[Frontiers in Bioscience 14, 1891-1901, January 1, 2009]

Cognitive and limbic effects of deep brain stimulation in preclinical studies

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TABLE OF CONTENTS

1. ABSTRACT

The use of deep brain stimulation (DBS) to control severely disabling neurological and psychiatric conditions is an exciting and fast emerging area of neuroscience. Deep brain stimulation has generally the same clinical effects as a lesion with respect to the improvement of clinical disability, but has more advantages such as its adjustability and reversibility. To this day, fundamental knowledge regarding the application of electrical currents to deep brain structures is far from complete. Despite improving key symptoms in movement disorders, DBS can be associated with the occurrence of a variety of changes in cognitive and limbic functions both in humans and animals. Furthermore, in psychiatric disorders, DBS is primarily used to evoke cognitive and limbic changes to reduce the psychiatric disability. Preclinical DBS experiments have been carried out to investigate the mechanisms underlying the clinical effects of DBS for at least three (interrelated) reasons: to increase our scientific knowledge, to optimize/refine the technology, or to prevent/reduce side-effects. In this review, we will discuss the limbic and cognitive effects of DBS in preclinical studies.

2. INTRODUCTION

The use of stimulation electrodes implanted in the brain to control severely disabling neurological and psychiatric conditions is an exciting and fast emerging area of neuroscience (1) As an example, DBS of the subthalamic nucleus (STN) has become the surgical therapy of choice for advanced Parkinson's disease (PD), and to date more than 30,000 PD patients worldwide have benefited from this procedure (2, 3) The relief of movement disability by stimulation of the STN is predictable as this nucleus is a critical part of the basal ganglia motor circuitry that is dysfunctional in PD patients (4, 5) However, the side-effects observed in PD patients with STN DBS (6) have also allowed us to highlight some of the non-motor functions of the STN that have originally been demonstrated by STN lesions in rats (7, 8) In PD, which is histopathologically characterized by selective, chronic and progressive nigrostriatal degeneration, the STN displays a continuous abnormal "bursting" mode of activity whereas in physiological conditions it exhibits more or less a regular pattern of discharge with intervals of burst activity (9-11) This so-called STN hyperactivity, reflecting the increase in firing rate, has been implicated in increasing the activity of

basal ganglia output nuclei, and consequently, excessive inhibition of their targets (4, 12) This mechanism is held responsible for at least part of the cardinal PD symptoms such as hypokinesia and rigidity (13) In order to surgically "silence" the hyperactive STN, DBS has been applied since the past decade.

DBS has generally the same clinical effects as a lesion with respect to the improvement of clinical disability, but has more advantages such as its adjustability and reversibility (14, 15) Nevertheless, the cellular effects of DBS and lesions are different: a lesion destroys and DBS modulates the (electro)physiological activity of neuronal elements (9, 16-18) To this day, fundamental knowledge regarding the application of electrical currents to deep brain structures is far from complete. A number of possible mechanisms have, however, been proposed such as depolarization block (9, 19) and silencing of target nuclei by stimulation of GABAergic afferents (20) Nevertheless, the similarity in clinical outcomes between DBS and lesion have led to the proposition that DBS inhibits the target neurons stimulated. Recordings made in the stimulated nucleus show inhibition or decreased activity during and after the stimulus train (21-23)

Despite improving key motor symptoms in movement disorders, DBS can be associated with the occurrence of a variety of changes in cognitive and limbic function both in humans and animals (6, 24-27) Furthermore, in psychiatric disorders, DBS is primarily used to evoke cognitive and limbic changes to reduce the psychiatric disability. In this review, we will discuss the limbic and cognitive effects of DBS in preclinical studies. The clinical effects are discussed in another article within this issue. First, we will summarize the effects of DBS in animal models of movement disorders, and in the second part, the effects of DBS in animal models of psychiatric disorders will be outlined.

3. HISTORICAL CONSIDERATIONS

Applying electrical current to the brain is nowadays very much in the public eye, but is actually an old technique. One of the first experiments, in which electrical current was delivered to the brain, was reported by Gustav Fritsch and Eduard Hitzig already in 1870 (published in german in *Arch. f. Anat., Physiol. und wissenschaftl. Mediz.*, *Leipzig, 37, 1870, 300-32*) They applied electrical current to various cortical regions in dogs. They found that stimulation of some brain areas caused muscle contractions whereas others caused eye movements. They provided the first evidence for a finer localization of function in the cortex, and introduced a totally new paradigm for exploring the brain. Numerous other scientists have used the technique of brain stimulation in the next century. Here, we will mention two other relevant scientists. Firstly, MacLean and Ploog (1962) were the first to use electrical stimulation through implanted electrodes in the non-human primate to investigate the brain control of erection. In their pioneering experiments, they mapped the proerectile regions of the brain in great detail (28) Secondly, Jose Delgado and associates performed a set of experiments showing they were able to stop and activate aggressive and defensive behaviour acutely in animals (29-31) Animals, primarily non-human primates, were implanted with a stimulating electrode which could be activated by a remote-controller (radio-control) One of Delgado's more publicly known experiments is the study in which they implanted electrodes into the brain of a bull and set it loose in the arena to charge a matador. The matador (Delgado himself) had a remote controller and just before the bull attacked him, he activated the electrode and the bull stopped immediately. These historical considerations show that brain stimulation has a long and highly fascinating past.

