Stimulate or Degenerate: Deep Brain Stimulation of the Nucleus Basalis Meynert in Alzheimer Dementia

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Key words
- Alzheimer disease
- Deep brain stimulation
- Nerve growth factor

Abbreviations and Acronyms
ACh: Acetylcholine
AD: Alzheimer dementia
BFA: Basal forebrain area
BFCN: Basal forebrain cholinergic neurons
DBS: Deep-brain stimulation
MCI: Mild cognitive impairment
NBM: Nucleus basalis Meynert
NGF: Nerve growth factor


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OBJECTIVE: **Deep brain stimulation (DBS) is a therapeutically effective neurosurgical method originally applied in movement disorders. Over time, the application of DBS has increasingly been considered as a therapeutic option for several neuropsychiatric disorders, including Gilles de la Tourette syndrome, obsessive compulsive disorder, major depression and addiction. Latest research suggests beneficial effects of DBS in Alzheimer dementia (AD). Because of the high prevalence and the considerable burden of the disease, we endeavored to discuss and reveal the challenges of DBS in AD.**

METHODS: **Recent literature on the pathophysiology of AD, including translational data and human studies, has been studied to generate a fundamental hypothesis regarding the effects of electrical stimulation on cognition and to facilitate our ongoing pilot study regarding DBS of the nucleus basalis Meynert (NBM) in patients with AD.**

RESULTS: **It is hypothesized that DBS in the nucleus basalis Meynert could probably improve or at least stabilize memory and cognitive functioning in patients with AD by facilitating neural oscillations and by enhancing the synthesis of nerve growth factors.**

CONCLUSIONS: **Considering the large number of patients suffering from AD, there is a great need for novel and effective treatment methods. Our research provides insights into the theoretical background of DBS in AD. Providing that our hypothesis will be validated by our ongoing pilot study, DBS could be an opportunity in the treatment of AD.**

DEEP BRAIN STIMULATION (DBS)

Since the late 1980s, DBS has substantially expanded the therapeutic possibilities of treating movement disorders such as Parkinson disease (7, 8). DBS refers to a complex neuromodulative procedure in which electrodes are stereotactically implanted into defined target structures of the brain. Despite many years of experience with DBS, the therapeutic effects are not yet well understood. There are various mechanisms of action being discussed, such as excitatory and inhibitory actions on the next processing stage (57, 58) or interactions with neuromodulators or receptors. The benefit of DBS in the field of movement disorders has repeatedly been documented, and the minimal invasiveness of the procedure and the rare and usually minor side effects open the implementation of DBS for other neurological and psychiatric indications (41). Along this line, the results of various studies have pointed out promising effects of DBS for the treatment of severe obsessive compulsive disorder, Tourette syndrome and major depression (35, 40, 48, 64, 68, 90). In the last 2 years, two investigations have even been published in which DBS has been used with the aim to improve cognitive abilities in patients with dementia (27, 50). Furthermore, improved memory processing in patients not affected by dementia has just recently been described (31, 82).

In this context a new target candidate is the nucleus basalis Meynert (NBM; see http://clinicaltrials.gov/ct2/show/NCT01094145). Theodor Meynert's neuroanatomic studies contributed to the development of the nineteenth-century "brain psychiatry" movement. His speculation that certain cognitive impairments resulted from an imbalance in blood flow between cortical and subcortical structures parallels modern controversies concerning the role of these brain regions in the pathophysiology of dementia. Meynert described a subcortical nucleus in the basal forebrain, the nucleus basalis of Meynert (i.e., NBM), which has been shown to provide cholinergic innervation to the cortex. Loss of cells within this structure may account for the loss of cortical cholinergic markers in Alzheimer disease (AD), a so-called "cortical" dementia, and in the dementia of Parkinson disease. The article by Whitehouse et al. revived the concept of a pivotal role of the NBM for the pathogenesis of AD (96).

An influential electrophysiological study (16) forwarded the concept that increased neuronal firing of the NBM provides a steady background of neocortical activity that may enhance the effects of other afferents to the neocortex (78). Thereby, the more general action of the NBM on the cortex was regarded as an analogue to the classical concept of Moruzzi and Magoun, who envisaged the reticular ascending fiber system as an arousal system (65). Since then, ample experimental evidence has been accumulated supporting the role of the NBM for cortical tuning and the consequences of the breakdown of this action by degeneration of this nucleus in the earliest stages of dementia.

