from multiple implanted electrodes in various brain regions, which

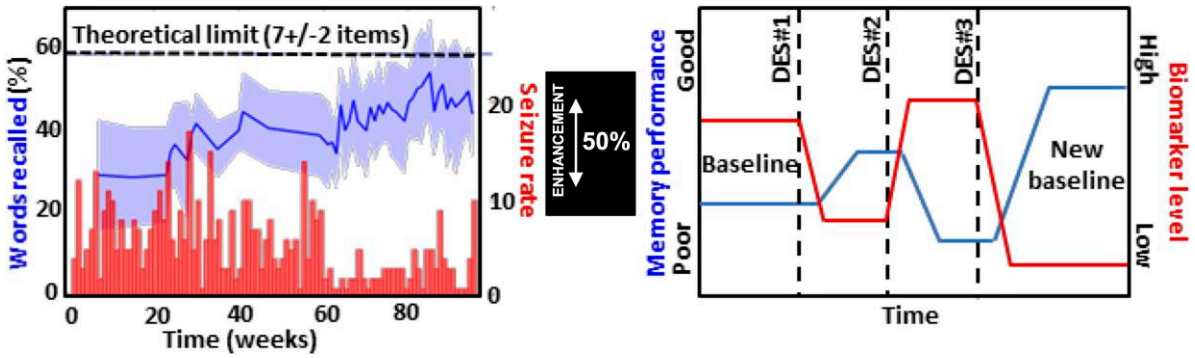

Figure 3 Long-term adaptive modulation of memory performance based on chronic continuous recordings of biomarker neural activities. In this particular example, the memory performance and the biomarker are quantified as the mean number of words recalled in a verbal memory task and the rate of electrographically detected seizures, respectively. DES with electrical currents at low or high frequency was used for a period of up to 2 years. The study showed an overall enhancement in verbal memory performance of ~50% and different effects of the two stimulation types. The model on the right summarizes an example profile of biomarker and behavioural responses to three different DES patterns with the former preceding the latter. Adapted from Marks *et al.*[135]

requires intense automated multi-channel analyses of the recorded signals. Particular electrode leads and activities thus have to be identified for DES on the basis of biomarkers of particular neural activities. Once established, these provide features for fully automated machine-learning classification,[124] which can be run in a closed loop on distributed external devices or in virtual cloud environments (Fig. 2). Exploring the large space of possible DES parameters to determine optimal settings can likewise be done by automated computational methods[125] on the basis of desired biomarker outcomes (if known). In this manner, the choice of particular electrode locations, parameters of the electrical current and DES timing has to be managed automatically using various intelligent data-driven tools to efficiently find optimal solutions. Such algorithms would determine the optimal parameters on the basis of the history of recordings and the effects on the biomarkers and behaviour. Otherwise, manually determining the parameters for modulation of cognitive processes becomes too time-consuming and elusive, given their dynamic nature in time and anatomical space and a variety of underlying neural activities.

This flexible adjustment of the locations and parameters of DES to find optimal settings over time is the defining feature for the concept of adaptive stimulation. The responsive stimulation approach is fixed on a set of parameters without longitudinal assessment of the outcome history of the stimulation settings. Adaptive stimulation compares the outcomes of various DES parameters to find the optimal setting. Hence, in principle, it can use other types of brain stimulation such as non-responsive open-loop or even continuous DES, as long as the biomarker outcomes of these are compared across the parameter sets. In its simplest form, it can use continuous DES at particular parameter sets that are fixed for a period of time and evaluated on the basis of the history of recordings and off-line manual expert analysis of biomarkers without any automated biomarker analysis. This is very similar to the continuous approach that is used for adjusting the DBS parameters for movement disorders or epilepsy during out-patient hospital visits, but with the critical difference that in the classic DBS therapy the parameter adjustment is made with no consideration of the long history of electrophysiologic recordings. In this classic case, the adjustment is made predominantly based on the patient's subjective report of symptoms and neurological exams. The defining feature of adaptive DBS would be the consideration of the history of electrophysiological recordings and of biomarkers such as epileptic discharges or pathological beta oscillations to guide the selection of optimal parameters. Thus, adaptive stimulation is not a new type of DES but rather a more general and flexible approach than the ones summarized in Table 1, which can use any combination of those to modulate brain functions.

