Deep Brain Stimulation for Disorders of Memory and Cognition

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Published online: 29 April 2014

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Abstract The next several decades will see an exponential rise in the number of patients with disorders of memory and cognition, and of Alzheimer's disease in particular. Impending demographic shifts, an absence of effective treatments, and the significant burden these conditions place on patients, caregivers, and society, mean there is an urgent need to develop novel therapies. Deep brain stimulation (DBS) is a neurosurgical procedure that is a standard-of-care for many patients with treatment-refractory Parkinson's disease, dystonia, and essential tremor. DBS has proven to be an effective means of modulating activity in disrupted motor circuitry, and has shown promise as a modulator of other dysfunctional circuits, including for mood and anxiety disorders. The deficits in Alzheimer's disease and other disorders of memory and cognition are also beginning to be thought of as arising from dysfunction in neural circuits. Such dysfunction may be amenable to modulation using focal brain stimulation. A global experience is now emerging for the use of DBS for these conditions, targeting key nodes in the memory circuit, including the fornix and nucleus basalis of Meynert. Such work holds promise as a novel therapeutic approach for one of medicine's most urgent priorities.

Keywords Deep brain stimulation · Alzheimer's disease · Memory · Cognition · Dementia

Introduction

Disorders of memory and cognitive function are increasing in incidence as several societies deal with the demographic reality of an aging population. At present, it is estimated that 25 million people worldwide are suffering from dementia caused by Alzheimer's disease (AD), with a predicted doubling in incidence every 20 years [1]. By 2040, the incidence of Parkinson's disease (PD)—in which dementia arises in 75 % of patients at 10 years and up to 87 % at 20 years [2]—will also have doubled [3]. The associated financial costs and burden of human suffering exacted by these illnesses will no doubt be immense. Unfortunately, considerable investigation into pharmacological approaches to AD and other dementing conditions has so far yielded few tangible breakthroughs.

Chronic, high-frequency, electrical deep brain stimulation (DBS) is a therapeutic technique that has been used for more than 30 years and has been proven to be effective in the treatment of movement disorders such as PD [4], essential tremor [5], and dystonia [6]. Novel applications of DBS in several neuropsychiatric disorders have also emerged over the last 10–15 years, including refractory depression [7], obsessive compulsive disorder [8], and anorexia nervosa [9], among others. It is estimated that over 100,000 patients worldwide have been implanted with DBS systems, with the rate of annual accrual increasing [10, 11]. The ability of DBS to modulate activity in neural circuits makes it an ideal approach to deal with disease-related dysfunction in networks responsible for cognition and memory [12, 13]. In this article, we briefly cover the basic therapeutic underpinnings of DBS, and then go on to review the limited—but exciting—preliminary

Electronic supplementary material The online version of this article (doi:10.1007/s13311-014-0275-0) contains supplementary material, which is available to authorized users.

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reported *in vivo* human experience with DBS in the setting of AD and other dementing disorders. We also touch on recent preclinical work addressing the structural effects of DBS, which may, perhaps, eventually play a role in slowing the progression of neurodegenerative dementias.

DBS: A Brief Review of Fundamental Principles

DBS involves the treatment of pathological brain states using continuous, direct electrical current, applied focally in a pulsatile fashion to neural elements, which may include dendrites, neuronal cell bodies, axons, glia, or some combination of these [14]. DBS typically influences several thousand such neural elements within a spatially focused region of the brain, differing from pharmacological approaches that exert greater brain-wide (and systemic) influence. Furthermore, unlike drug therapy or permanent lesioning procedures of the brain, DBS is reversible, adjustable, and titratable [15]. Modern DBS systems consist of intracranial stimulating leads with electrode contacts at their tips that are implanted into the brain using image-guided stereotactic neurosurgical techniques. DBS leads are connected via lead extensions to an implanted pulse generator typically seated in the chest wall immediately inferior to the clavicle. Stimulation parameters are programmed into the implanted pulse generator by a trained clinician using an external magnetic programmer. In typical DBS systems, there are four modifiable stimulation parameters: 1) amplitude; 2) frequency; 3) pulse width; and 4) electrode configuration (i.e., which contacts are active during stimulation, and which function as anodes or cathodes). Stimulation parameters are usually set in such a way as to optimize the electrical field within the target, while minimizing current spread to surrounding off-target structures, with the aim of achieving clinical benefit free of stimulation-related side effects.