Specific modifications of NBM stimulation on cortical processing have also been demonstrated. Episodic electrical stimulation of the nucleus basalis, paired with an auditory stimulus, accomplished massive and progressive reorganization of the primary auditory cortex in the adult rat that also outlasted stimulation for hours and suggested that the basal forebrain plays an active instructional role in representational plasticity (45).

The wealth of experimental data provides the background for clinical applications that try to modify NBM function by either molecular or electrical neuromodulative methods. The objective of this article is a state-of-art discussion of the current rational for this type of approach. Neuromodulation of the basal forebrain structures could open a new avenue for compensating for subcortical dysfunctions that characterize degenerative diseases by modifying cortical functions, and may even provide some insight into the pathophysiology and pathogenesis of AD.

ALZHEIMER DEMENTIA

AD is characterized by a chronic progressive cognitive deterioration, frequently accompanied by psychopathological symptoms, reduced functional ability, changes in personality, social isolation and loss in quality of life. With a proportion of 70%–80%, AD is the most prevalent form of dementia and, because of its limited treatment options, a severely disabling disorder not only for the patient concerned but also for the relatives providing care (26, 79).

Besides a polygenetic predisposition, multifactorial causes contribute to the development of AD. Despite great efforts, so far no scientific consensus of a convergent concept about the neurobiological processes in AD has been achieved. The most frequently cited idea is the "amyloid cascade hypothesis," which states that the extracellular formation and aggregation of β-amyloid peptides, so-called cerebral amyloid plaques, and the synthesis of intracellular neurofibrillary bundles of hyperphosphorilated tau proteins are the initial steps in the development of AD and eventually result in the elective inexorable atrophy of neurons (20, 44, 71). Based on the amyloid cascade hypothesis, some modern therapeutic approaches focus on preventing or reversing the formation of amyloid, including active and passive immunization against β-amyloid (51, 83). Unfortunately, up to now this treatment approach could not achieve sustained success.

The lack of an effective treatment is all the more disappointing as a major progress has been made regarding diagnostic procedures over the past years. Detecting and diagnosing the disease earlier is now possible by the detection of amyloid deposition through positron emission tomography (PET), cerebrospinal fluid markers, and the clinical concepts of mild cognitive impairment (MCI) and pre-MCI (19, 24, 81, 94).

Until now, the treatment of choice is still based on the administration of antidementive medication such as memantine, donepezil, galantamine or rivastigmine (95). Although their positive effect on cognitive abilities in patients with AD is unquestioned, effect sizes (d) are rather small and vary between 0.1 and 0.4 (6, 23, 62). With the exception of memantine (an NMDA glutamate receptor antagonist), all substances modify the inhibition of cholinesterase.

The approach to treat AD by enhancing cholinergic functioning originated in the cholinergic hypothesis by Bartus et al. (6), who states that the development of AD is a response to a reduced synthesis of acetylcholine (ACh) caused by the progressive neuronal degeneration.

ACh is essential for cognitive functioning and memory processing. The release of ACh is voltage-dependent and mediated through the initiation of action potentials. The disposal of ACh is carried out in parcels of 10,000 molecules. The postsynaptic excitation through ACh triggers a complex intracellular signaling cascade (25), which is based on a subtle interplay between muscarinic and nicotinic postsynaptic receptor activation (23, 33, 62). It could be demonstrated that an elevation of ACh levels in healthy adults as well as in demented patients enhances memory capacity and improves performance on several cognitive tasks including verbal and object learning (38, 62, 63).

In more detail, Kukolja et al. (49) could show that nicotinergic stimulation with physostigmine facilitates encoding of spatial contextual information and is associated with increased neural activity in the right hippocampal formation. In addition, it could be demonstrated that participants who were worse at the baseline examination benefited more from cholinergic stimulation than participants with better baseline scores on a test assessing cognitive functioning. Bearing this in mind, it can be assumed that reduced ACh levels impair cognitive functioning not only in patients with dementia but even in healthy subjects. The witnessed correlation of cognitive functioning and the level of ACh has also been emphasized by other investigations: If the cholinergic transmission is blocked in humans and monkeys, cognitive abilities are reduced in a similar way as they are in patients with mild and moderate AD (5, 10). Furthermore, it appears that the severity of the symptoms in dementia is dependent on the level of cholinergic loss and that vice versa the treatment with antidementive medication and cholinergic modulators improves the symptoms of AD (10, 12, 15). The principle sources of ACh are the cholinergic neurons in the basal forebrain, wherefrom cholinergic fibers project to all layers of the neocortical mantle and to the hippocampus and amygdala (18). Apart from this, there are cholinergic interneurons in the striatum.