The technique currently known as DBS is the refined version of the old technique as discussed above and was introduced in 1987 by Benabid and co-workers for the treatment of parkinsonian patients (32) In this review, we will primarily focus on this new technique and its application in preclinical experiments. Preclinical DBS-experiments have been carried out to investigate the mechanisms underlying the clinical effects of DBS for at least three (interrelated) reasons: to increase our scientific knowledge, to optimize/refine the technology, or to prevent/reduce side-effects. Only few studies have been carried out in non-human primates and were focused on motor behaviour (33, 34) All studies on the cognitive and limbic effects of DBS have been performed in rodents so far. Some of the studies were carried out also on intact animals to provide more information regarding the involvement of the STN in behavioural functions

4. DEEP BRAIN STIMULATION IN ANIMAL MODELS OF MOVEMENT DISORDERS

4.1. Models of Parkinson's disease

The first study in a freely moving rat (intact and model of PD) on the effects of unilateral DBS was published in 2003. Darbaky and colleagues performed unilateral STN stimulations in control rats and in rats with unilateral nigral injections of 6-OHDA (35) Using platinium bipolar electrodes, they set the stimulation parameters at a frequency of 130 Hz and a pulse width of 60 μs. The amplitude of the stimulation (50 μA) was set just below the dyskinesia-inducing threshold. They first showed that STN DBS had a beneficial effect on basic motor deficits induced by either haloperidol treatment or unilateral 6-OHDA nigral depletion. Indeed, STN DBS decreased haloperidol-induced catalepsy and also reduced apomorphine-induced circling behaviour in DA-depleted rats.

Reaction time (RT) performance is frequently used in animal models to evaluate cognitive and motor performance (36) This task is based on operant conditioning and is very suitable to use in DBS experiments, since the subject can be tested repeatedly while cognitive and motor performance are evaluated simultaneously. There are various forms of RT tasks generally divided into simple RT (SRT) and choice/complex RT (CRT) tasks.

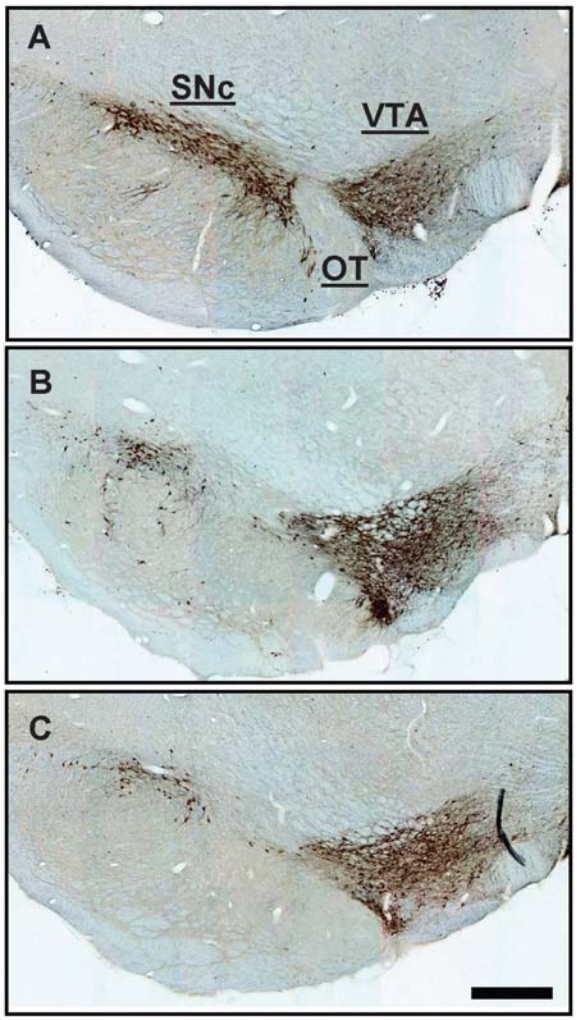

Figure 1. Representative low-power photomicrographs of 30 μm-thickfrontal sections immunoprocessed for TH, showing the ventral tegmental area (VTA) and the SNc in the brain of a rat subjected to stereotactic bilateral vehicle injection into the striatum (sham), a rat subjected to stereotactic bilateral 6-OHDA injection into the striatum (6-OHDA), and a rat subjected to both stereotactic bilateral 6-OHDA injection into the striatum and stereotactic implantation of electrodes to stimulate the STN (6-OHDA + stimulation) The photomicrographs show similar frontal levels in the midbrain in which the optic tract (OT) divides the THir cells into the VTA (medial) and SNc (lateral) regions. Bilateral 6-OHDA lesion resulted in a substantial reduction in the number of THir cells in the SNc (B, C) (scale bar = 500 μm) Adapted with permission from Temel *et al.* (39).