The mechanisms of action underlying DBS are still a matter of debate and ongoing investigation. At the cellular level, DBS may affect the release of various neurotransmitters [16], while variably producing hyperpolarization or depolarization of neurons in the target zone [15, 17]. However, the longstanding belief that the net effect of these local mechanisms is to produce a reversible “lesion” of the target, with a corresponding net reduction in neural outflow, has evolved in recent years [15]. The current leading conceptualization is that DBS modulates pathological activity within various brain circuits by acting on specific nodes within these circuits—whether neuronal or axonal—that can be accessed by DBS leads [18]. Therefore, DBS may restore a predisease state of activity within these circuits, or, alternatively, replace pathological activity with a new therapeutic pattern [15]. Viewed from this perspective, DBS has the potential to affect regions of the brain upstream and downstream of the stimulation target, and therefore to counter the dysfunction occurring in

memory and cognitive circuits in AD and other dementing conditions. It is worth emphasizing that DBS is primarily a symptomatic therapy and there is no in-human evidence that it has a disease-modifying effect either in patients with cognitive disorders or any in other neurological condition. That being said, by selectively targeting specific neural circuits, DBS is much less likely to cause brain-wide or systemic side effects which can often limit the effectiveness of conventional drug therapy.

At present, there is US Food and Drug Administration approval for the use of DBS to treat the motor symptoms of PD, essential tremor, and—under a humanitarian device exemption—dystonia. In addition, a humanitarian device exemption has been granted for DBS in patients with severe, medication-refractory obsessive-compulsive disorder [11]. Consequently, all applications of DBS to the treatment of memory and cognitive disorders are still considered experimental, having been attempted either in the context of clinical trials with appropriate ethical approval, or with special permission for off-label use.

Human Studies of DBS Explicitly for the Treatment of Dementia by Target

Table 1 summarizes human studies of DBS in AD and other dementias published to date. In this section, we consider these studies in greater detail, along with related supporting work, classified by stimulation target.

Fornix Stimulation

The fornix has so far emerged as the leading target for DBS for memory loss and cognitive decline. A fiber pathway consisting of hippocampal pyramidal axons, the fornix connects the subiculum and hippocampus proper to the mammillary bodies and the septal nuclei, and constitutes an integral part of the classical Papez circuit critical to memory function (Fig. 1) [23, 24]. The fornix also conveys cholinergic axons from the septal area to the hippocampus. Lesions of the fornix are known to produce various amnesic syndromes [23, 25].

In a 2008 case report, our group at the University of Toronto reported on a 50-year-old man with morbid obesity treated with bilateral DBS targeted to the hypothalamus, aimed at producing appetite control [24]. Though DBS ultimately failed to affect the feeding behavior in this patient, several unexpected stimulation-related effects on memory were observed. Intraoperatively, the application of electrical current at different electrode contacts produced a stimulation-time-locked and reproducible feeling of “*déjà vu*”. This sensation was accompanied by recollections of scenes from the patient’s past, such as conversing with an ex-girlfriend, an event that had occurred more than 20 years prior to surgery.

Table 1 *In vivo* human studies of deep brain stimulation for dementia

Study authors [ref.]	Year	Target	Indication	N	Comments/Outcome
Turnbull et al. [19]	1985	NBM	AD	1	Unilateral, left-sided electrode. No serious adverse effects. No significant clinical response at 8 months following surgery, but increase in ipsilateral temporo-parietal metabolic activity.
Freund et al. [20]	2009	NBM	PDD	1	Bilateral electrodes in NBM and in STN. No serious adverse effects. Improvement in neuropsychologic function at 2 months, as well as in pre-existing ideomotor apraxia. Rapid decline within 24 h of discontinuing stimulation; neuropsychological outcomes rescued within 24 h of resuming stimulation.
Laxton et al. [21]	2011	Fornix	AD	6	Bilateral electrodes. No serious adverse effects. Some slowing in rate of decline in MMSE score in the year following implantation. Reversal of AD-related hypometabolism in temporo-parieto-occipital regions.
Fontaine et al. [22]	2012	Fornix	AD	1	Bilateral electrodes. No serious adverse effects. At 12 months, MMSE scores stabilized compared to baseline. Increase in mesial temporal metabolic activity.