THE BASAL FOREBRAIN AREA AND THE NBM

The basal forebrain area (BFA) has a complex architecture (60). It comprises the basal forebrain cholinergic neurons (BFCN) within the medial septal nucleus, the diagonal band nucleus and the nucleus basalis of Meynert (NBM) (**Figure 1**). The NBM, also termed CH4 group, has the largest volume. It could be demonstrated that approximately 90% of

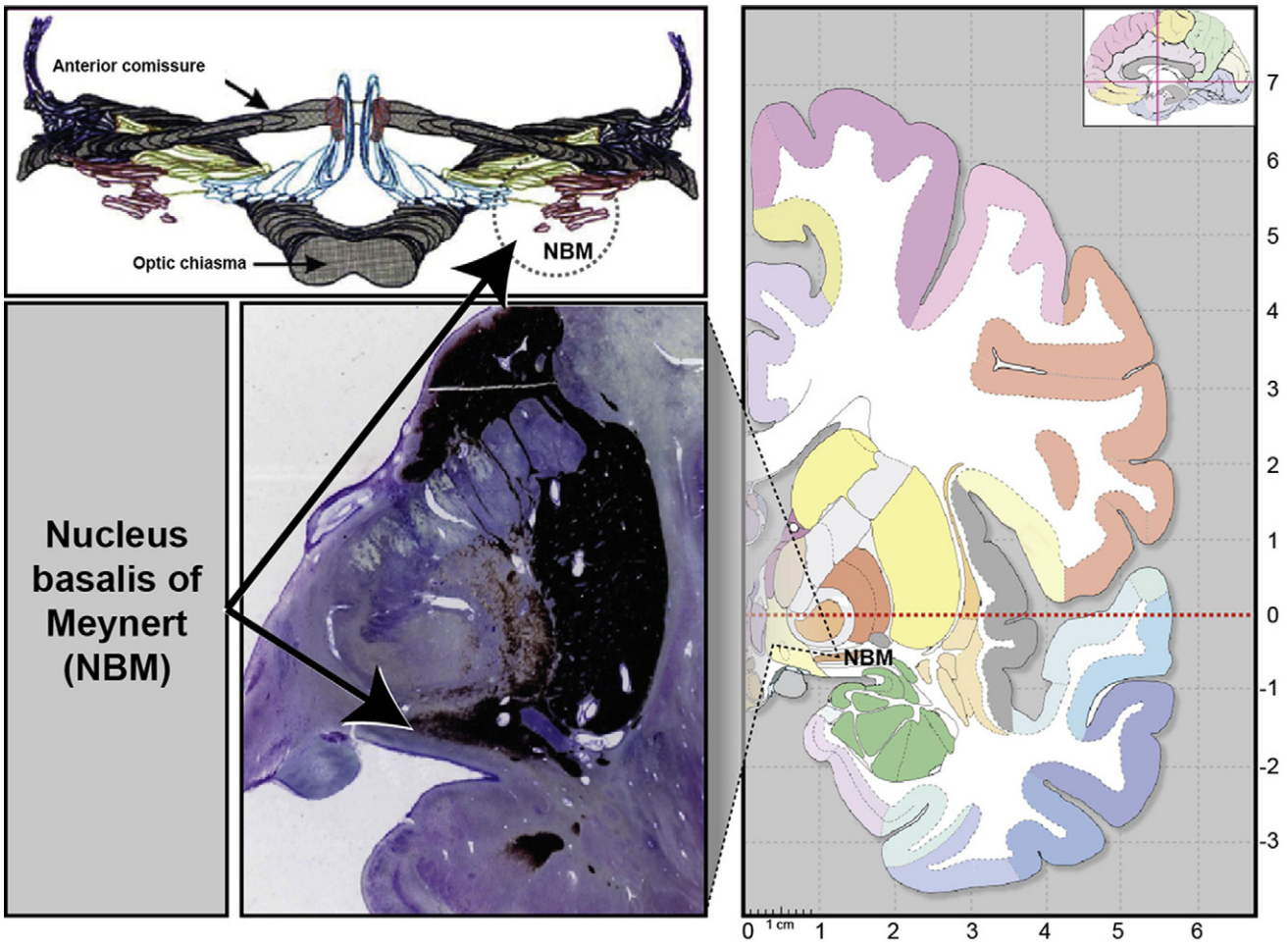

Figure 1. Histological and graphic presentation of the nucleus basalis Meynert. (Used with permission from Mai J, Voß T, Paxinos G: Atlas of the Human Brain. 3rd ed. San Diego: Elsevier Academic Press; 2008.)