Darbaky and co-workers tested the effects of STN DBS in rats trained to perform a CRT task, in which the rats were required to sustain a nose-poke in a central hole and wait for a light presented either at the left or right side-hole before responding by making a nose-poke in the illuminated hole. The effects of STN DBS were not as strong as on basic motor tests. STN DBS, indeed, had beneficial effects, only in those animals that were able to perform the task after the unilateral 6-OHDA lesion, by slightly improving their neglect towards the contralateral side of the lesion. In those animals not able to perform the task after the dopaminergic lesion, the STN DBS had no "awakening" effect and was unable to help them perform the task. The authors suggested that STN DBS was beneficial in alleviating the motor deficit, but unable to help improving the performance when a cognitive load was required.

Temel and associates reported the effects of bilateral STN DBS in rats (37) Before this study was performed, the authors faced the problem of correct stimulation settings to perform STN DBS in their rat models. They observed a substantial amount of histological damage when applying previously published stimulation parameters in anesthetized rats and found out that this was due to the difference in polarity which was responsible for the occurrence of histological damage (38) The stimulation parameters were therefore adjusted to prevent histological damage in their rat models

In their next study, DBS was applied to the STN of non-depleted rats with various stimulation parameters during a CRT task (37) Results showed a significant linear decrease in premature responding with decreasing amplitudes and high frequencies only. It was suggested that a decrease in premature responding could be attributed to a stimulation-dependent increased activation of pre-motor cortical areas associated with the 'motor readiness potential' resulting in modulated cognitive performance. The same group conducted a second study in which bilateral STN DBS was applied in bilateral striatal 6-OHDA depleted rats again during a CRT task (Figure 1) (Figure 2) (39) Stimulations were performed at 130 Hz (frequency) and 60 μs (pulse width) because these parameters were shown to be effective in the previous study (37) In addition, varying amplitudes of 1, 3, 30 and 150 μA were applied. Bilateral STN DBS with an amplitude of 3 μA significantly decreased 6-OHDA-induced deficit in premature responding. Stimulation with an amplitude of 30 μA reversed the lesion-induced motor deficits. These data showed that bilateral STN DBS could acutely and separately influence the 6-OHDA-induced motor- and cognitive deficits. The authors attributed these findings to unique physiological properties of the basal ganglia-thalamocortical motor and associative circuits, responsible for specific motor and cognitive performances.

Very recently, Baunez and co-workers reported the effects of bilateral STN DBS in the five-choice serial reaction time task. This task is particularly adapted to assess divided and sustained attention (40) In this task, the rats were trained to wait and detect a brief light presented at one of five possible locations and had then to make a nose-poke in the illuminated hole. Bilateral STN lesion effects had been characterized in this task and revealed multiple and independent deficits, suggestive of attentional deficits, disinhibition and perseverative problems as well as motivational exacerbation (8) A further study characterized the effects of bilateral 6-OHDA striatal lesion expressed mainly by a slight attentional deficit and perseverative behaviour in addition to motor impairment. Most of the cognitive impairments induced by this dopaminergic depletion were not alleviated by a bilateral STN lesion (41) Bilateral STN DBS applied at similar