Adaptive stimulation of the anterior nuclei of the thalamus provides a pertinent case study for chronic modulation of memory and possibly other cognitive functions related to attention or mood.[126] This deep anatomical structure has become an attractive target originally for epilepsy management[127] and, more recently, also for modulating memory and cognition.[128–134] It was shown that continuous stimulation of this structure leads to improvements in memory task performance.[93] Longitudinal follow-up studies from a clinical trial of continuous stimulation for epilepsy management reported beneficial effects on cognitive functions assessed in periodic neuropsychological testing.[90,107] Hence, the anterior thalamic nuclei became an attractive target to study and test the effects of DES on chronically implanted patients. Repeated probing of memory performance and the underlying neural activities with DES is now possible with the current technology at an unprecedented timescale of months and years. Continuous recording of neural activities and simultaneous assessment of behavioural performance revealed a strong effect of DES in anterior nuclei of the thalamus on electrophysiological activity and verbal memory, i.e. significant changes in the theta power and parallel improvements in the number of remembered words of up to 50% relative to the baseline.[108,135] Specifically, a performance of roughly four remembered items was changed to an average of six items in response to anterior thalamic stimulation (Fig. 3). Duration of this improvement was observed on the scale of 1 year, compared to 1 month reported in the most recent study using non-invasive transcranial electrical stimulation.[63] This powerful effect of adaptive modulation in the anterior nuclei of the thalamus correlated with (and was possibly driven by) reductions in epilepsy pathophysiology as well as with modulation of physiological biomarkers of anterior thalamic-hippocampal interactions that were induced by memory processing.[135] Such biomarkers are ideally suited for long-term adaptive DES targeting both epilepsy pathophysiology as well as restoration of cognitive functions. In this particular example, a moderate-to-severe deficit in recall of verbal memory was restored across almost 2 years of stimulation to a normal performance, reaching almost the level typical for healthy participants (Fig. 3). DES with electrical currents

at low frequency (2–7 Hz) proved more effective in driving this effect over months of the adaptive stimulation therapy. The chronic nature of this DES-driven improvement is a major advancement compared to the more short-term effects of much lower magnitude reported in the previous studies.

This type of longitudinal recordings with adaptive optimization of stimulation based on objective biomarkers presents exciting perspectives for treating and studying disorders of memory and cognition. First of all, they are addressing basic research questions about the approach to improving memory and cognitive performance: is it better to tune or entrain a weak physiological process or activity that is about to fail, or rather to maintain and preserve a strong one that is likely leading to a successful memory outcome?[53,64,66,67,79,80] Alternatively, one could specifically interfere with pathological activities, e.g. related to epilepsy, that are detrimental to memory functions. Clinically, it is important to realize that the stimulation parameters and the timing that are optimal for controlling disease, such as epilepsy, may be different from optimal parameters for consolidating memory. This point highlights the possibility of multilead devices targeting different brain circuits and processes independently to optimally treat neurologic disease as well as associated comorbidities.

Second, the longitudinal recordings with adaptive DES open avenues for Big Data analysis of signals recorded continuously over months and years of daily lives. Supervised and unsupervised machine-learning tools will be indispensable for mining and interpreting the volumes of data that are already generated from the brains of implanted patients around the world. Deep-learning is another tool that can potentially be applied to linear iEEG signals. All this, in turn, will lead to development of new biomarkers and therapies that can be flexibly adjusted over time by human experts supported by insights from machine-learning tools. The entire process of adaptation could at some point be fully automated and driven solely by biomarker analysis. For example, fading attention and memory functions, as signalled by changes in biomarker features, would be automatically detected and trigger administration of memory testing or a specific DES treatment. The treatment would be determined from a large space of possible localization, timing and parameter options competing for selection by optimization algorithms. This is a highly multidimensional space that includes configurations of individual or multiple stimulating electrode(s) configurations, current amplitude, frequency and patterns of stimulation such as single-pulse, sine or square waves or complex waveforms. The algorithms as well come in various types and flavours. In other words, it would be a virtual *in silico* 'survival of the fittest' combination of parameters automatically probed and selected by the algorithms based on the optimal output response that can either be a change in memory performance or of an electrophysiological biomarker.