NBM=Nucleus Basalis of Meynert; AD=Alzheimer's disease; PDD=Parkinson's disease dementia; STN = subthalamic nucleus; MMSE = Mini-Mental Status Examination

Furthermore, the scenes became increasingly more vivid in detail with increasing stimulation amplitude, before adverse stimulation-related side effects—including a generalized “warming”, facial flushing, and sweating—occurred at voltages >5 V. Postoperatively, when the DBS system was turned on at 2 months, stimulation was again associated with autobiographical memory effects similar to those observed intraoperatively, with experiential sensations occurring reproducibly in response to either left- or right-sided stimulation. Following 3 weeks of continuous bilateral stimulation with parameters (2.8 V, pulse width 60 μ s, and a frequency of 130 Hz) that did not produce any outwardly observable effects, neuropsychological evaluation showed evidence of

statistically significant improvement in the California Verbal Learning Test and the Spatial Associative Learning Test, while memory assessment showed improved hippocampus-dependent recall. Based on postoperative imaging and evaluation with electroencephalographic source localization showing that DBS activated the hippocampus and entorhinal cortex (EC) remote to the stimulation site, it was concluded that DBS might be exerting its memory and cognitive effects through orthodromic or antidromic stimulation of the fornix, which was situated in close proximity to the active stimulation contacts.

On the basis of this case report, our group embarked on an open-label phase I trial of DBS targeting the fornix in AD

Fig. 1 Schematic illustration of the components of the Papez circuit, critical to human memory function. The fornix connects the hippocampus to the mammillary bodies and septal nuclei of the hypothalamus via its postcommissural segment. The mammillary bodies project via the

mammillothalamic tract to the anterior nucleus of the thalamus, which, in turn, projects to the cingulate gyrus. Neocortical projections from the cingulate eventually feedback to the hippocampus through the entorhinal cortex, completing the circuit (reproduced with permission from [15])

[21]. Six patients with a recent diagnosis of probable AD (within the last 2 years), of mild-to-moderate severity [Clinical Dementia Rating Scale of 0.5 or 1.0, Mini-Mental Status Examination (MMSE) score of 18–28/30], and on stable doses of cholinesterase inhibitors were enrolled. Patients underwent implantation of bilateral DBS leads targeting the fornix (Fig. 2), with 2/6 reporting experiential memory phenomena during intraoperative test stimulation. Implanted DBS systems were turned on 2 weeks after surgery. The chronic stimulation parameters used were 3.0–3.5 V, 90 μ s, and 130 Hz. Again, these parameters did not produce any overtly observable effects. The primary outcome measure was the 12-month change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score [26]. Patients also underwent a battery of neuropsychological, electroencephalographic, and functional imaging assessments during follow-up.

The principal conclusion of the trial was that bilateral fornix stimulation was safe and well-tolerated in all 6 patients, with no serious adverse events. Change in ADAS-cog scores varied across patients, with 4/6 patients showing a perhaps slower than expected rate of decline at 1 year. MMSE scores also suggested a possible slowdown in the rate of cognitive decline: in the 11 months preceding DBS implantation, MMSE score decreased by an average of 2.8 points, while the mean decline was only 0.8 points in the 11 months following the initiation of continuous stimulation. Two additional key findings emerged from this study. First, as in the original case report, electroencephalographic analysis showed that fornix DBS was able to drive neural activity in the memory circuit, particularly in the cingulate cortex, EC, and hippocampal nodes. Second, fluorodeoxyglucose positron emission tomography at 1 and 12 months after the onset of stimulation showed a significant and sustained partial reversal of hypometabolism in the temporo-parieto-occipital regions typically affected in AD [27]. These promising results have since prompted the initiation of an ongoing multicenter, phase II, double-blind, sham-controlled trial of fornix DBS in patients with AD [28].