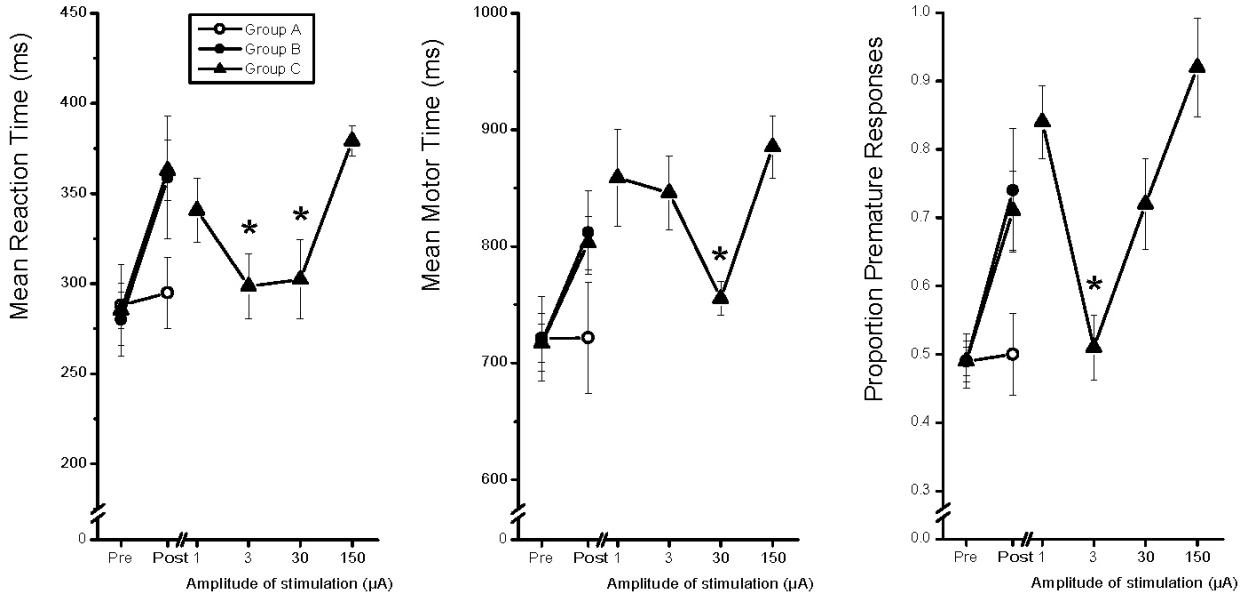

Figure 2. Results of the behavioural testing of rats subjected to vehicle injection into the striatum (group A), rats subjected to 6-OHDA injection into the striatum (group B) and rats subjected to both 6-OHDA injection into the striatum and implantation of electrodes to stimulate the STN (group C) Data are shown as mean ± S.E.M., and are given as mean reaction time (RT; on the left), mean motor time (MT; middle) and proportion of premature responses (PR; on the right) in a specific choice reaction time task (36) On the x-axis, data are organized in the following order: preoperative data from all rats (Pre), postoperative data from all rats (Post; note that these data also represent the stimulation off data from rats in group C), and stimulation-dependent data from rats in group C as a function of the stimulation amplitude. Repeated measures ANOVA revealed significant differences in the post-operative data between the groups ($p < 0.05$) as well as significant differences between the post-operative data and the stimulation-dependent data of group C. The p values from the corresponding post-hoc LSD tests are provided as * ($p < 0.0125$) Note that bilateral STN DBS significantly improved RT at both 3 µm and 30 µA, MT only at 30 µA, and PR only at 3 µA. Adapted with permission from Temel *et al.* (39).

parameters to those used in a previous study (35) induced comparable deficits to those observed after STN lesions in intact rats ((attentional deficit, perseverative behaviour, as well as increased perseverations towards the magazine, this latter being suggestive of motivational exacerbation), although some of these deficits were only transient under DBS (27) Interestingly, when DBS was applied in 6-OHDA lesioned rats, it did not impair their performance further, but did not alleviate the deficits induced by the DA lesion either. The most relevant effect observed after STN DBS in both intact and parkinsonian rats was the increased perseverations towards the food magazine, suggestive of increased motivation for the food reward (Figure 3) (27)

4.2. Models of Huntington's disease

In a different model of a movement disorder, a transgenic rat model (tgHD) of Huntington's disease (HD), Temel and associates studied the effects of globus pallidus (GP, equivalent of the globus pallidus externus in primates) DBS on cognitive and motor symptoms. This rat model has recently been generated and carries a truncated huntingtin cDNA fragment with 51 CAG repeats (42) Before performing DBS, the authors first tested the tgHD (homozygotic and heterozygotic) rats behaviourally in a CRT task and open field task at an age of 15 and 20 months (43) Their results showed that tgHD rats exhibit an age-, and genotype-dependent deterioration of the psychomotor performance and choreiform symptoms, closely mimicking the clinical time course changes of psychomotor symptoms of HD patients. In a second study, the same group evaluated the histopathological characteristics of tgHD rats. They found that tgHD rats show adult-onset neuron loss in striatum and frontal cortical layer V, exhibiting enlarged ventricles, striatal atrophy and pycnotic pyramidal cells in frontal cortical layer V. No alterations in mean total numbers of striatal neurons were found in six-month-old animals. With these two studies, the authors demonstrated that tgHD rats share adult-onset cardinal features of the human HD neuropathology and show progressive cognitive and motor symptoms similar to human HD. After these two model-validation studies, the authors implanted tgHD rats with stimulating electrodes at the level of the GP (Figure 4) (44) Rats were evaluated in a CRT and an open field task. Stimulation of the GP clearly reduced the number of premature responses. Premature responding is thought to reflect the inability to inhibit unwanted responses (6) and is a key feature of cognitive dysfunction in HD (45) DBS with medium amplitude (30 µA) decreased premature responses most effectively, while DBS with the higher amplitude (150 µA) significantly reduced the choreiform movements in the tgHD rats (Figure 5) (44).