This analogy to the process of natural selection plays well with the concept of intelligent adaptation of DES based on the history of data recordings and adjustment of hypothetical future outcomes. With progress in neurotechnologies for probing and analysing the neural activities underlying memory and cognition, we will be entering into a new era of brain–computer interfaces for neural engineering of the human mind.[10,34,136] It would be a point of machine-learning literally encountering human learning at a neural interface. Such interfaces would be qualitatively different from the current ones employed for movement or speech generation, which arguably require skills that are already mostly learnt and thus less dynamic. The new interfaces for modulating dynamically changing memory processing will need to adapt continuously over extended periods of time. This adaptation would need to consider the changing brain states of wakefulness and sleep, and likely require continuous tracking of slow wave sleep, which is now possible from single intracranial electrode contacts.[137]

Conclusions

In the past 20 years we have seen an emergence of invasive and non-invasive studies to enhance memory performance. Most of them focused on acute effects of stimulation in relatively small subject numbers in a limited time frame, resulting in challenges for consistency and reproducibility of the findings. Larger clinical trials using continuous stimulation over extended time periods yielded limited effects on long-term memory performance. Despite impressive technological progress and a growing body of literature showing positive effects of DES on memory and cognitive functions, our understanding of the electrophysiological responses to stimulation tracked over extended periods of time is limited, partly because of the lack of appropriate tools.

In addition to these challenges on a neurophysiological and technological level, it is still an open question as to which patient populations may benefit the most from DES. Previous DES studies were either conducted in presurgical epilepsy patients or in patients with more or less advanced Alzheimer's disease. In patients with Alzheimer's disease, any interventions—be they based on DES or pharmacological treatments—are most promising when applied in very early or even preclinical disease stages. But then, conducting an invasive procedure in preclinical patients is problematic in general and would require very reliable and specific predictors of disease progression. The possibility of reversing advanced disease processes with brain stimulation is more questionable and remains to be demonstrated in patients.[138]

Nevertheless, important lessons have been learnt about principled approaches to modulating memory and cognition. There are many ways to stimulate the brain and modulate memory performance. Targeting specific neural activities that support or interfere with memory processing may be an effective strategy to achieve robust behavioural outcomes. Validating biomarkers of these activities is key to monitoring and optimizing new responsive DES approaches chronically. This is proving particularly useful for the new implantable technologies for chronic recording and stimulation. Adaptive DES emerges as an attractive approach for tracking and modulating the highly dynamic processes of memory formation. Chronic intelligent adaptation of DES based on personalized biomarker-driven analysis promises to deliver powerful and lasting therapeutic effects in not only neurological, but also neuropsychiatric brain disorders.[139–141]

We foresee that the new chronic biomarker approach to adaptive DES will drive further development in technologies for high-density multi-channel recordings that are capable of sampling large-scale electrophysiological activities, ranging from action potentials of neuronal assemblies to network oscillations across widespread neural populations. These technologies will inevitably produce large volumes of data that require automated machine-learning tools distributed over local and remote processing environments. The technological development will, in turn, open new opportunities for extending the loop of data analysis for responsive brain stimulation to the virtual environments of internet and cloud computations. It presents unprecedented advantages and possibilities for modulation and interfacing with memory and the associated cognitive processes of the human mind. The ensuing

neuroethical issues are already becoming a challenge to the 'brave new world' of DES for modulating human declarative memory.

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Competing interests

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