Fontaine et al. [22] recently published on their experience with fornix DBS for AD in 1 patient. The continuous stimulation parameters employed were 2.5 V, 210 μ s (considerably higher than in our study), and 130 Hz. As in our experience, there were no serious adverse events, and DBS implantation was well tolerated. Similarly, the authors found evidence of increased metabolic activity in response to fornix stimulation, though limited to the mesial temporal lobes. The single treated patient showed evidence of stabilization of MMSE and ADAS-Cog scores at 1-year follow-up, and expressed a subjective feeling of improvement. Though they need to be interpreted with caution, these preliminary results also point to the feasibility and safety of fornix DBS as a therapeutic approach to memory and cognitive disorders.

One recent additional study adds to our growing confidence that fornix stimulation indeed influences memory in humans. Koubeissi et al. [29] studied 11 patients with intractable epilepsy in whom they implanted depth electrodes for the purpose of mapping seizure activity. They applied high amplitude, low pulse width, low frequency (8 V, 0.2 μ s, 5 Hz) stimulation to the fornix for 4 h with the aim of reducing seizure activity and interictal epileptiform discharges. Patients were blinded to stimulation. Stimulation-associated evoked responses were observed in the hippocampus, and overall seizure activity appeared to be diminished. Interestingly, hourly poststimulation MMSE scores showed an increase compared with prestimulation scores, largely due to recall. While we acknowledge that this improvement in memory could be due to practice effects, the study nevertheless adds to our understanding of the therapeutic potential of fornix stimulation for disorders of memory and cognition. It also underscores the need for additional work in identifying optimal stimulation parameters for maximal memory effect.

Nucleus Basalis of Meynert Stimulation

The Nucleus Basalis of Meynert (NBM) is a region of the basal forebrain characterized by widespread ascending cholinergic projections constituting the main source of cholinergic innervation to the cortical mantle [30]. Given the importance of cortical cholinergic function in the acquisition of new memories [31], the NBM has been implicated in memory function, and has been considered part of the human memory circuit (see Fig. 1). It has also been implicated in the maintenance of attention and arousal [32]. The NBM undergoes degeneration in both AD and in PD dementia, and it appears that the degree of NBM atrophy is well correlated with the degree of objectively measured cognitive decline [33–35]. As a result, pharmacotherapy with acetylcholinesterase inhibitors aimed, in part, at increasing cholinergic outflow from the NBM has been employed with minimal therapeutic effect in AD [36]. Similarly, targeting the NBM or its ascending cholinergic projections with electrical stimulation represents a logical strategy to treat disorders of memory and cognition [32].

In a case report published in 1985—prior to the current modern era of DBS—Turnbull et al. [19] were the first to target this region, implanting a stimulating electrode in the left NBM in a single patient with AD. Stimulation was applied in a cyclic fashion for 9 months. Compared with the nonstimulated right side, glucose utilization was relatively preserved in the left cerebral hemisphere, particularly in the temporal and parietal areas. However, the authors did not find any convincing evidence of clinical improvement on memory or other cognitive measures at the end of the follow-up period.

Freund et al. [20] revisited the notion of NBM stimulation in a recent case report of a 71-year-old man with PD suffering

Fig. 2 Sagittal magnetic resonance imaging (MRI) slice in a patient with Alzheimer's disease, showing an implanted deep brain stimulation (DBS) lead targeting the fornix (left), and a corresponding sagittal image 3.5 mm lateral to midline showing a schematic projection of the DBS lead and its relationship to the fornix (right). The electrode contacts appear as dark artifacts on MRI. Each DBS lead has 4 contacts and leads were positioned immediately anterior and parallel to the vertical segment of the fornix bilaterally (adapted with permission from [21])