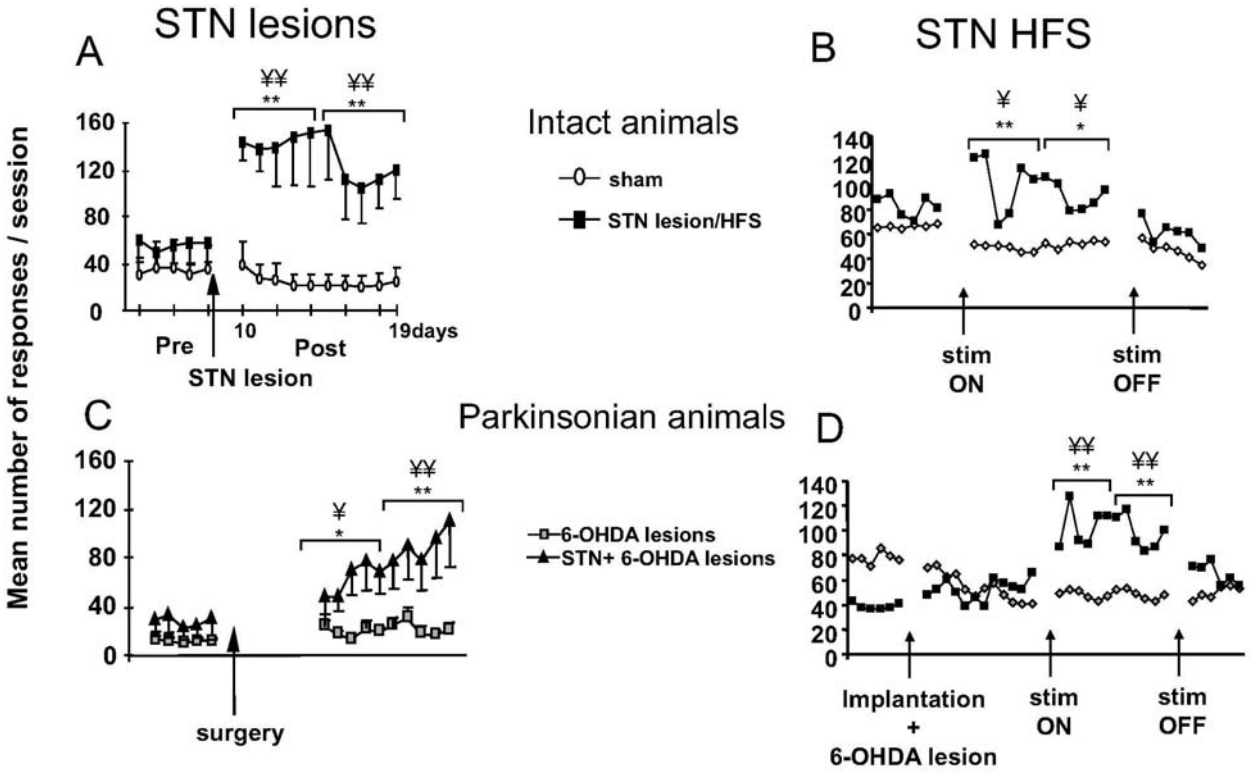

Figure 3. Effects of bilateral STN lesions (left; A, C) compared with STN High Frequency Stimulation (HFS) (right; B, D) on the number of perseverative responses in the food magazine recorded during the performance of the attentional task (5-choice serial reaction time task) in intact animals (upper part; A, B) and in parkinsonian rats (bilateral infusion of 6-OHDA in the dorsal striatum) (lower part; C, D) Sham performance is illustrated in empty symbols while STN lesions or HFS in black filled symbols (A,B) 6-OHDA performance is illustrated in grey-filled symbols and 6-OHDA + STN lesion of HFS in black filled symbols (C, D) *,**: $p<0.05$, 0.01 respectively when compared with sham control group (intact animals), or 6-OHDA group (parkinsonian animals), ¥, ¥¥: $p<0.05$ and 0.01 respectively when compared with pre-operative performance. Adapted with permission from from Baunez *et al.* (8) (27)

5. DEEP BRAIN STIMULATION IN ANIMAL MODELS OF PSYCHIATRIC DISORDERS

5.1. Animal models of obsessive-compulsive disorder

Van Kuyck and colleagues used a rodent model for obsessive-compulsive disorder (OCD) and evaluated the effects of DBS of the nucleus accumbens in a freely moving animal (46) Rats that received 8-OH-DPAT, a 5-hydroxytryptamine (5-HT = serotonin) 1A agonist, showed a reduction of spontaneous alternation behaviour in the T-maze. According to the authors, this behaviour models the compulsive and repetitive behaviour of patients suffering from OCD. Both 5-HT lesions and DBS (5 Hz and 100 µA) significantly reduced spontaneous alternation behaviour, which reflects an increase in compulsive behaviour. In this study 5 Hz was used as stimulation frequency. High frequency stimulation was not evaluated. In a study with humans, high frequency stimulation of the nucleus accumbens was effective in reducing OCD symptoms (47) These results clearly show that the nucleus accumbens is involved in compulsive behaviour. Further investigations are necessary to evaluate the therapeutic value of the nucleus accumbens as a target for DBS in animal models of OCD. More emphasis on the effects of different stimulation paradigms is needed.

5.2. Animal models of depression

The forced swim task (FST) is a well-validated animal model of depression that is sensitive to changes in 5-HT (48) In this animal model of depression, Temel and co-workers showed that DBS of the STN in rats worsened the depressive symptoms (49) The FST task has originally been developed by Porsolt and colleagues (50) and later modified by Detke and Lucki (51) This test is based on exposure to a learned inescapable stressor, and the measurement of immobility that is thought to reflect a failure of persistence in escape-directed behaviour, also referred as behavioural despair (48, 50, 52) The duration of immobility has been shown to correlate significantly with the antidepressant effect of antidepressant drugs: the lower the duration of immobility, the greater the antidepressant effect of the drug. Temel and co-workers showed that bilateral DBS of the STN (130 Hz, 60 µs, 150 µA) caused a striking increase in immobility and a decrease in climbing time of stimulated rats compared to non-stimulated controls, thereby indicative of the induction of behavioural