the NBM neurons release the neurotransmitter ACh (59, 60, 69, 73). These neurons predominantly project diffusely to the neocortical mantle, where the primary physiological effect of ACh is to modulate the response of pyramidal cells to other—particularly glutamatergic—cortical input (11, 55). This innervation of the neocortex by BFCN is an integral part of cortical activation as it supports cognitive functions, such as alertness, memory, attention and learning. In simplified terms, the function of the BFCN is sometimes described as a kind of "background tuning" (27, 75, 76). The exceeding importance of the NBM for a presynaptic tuning of the entire neocortex has been subject to many animal studies (92, 93). In an investigation of McGaughy et al. (56), the relationship between selective damage to the NBM, cortical ACh levels and attentional functioning was examined in rats. The immunotoxin 192 IgG-saporin was infused to the NBM, causing lesions in this region. Rats with extensive damage in the NBM showed an elevated impairment in a serial reaction time task (i.e., the five-choice serial reaction time task) used to assess visual attention. These behavioral deficits were associated with a severe impairment in central executive functions. The outcome in the attention task correlated significantly with the number of choline acetyltransferase–immunoreactive cells. Rats with more extensive lesions in the NBM had significantly lower levels of cortical ACh release. In humans pharmalogical manipulations of cholinergic receptors also are known to affect attentional performance (9).

Much about memory encoding and synaptic plasticity is not yet completely understood, for example, the "plasticity-stability" dilemma (1). However, the importance of the cholinergic BFA system as well as the glutamatergic system, which communicates via NMDA receptors and plays a decisive role in long-term potentiation, has been more clearly formulated already. The BFA appears to promote cortical plasticity by allocating the cortex to operate specifically on behaviourally arousing stimuli. It is assumed that higher ACh levels contribute to an enhancement of hippocampal theta oscillations, which are associated with improved memory encoding (33, 89). In this context, lesion studies demonstrated that the activity of the NBM serves as a reinforcement signal in order to stimulate cortical plasticity (46, 59, 61, 97).

Furthermore, the basal forebrain neurons appear to modulate the cerebral regu-

lation of blood supply in the neocortex and thereby glucose metabolism. This process is regarded as an elementary prerequisite for cognitive functioning. Their terminal axons form not only synapses with cortical pyramidal cells but are also distributed along small cortical blood vessels, where they work to increase cortical blood flow by activating ACh receptors of both the nicotinic and the muscarinic type (88). In summary, a large body of evidence points out to a specific vulnerability of the basal forebrain cholinergic system in the pathology of AD (85).

Basal Forebrain Degeneration in AD

Structural magnetic resonance imaging has shown that brain regions including the NBM degenerate in patients with AD and in the process of the cellular loss, the cell nucleus withers completely (77). The apparent neuronal loss is assumed to be the substantial factor responsible for the subsequent decrease of ACh in the cortical projection area (34). By using a deformation-based approach and a recently developed probabilistic map of different basal forebrain magnocellular compartments in the Montreal Neurological Institute space (99) Grothe et al. (30) found a significant atrophy in the NBM (especially in the cell groups of the Ch4) in patients with MCI, who represent a high-risk population to develop AD. The volumes of the degenerated cholinergic regions correlated highly negative with the patients' cognitive capacity but positive with a statistically significant loss of gray matter volumes in the affected compartments. This correlation was also observed in patients with an established dementia (42).

In an animal model, Boncristiano et al. (14) investigated the impact of cholinergic basal forebrain degeneration on cortical amyloid deposition. Eight months after a unilateral lesion of the NBM, the transgenetic amyloid precursor protein (APP23) mice showed a 38% reduction in choline acetyltransferase activity as well as a significant fiber loss of 30% decrease in the ipsilateral frontal cortex. The significant fiber loss in the animals correlated with the cortical Aβ levels, indicating that the cortical cholinergic deficit in the APP23 mice is probably induced by Aβ accretion. The observed dystrophic cholinergic fibers surrounding the amyloid deposition were found to resemble the neuropathological changes observed in brains of patients with AD whereas the ratio of A40 to A42 remained stable.