from progressive cognitive decline (i.e., PD dementia), particularly in memory function, over a period of 2 years. They implanted DBS leads bilaterally into the subthalamic nucleus (STN)—a standard and effective target for motor symptom relief in PD—and implanted 2 additional leads bilaterally into the laterodorsal portion of the intermediate sector of the NBM. Neuropsychological testing was conducted 1 week prior to implantation and during 4 subsequent blinded postoperative evaluation phases: 1) a period of isolated bilateral STN stimulation at standard high frequency (130 Hz); 2) combined STN and low-frequency (20 Hz) NBM stimulation; 3) a 1-week phase of STN stimulation with sham NBM stimulation; and 4) a second period of combined STN and NBM stimulation. Low frequency was chosen for NBM stimulation based on prior theoretical work suggesting that it might evoke “excitatory effects of...residual NBM output” [37]. Predictably, isolated STN DBS led to significant motor improvement, without significant change in memory function. Once bilateral NBM stimulation was added, “significant and impressive” cognitive improvement was observed: scores on the Rey Auditory Verbal Learning Task were significantly higher than those seen with STN stimulation alone, and the patient showed an improvement in pre-existing ideational and ideomotor apraxic symptoms manifest as better performance on the Trail-Making Test A and the Clock Drawing Test [20, 38]. Furthermore, there was a more global improvement in mood, personality, and social communication. These results remained effectively stable over a 2-month period. However, within 24 h of beginning the “sham” NBM stimulation phase, “major” deterioration in cognitive function was observed, with a near-total return to presurgical baseline scores. Interestingly, cognitive function was rescued within 24 h of restarting NBM stimulation, with a restoration of scores back

to the maximum levels seen during the initial STN and NBM co-stimulation phase.

These preliminary results suggest that targeting the NBM with DBS may be a feasible means of improving memory function in dementia. NBM stimulation may also have the capacity to improve cognitive and attentional function more globally as opposed to the apparent memory-specific effects of fornix stimulation, but the existing data are far too preliminary to make any meaningful comparisons between stimulation targets at this time. It is worth noting that in the case report by Freund et al. [20] the patient in question was unable to provide informed consent given the severity of his cognitive impairment, with consent having ultimately having been provided by a surrogate medical decision maker. This raises important ethical questions pertaining to the selection and consent process in dementia patients who may be candidates for DBS. A recently initiated—and as yet unpublished—phase I trial of NBM stimulation in 6 patients with mild-to-moderate AD will hopefully shed further light on issues of ethics and efficacy in this context [37, 39].

Human Studies of Brain Stimulation Reporting Effects on Memory

In rodents and rabbits, high-frequency electrical stimulation of the perforant path—which connects the EC to the hippocampal formation—has been hypothesized to improve encoding of new information into memory, possibly due to phase resetting of theta activity, the release of acetylcholine, and subsequent long-term potentiation [40–42]. Conversely, human work on direct stimulation of the hippocampus has consistently been associated with memory impairment, particularly

above after-discharge threshold [43, 44]. On this basis, Suthana et al. [45] hypothesized that stimulation of the EC could enhance memory performance if applied during memory encoding. In 7 patients with pharmacologically resistant epilepsy—some with memory and cognitive impairment, though none with frank dementia—they implanted depth electrodes to characterize the pattern of seizure activity. Six patients had electrodes implanted into the EC and 5 into the hippocampus, with 4 having electrodes in both targets simultaneously. The authors applied stimulation to either the EC or hippocampus while patients completed a spatial learning task consisting of navigation through a virtual environment in order to deliver passengers to stores. To assess the influence of stimulation on spatial learning, stimulation was applied while patients learned some locations, but not others. Current amplitudes were between 0.5 and 1.5 mA, at a pulse width of 300 μ s, and a frequency of 50 Hz, and cycled between 5-s on and off periods. Stimulation amplitude was determined in each patient as the maximum possible amplitude below after-discharge threshold.

The principal finding was that memory performance was significantly improved for locations learned during EC stimulation compared with those locations learned in the nonstimulated condition. This effect was seen in all patients, irrespective of baseline memory and neuropsychological status. By contrast, hippocampal stimulation did not similarly improve memory performance. Electrophysiologically, the authors were able to measure a significant increase in theta power in the hippocampus during EC stimulation, consistent with the theory that theta resetting plays a role in effective memory encoding. These preliminary findings point the way to the potential application of EC stimulation using conventional DBS systems in patients with memory disorders and dementia. Indeed, the findings from Suthana et al. [45] are in line with the circuit theory of DBS action, as the EC—like the fornix—is a component of the Papez memory circuit (see Fig. 1). However, one potential stumbling block is that in AD, the EC exhibits pathological involvement and neurodegeneration early in the disease process [46, 47], with the result that severe EC atrophy may occur before patients can even be considered for DBS, rendering EC stimulation unsafe or ineffective.