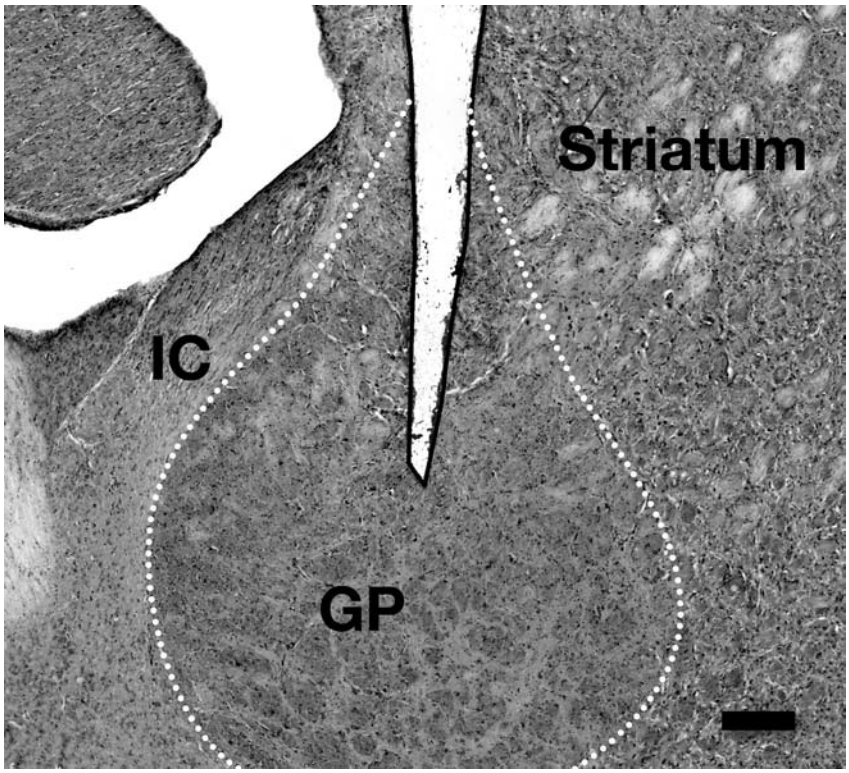

Figure 4. A representative low-power photomicrograph of a 30 μm-thick frontal section from the brain of a rat with bilateral electrode implantation in the globus pallidus (GP, equivalent of globus pallidus externus (GPe) in primates) The tip of the electrode is situated within the GP (scale bar = 200 μm) The surrounding structures are the striatum and the internal capsule (IC) The white dotted line shows the boundaries of the GP and the dark line delineates the boundaries of the electrode trajectory. Adapted with permission from Temel *et al.* (44)

'despair. This effect was present both in normal and parkinsonian (6-OHDA model) animals. Importantly, the effects of DBS of the STN stimulation in the FST were completely prevented by a prior course of treatment with the selective 5-HT reuptake inhibitor, citalopram, at a dose (10 mg/kg s.c., once daily for 14 days) that by itself had no significant effect in non-stimulated controls (Figure 6) (49) To exclude any motor effect of STN DBS that may confound the results of the FST, the authors demonstrated that in an open field paradigm, DBS of the STN had no effect on motor activity. In contrast, we found that DBS of the STN (using the same stimulation parameters) reversed motor-time deficits in parkinsonian lesions in agreement with previous results (39) These data show that STN DBS in rats causes an acute induction of depression-like behaviour. This link between the STN and 5-HT system supports the existence of a novel 'motor-limbic interface' that may contribute to mood disturbances in basal ganglia disease.

Besides the abovementioned study in which the authors induced depression by DBS, the authors are not aware of a published preclinical study in which DBS reduced the depressive symptoms.

5.3. Animal models of panic disorder

Electrical stimulation of the dorsal periaqueductal gray (PAG) is a well-known animal model for panic disorder (53) It has been demonstrated that electrical stimulation of this area in rats leads to "escape behavior" characterized by running, jumping, and galloping (54) To date, experiments involving PAG stimulation were designed to evoke rather than to inhibit the panic-like behaviour. Stimulation paradigms used in these studies were relatively simple and stimulation frequencies were usually in the range of low frequency. In a recent study, Lim and co-workers addressed the question whether DBS (brain stimulation paradigm using state of art technology) at high frequencies of the PAG could inhibit panic-like behaviour (55) In addition, in the same study they investigated the effect of different stimulation frequencies on escape behaviour. All animals were subjected to the stimulation parameters at: pulse width (100 μs), frequency (1- 300 Hz) and amplitude (1- 650 μA) Their results showed that stimulation with any stimulation frequency between 1 and 300 Hz induced escape behaviour. Furthermore, they also noticed the effect of post-stimulation in which the stimulated animals displayed intense fear or immobility after the animals were placed back to the same open field arena of stimulation. It is noteworthy, that this type of behaviour, the unconditioned fear or anxiety generated by the dorsal lateral PAG stimulation has been considered for future research development in psychopharmacological challenge of anti-panic and anti-anxiety drugs.