On the basis of these findings, the authors concluded that the cholinergic deficit in AD is, on the one hand, caused by a loss of cholinergic forebrain neurons and, on the other hand, by an abnormal local deposition of amyloid protein (amyloidosis) in the neocortex and hippocampus. The amyloid plaques and the cerebrovascular amyloid are found throughout the entire neocortex and hippocampus, whereas only a modest amyloid deposition is observed in the basal forebrain, including the NBM (14). It has previously been observed that even small quantities of Aβ can induce a long-term down-regulation of the cholinergic activity in cholinergic SN56 cells (70). Accordingly, it has been hypothesized that the concentration of Aβ in the mice's brain is probably sufficient to induce cholinergic hypoactivity as well as neural shrinkage. Unfortunately, it remains unclear why these regions are predominantly affected.

Given the apparent connection between AD-related NBM degeneration and diminished cholinergic transmission as well as cognitive functioning, supporting, protecting and restoring the basal forebrain cholinergic neurons seems essential. One option to pursue this therapeutic objective would be the use of nerve growth factors (NGF), proteins essential for the neurite outgrowth, synapse formation and survival of cholinergic neurons. Levels of NGF are vulnerable to aging and are pathologically low in patients with AD, especially in the basal forebrain cholinergic neurons (BFCNs) of the NBM (22), which is also reflected by the correlation between decreased NGF level, the severity of AD, and basal forebrain degeneration (53, 74). In reverse, it can be assumed that the treatment with NGF can provide a long-lasting cholinergic trophic support and, as a consequence, is able to reduce or even prevent cognitive deterioration in patients with AD. Unfortunately, the treatment with NGF remains an important challenge because the delivery of NGF to the brain causes undesired adverse nociceptive side effects (17). Furthermore, NGF does not penetrate the blood–brain barrier and its therapeutic use therefore depends on invasive approaches requiring neurosurgery (28).

Bishop et al. (13) demonstrated that by injecting CERE 110, a gene therapy product to deliver NGF into the rats' NBM, stable and sustained NGF levels could be achieved, lasting up to 12 months. The attempt to manipulate the NGF release had both a neuroprotective and a neurorestorative effect (13). Other animal models could likewise demonstrate that the treatment with NGF can reduce the shrinkage of BFCNs, which was induced before through lesions to the fornix (47, 72, 87). Furthermore, research indicates that the administration of NGF to the NBM area prevents the shrinkage of the human BFCNs after brain injury (43, 84), facilitates the reversal of age-related brain atrophy (66) and even induces the recovery of cognitive functions such as learning and memory (21, 52).

DOES DBS INDUCE NEUROPROTECTIVE EFFECTS?

In the context of AD-associated dysregulations in NGF levels, it seems to be of particular interest to examine whether the application of DBS might lead to an increased NGF release.

Indeed, the idea of an increased NGF release through electrical stimulation appears plausible considering recent findings of in vitro research. Electrical stimulation was applied to cultured Schwann cells and effectively enhanced NGF release. Stimulation parameters of 1 Hz achieved the greatest NGF release. Greater frequencies (50 or 100 Hz) resulted in lower amplitudes of NGF release (39). On the contrary, other studies demonstrated a greater BDNF release at greater (100 Hz or more) than at lower frequencies (5, 10, or 25 Hz) in hippocampal neurons (2, 3). It can be assumed that the observed differences regarding the stimulation frequencies are due to the different sensitivity of the different cell types.

Animal studies replicated similar effects in the NBM. In a recent investigation the effects of electrical stimulation on NGF levels in the cerebral cortex were investigated in 36 rats by the use of high sensitivity enzyme-linked immunosorbent assay, a procedure to detect minimally expressed antigens. Unilateral NBM stimulation (for an overview, see Hotta et al. [36]) resulted in an increase of ipsilateral extracellular NGF levels. Interestingly, the NGF secretion was completely abrogated by a nicotinic ACh receptor antagonist, implicating that the cho-

linergic basal forebrain projections to the cortex seem to be responsible for the NGF increase. However, the investigations have been performed in adult rats and not in a valid animal model mimicking AD (37).