One additional study in the literature adds to our understanding of the memory-related effects of stimulation in the mesial temporal region. Fell et al. [48] studied 11 patients with intractable epilepsy undergoing invasive monitoring with depth electrodes. They applied continuous low amplitude (0.01 mA) stimulation at 40 Hz to the rhinal cortex (encompassing both the EC and the perirhinal region) and simultaneously to the hippocampus during the Verbal Learning and Memory Test for declarative memory. Stimulation was applied in 1 of 3 conditions: 1) in-phase (zero phase-lag) stimulation to both rhinal cortex and

hippocampus; 2) antiphase stimulation to both rhinal cortex and hippocampus; and, 3) sham stimulation. Though no experimental conditions produced statistically significant results, there was a trend towards greater word recall and fewer intrusions in the in-phase condition, with impairment of memory in the antiphase condition. These preliminary results again support the potential utility of the entorhinal region as a target for DBS for memory and cognitive disorders. They also raise questions about the specific influence of stimulation parameters and the role of stimulation synchrony on memory enhancement, which may need to be considered in forthcoming human trials.

Preclinical Studies of DBS and Memory: Moving Beyond Circuit Activity

Recent preclinical experiments in animal models of DBS have shown that stimulation applied to key nodes in the memory circuit may do more than simply influence circuit-wide neural activity. An interesting aspect of this work is that DBS may be associated with the generation of new and functional hippocampal neurons, with the tantalizing prospect of not only changing circuit function, but also potentially producing stimulation-induced neuroregenerative effects. In one of the earliest studies, Toda et al. [49] found a 2–3-fold increase in the number of newborn bromodeoxyuridine staining-positive neurons in the dentate gyrus of rats who underwent 1 h of constant stimulation of the anterior nucleus of the thalamus compared with nonstimulated animals. A follow-up study confirmed the finding of increased neurogenesis in rats receiving anterior nucleus DBS; further, they found evidence of improved memory on a delayed nonmatching-to-sample task, which was the first demonstration of behavioral improvement together with DBS-associated hippocampal neurogenesis [50]. More recently, Stone et al. [51] showed that DBS applied to the EC of rats led to: 1) the generation of new and viable hippocampal neurons in the dentate gyrus; 2) the integration of these neurons into functional memory networks; and 3) improved memory function on a water-maze task 6 weeks after bilateral EC stimulation. Critically, it also appeared that these memory effects were neurogenesis-dependent, as they were successfully blocked by known inhibitors of neurogenesis such as temozolamide. Of course, it remains unclear to what extent neurogenesis, or its failure, plays a role in AD and other dementing illnesses. However, these early results do suggest that DBS may offer an opportunity not only to alter the function of disrupted memory circuits, but also to influence their structure. Further work directed specifically at identifying the effects of DBS in animal models of AD—which is, to date, lacking—will be vital in proving this hypothesis.

Conclusion

Human studies of DBS have shown that targeting key nodes in memory and cognitive circuits is safe and can adaptively drive activity in these circuits. Early clinical data in some patients with AD and other dementias suggest that DBS may be associated with stabilization or improvement in memory and cognitive impairment. However, much is as yet unknown about the optimal DBS target and stimulation parameters in these illnesses, which have been chosen empirically based on a priori knowledge of neuroanatomy and clinical experience with DBS in other diseases. Even less is known about the potential for DBS to alter neurodegeneration through structural effects; ongoing preclinical work may help to define the extent and therapeutic value of these effects. Though the results to date are cause for cautious optimism, ultimately the outcomes of sham-controlled, randomized trials—some of which are currently ongoing—will help inform the role, if any, that DBS will play in the management of memory and cognitive disorders.

Acknowledgments A.M.L. is a Canada Research Chair in Neuroscience and is supported by the R.R. Tasker Chair in Functional Neurosurgery. Additional support was provided by the Dana Foundation and Krembil Neuroscience Discovery Fund. A.M.L. is a consultant to Medtronic, St Jude, and Boston Scientific. A.M.L. serves on the scientific advisory board of Ceregene, Codman, Neurophage, Aleva and Alcyone Life Sciences. A.M.L. is co-founder of Functional Neuromodulation Inc. and holds intellectual property in the field of deep brain stimulation. All other authors declare no relevant conflicts of interest.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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