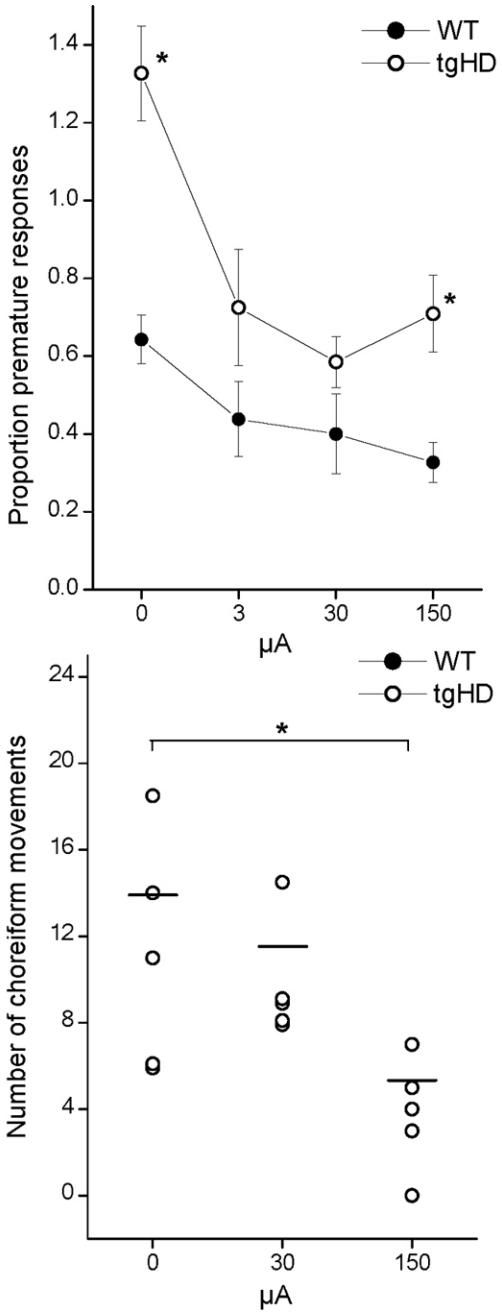

Figure 5. Means and standard errors of the proportion of premature responses (PR) (left figure) and the number of choreiform movements (right figure) in both wildtype (WT) and transgenic Huntington's disease rats (tgHD) in relation to different stimulation amplitudes. Deep brain stimulation of the globus pallidus (GP) improved significantly the cognitive deficit (PR) and the motor disorder (choreiform movements) in tg HD rats. **P*<0.05. Adapted with permission from Temel *et al.* (44)

6. DISCUSSION

In this review we have summarized the cognitive and limbic effects of DBS in preclinical reports. These reports can be divided into studies focusing on models of movement disorders and psychiatric disorders. With respect to movement disorders, experiments have shown that STN DBS in parkinsonian and in intact rats have profound effects on cognitive and motivational parameters, while improving parkinsonian motor deficits (27, 35, 37, 39)

The involvement of the STN in non-motor functions was already demonstrated by Baunez and associates (7, 8) before STN DBS was performed on such a large scale in PD patients. Due to the profound effects of STN DBS on cognitive and limbic functions, clinicians should evaluate each individual PD patient carefully before considering them for STN DBS. On the other hand, these results suggest that STN DBS might also be a target for cognitive and limbic disorders. For instance, it has been shown that STN DBS increased perseverative visits to the food magazine. This effect, interpreted as an increased motivation for the food reward, is in line with the effects described after STN lesions on motivation for food (56, 57) Interestingly, it has been shown that STN lesions increase motivation for food, but decrease motivation for cocaine (57) Taking into account the fact that STN DBS mostly mimics the behavioural effects of STN lesions, it is thus tempting to suggest that STN DBS could be an interesting surgical therapeutic tool for the treatment of cocaine addiction.

In the transgenic rat model of HD, DBS is currently being evaluated as a treatment option. HD is characterized by progressive deterioration in cognitive and motor functions (58) Cognitive symptoms often precede the choreiform movement disorder (59) Although the movement disorder can be treated pharmacologically to some extent, no effective therapies are available to treat the cognitive symptoms (58) Therefore, it is usually the cognitive dysfunction that determines the quality of life of the HD patient. In the pilot studies presented in this review, the authors have shown that DBS of the GP has the potential to improve cognitive and motor symptoms of transgenic HD rats. Currently, experiments are carried out to further evaluate the value of DBS in animal models of HD.

In the field of psychiatric disorders such as OCD, depression and anxiety, DBS is being evaluated as a possible tool to treat refractory patients. However, before DBS can be applied to new indications, preclinical studies are required to test its potential effects. There are only few preclinical studies published in this area, but the expectation is that the number of studies will increase over time substantially. Nevertheless, these few published reports are promising and supports the usefulness of DBS in psychiatric disorders.