Nevertheless, the stimulation-related increase of NGF release is a highly relevant aspect that we hope to induce by applying DBS in AD patients. Previous research could show that DBS apparently has a protective effect, probably by inducing the synthesis of NGF. Hamani et al. (32) administered corticosterone, a steroid hormone of the corticosteroid type, to rats to diminish neurogenesis and as a consequence induce memory deficits. Treating the animals with anterior thalamic nucleus high-frequency stimulation resulted in improved performance on a delayed-nonmatching-to-sample-task. The positive effect of anterior thalamic nucleus high-frequency stimulation in corticosterone treated rats on memory functioning was only observed when the delay between stimulation and behavioral testing was 33 days. When the stimulation was administered only 4 days before the behavioural testing, no significant changes could be found. These results indicate that an increase in hippocampal neurogenesis may be responsible for the enhanced memory performance. Therefore, it can be hypothesised that plasticity changes possibly occur through the development of new dentate gyrus cells and are responsible for this effect (32).

In a phase 1 study, Laxton et al. (50) treated six patients with early AD with DBS in the fornix, a major fiber pathway connecting the hippocampus with the mammillary bodies and the septal nuclei. Neuropsychological tests, administered to the patients 1, 6, and 12 months postsurgery, showed that the rate of cognitive decline decreased. Furthermore, the neural activity measured by means of fludeoxyglucose-positron emission tomography in memory circuits, including the entorhinal and the hippocampal area, was enhanced after the application of DBS. The stabilization of the cognitive performance correlated significantly with sustained changes in the impaired glucose metabolism in temporal and parietal lobes, even at the 1-year follow-up assessment (80).

Although the exact mechanisms of DBS are still unknown, the authors hypothesized that stimulation of the fornix leads to an enhanced neurogenesis and the release of neurotrophic factors in the hippocampus (50). This notion might be supported by the observation that patients with better cognitive functioning were more likely to benefit from the treatment, whereas more affected patients were more likely to cognitively decline after initiation of DBS. A possible explanation of these findings could be that patients with better cognitive baseline functioning benefit more from the neuroprotective effects of DBS because their brain tissue has not yet been subject to such a dramatic neuronal loss as it is characteristic for the late stage of AD.

At our research site, a patient suffering from proceeded Parkinson dementia with advanced symptoms regarding working memory, concentration and attention deficits as well as apraxia, was treated with DBS of the NBM. After surgery, the patient demonstrated slight but sustained improvement in various aspects of cognitive functioning, such as attention, concentration, alertness, drive, and spontaneity, as well as apraxia and ataxia (4). In addition, memory functions improved, although they remained deficient compared with healthy controls. It is remarkable that the reported positive effects were observable at frequencies less than 20-Hz stimulation but not under high-frequency stimulation of 130 Hz, which is commonly used in movement disorders. This observation supports the assumption of low-frequency stimulation having an excitatory, and high-frequency stimulation having a rather inhibitory, effect (e.g., [67, 98]). The achieved stabilization of cognitive functioning could be maintained about more than 2 years (unpublished data). We assume that these positive effects were decisively induced by the release of NGF in the NBM as a consequence of the stimulation.

Because the neuropathology of both PD dementia and AD involve similar features and because the clinical picture of both is characterized by deficits in working memory, attention and concentration, a partial generalization of these findings to AD, at least, appears appropriate. Based on this idea, these pilot results formed the basis for our ongoing study on DBS of the NBM to treat cognitive deficits in light-to-moderate AD (http://clinicaltrials.gov/ct2/show/NCT01094145). Concerning its methodology, the study has been designed to include six patients with AD, whose progress on the Alzheimer disease assessment scale (i.e., ADAS-cog), our primary outcome measure, is to be observed for up to 1 year after stimulation onset including a double-blinded sham control period.

ACUTE EFFECTS ON COGNITION BY DBS

In addition to the aforementioned potential mechanisms regarding the stimulation-induced enhanced NGF release, yet another stimulation effect might be conceivable in the context of dementia, namely a positive impact on neuronal oscillations. As we currently understand, neuronal oscillations are essential for the processing of information and for enabling communication between different brain structures. As can be shown by the example of Morbus Parkinson, DBS is nonetheless able to modify pathological patterns of oscillations (29, 86). In this context, it is possible that DBS is able to reset destabilised patterns of neuronal oscillations in AD. Particularly the hippocampal theta rhythm is assumed to play an important role in the context of learning and memory (50).