7. PERSPECTIVE

Deep brain stimulation in freely moving animals is a recently developed technology and is extremely suitable to investigate clinically driven research questions in the field of neuromodulation, which is a fast-emerging and exciting field of neuroscience. So far, the most commonly targeted structure in preclinical experiments is

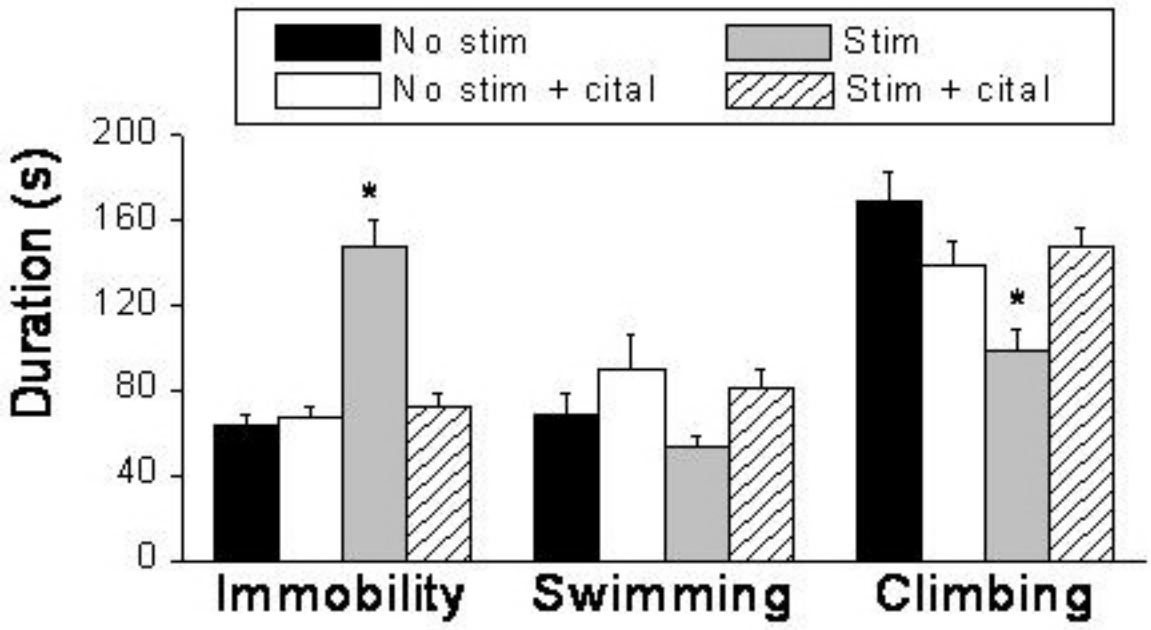

Figure 6. Effect of high-frequency stimulation of the STN on different behavioural measures in the forced swimming test. Four groups of rats (6 per group) were implanted with electrodes in the STN. Group treatments were as follows: i) no STN stimulation during test (No stim), ii) pre-treatment with citalopram followed by no STN stimulation during test (No stim + cital) , iii) STN stimulation during test (Stim), and iv) pre-treatment with citalopram followed by STN stimulation during test (Stim + cital) Stimulation parameters were 130 Hz and 150 μA for the duration of the test. Citalopram pre-treatment comprised 10 mg/kg i.p. for 14 days. Bars represent mean±s.e.m. values (n=6) Statistical analysis (2-way ANOVA with repeated measures, post hoc Duncan's test) revealed that STN stimulation was significantly different from other groups with respect to immobility and climbing (F-values>11.4, *P<0.05) Adapted with permission from Temel *et al.* (49)

the STN. Results show that STN DBS can have profound effects on cognitive and limbic functions, and suggest that the STN is not only a target for movement disorders but also for psychiatric conditions. Particularly, the applicability of STN DBS in drug addiction is currently under investigation.

In other areas, the usefulness of DBS as a therapy is currently being evaluated in several animal models of neurodegenerative disorders such as HD and psychiatric disorders such as OCD. These experiments are extremely important both scientifically, to increase our understanding of brain function and dysfunction, and ethically, since these experiments offer researchers the possibility to evaluate this therapy in preclinical conditions before applying to humans.

8. ACKNOWLEDGEMENTS

The deep brain stimulation program of Yasin Temel and colleagues received support from the Dutch Medical Research Council (ZonMw and NWO), the Dutch Brain Foundation (Hersenstichting Nederland), and the Prinses Beatrix Foundation. The STN deep brain stimulation program run by Christelle Baunez and colleagues was supported by the CNRS, the 5th PCRDT of the European community (QLK6-1999-02173) and the Association France Parkinson.

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Abbreviations: DBS: deep brain stimulation, STN: subthalamic nucleus, PD: Parkinson's disease, RT: reaction time, SRT: simple reaction time, CRT: complex reaction time, tgHD: transgenic Huntington's disease, HD: Huntington's disease, GP: globus pallidus, OCD: obsessive-compulsive disorder, 5-HT: 5-hydroxytryptamine, FST: Forced swim task, PAG: periaqueductal gray

Key Words: Animal models, Subthalamic nucleus, Parkinson's disease, Huntington's disease, Deep brain stimulation, Neurological, Psychiatric, Panic, Depression, Obsessive-compulsive disorder, Nucleus Accumbens, Basal Ganglia, Serotonin, Forced Swim Task, Review

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