The potential relation between DBS, oscillatory patterns and memory could recently be demonstrated in patients with pharmaco-resistant epilepsy, who were treated with DBS. In seven patients, DBS was applied to targets in the hippocampus and the entorhinal area while they performed a spatial memory task. The results demonstrated that spatial learning performance was enhanced by electrical stimulation of the entorhinal region.

Furthermore, the entorhinal stimulation (50 Hz) led to a theta phase resetting measured through hippocampal depths electrodes. Previous research findings already suggested that theta phase resetting improves memory functioning in an animal model because it supports the mechanisms underlying selective attention and as a consequence enables the best possible encoding of incoming information (82). Furthermore, it could likewise be demonstrated that electrical stimulation of the perforant pathway in rodents triggers a theta phase resetting, thereby creating favourable conditions for long term potentiation (54). These results confirm the hypothesis that resetting theta activity facilitates the poten-

tiation and encoding of relevant incoming stimuli.

Hamani et al. (31) published a case report of an obese patient, who was treated by DBS in the fornix. The morbid obesity remained stable, whereas the stimulation unexpectedly evoked detailed autobiographical memories (pilot patient to the before mentioned phase 1 study), suggesting that DBS of the fornix modulates limbic activity and enhances memory functions. Through the examination of the stimulated brain regions, it could be demonstrated that DBS significantly enhanced the activity in the hippocampal and parahippocamal regions. These results likewise indicate that DBS might have induced a modulation of oscillatory activity.

Although the influence of DBS on oscillatory activity is not yet proven, the acute effects observed in one of our patients suggest a similar working mechanism. As mentioned previously, we observed an enhancement of memory functions in the Parkinson patient, who received DBS in the NBM. In addition to the insightful observation of beneficial long-term effects, we also could assess acute effects. After the intermittent OFF condition (24 hours without stimulation), a major cognitive deterioration was observed.

Given these immediate stimulation effects, it must be assumed that DBS also impacts upon neural oscillations, considering that a time interval of 24 hours is too short to solely let a stimulation-induced neurogenesis account for the witnessed difference between the ON and the OFF condition.

Both forms of dementia—Parkinson and Alzheimer—posses a similar neuropathology, particularly as the NBM is to a large extent degenerated in both diseases (27). We therefore aspire to attain similar positive cognitive effects after DBS of the NBM in patients with Alzheimer's disease.

CONCLUSION

The impressive results regarding the application of DBS in neurological and psychiatric diseases during the past years are very promising and the consideration of new therapeutic opportunities to treat other diseases, which are, until now only insufficiently treatable.

Despite the substantial therapeutic progress that has been made during the last few decades, AD remains a progressive and barely controllable disease. Although, the exact mechanisms of action underlying DBS are still not completely understood, there is first evidence that DBS in neurodegenerative diseases could unfold neuroprotective mechanisms, e.g., through the induction of NGF-synthesis. Given that the NBM plays an important role regarding the neuroprotective mechanisms and cognitive processes described previously, the nucleus is considered a promising target structure. However, it has to be taken into account that accessing the NBM stereotactically is highly demanding since it is a very flat and almost horizontal cell structure, which requires a deep frontotemporal approach. At the same time the CH_4 area of the NBM can be localized well through MRT.

In addition to its long-term effects, DBS appears to induce acute effects as well, possibly by modulating oscillatory rhythms crucial for memory processing. However, further research is necessary to gain more information about the underlying mechanisms of DBS and to possibly contribute to the elucidation of how to decelerate the progress of AD. Despite the enthusiasm for DBS as a treatment for AD, it is nonetheless important to consider the possible side effects carefully, these being first and foremost perioperative complications, which are, based on the experience with other neurodegenerative diseases, for example, Parkinson dementia, rather predictable (91). Moreover, the first study on DBS in AD published thus far did not indicate another risk assessment concerning this matter (50).

Completely unknown, however, are the side effects possibly induced by stimulation of the new target structures, for example, the fornix and NBM. Experience with these neural targets should be documented carefully during the next years since it will decide about further investigations of the possible benefit of DBS in AD. Taking into consideration the benefit-risk profile, it remains to be seen whether DBS is an effective treatment option for patients with AD.

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