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The Translational Value of the MPTP Non-Human Primate Model of Parkinsonism for Deep Brain Stimulation Research

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Abstract—**Deep brain stimulation (DBS) has been applied in more than 70000 patients worldwide during the last two decades. The main target is the subthalamic nucleus (STN) for the treatment of motor complications in late stage Parkinson's disease (PD). Positive results in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primates have set the grounds for its successful translation to PD patients. Since then, this model has allowed gaining significant insights in the underlying mechanisms of action of DBS and is currently being used for the development of new stimulation techniques. Altogether, this underpins the high potential of this preclinical model for future translation of DBS research in PD.**

I. Introduction

DEEP brain stimulation (DBS) has been applied in more than 70000 patients worldwide during the last two decades. DBS is mainly applied in the subthalamic nucleus (STN) in Parkinson's disease (PD) [1-3], the globus pallidus internus (GPi) in dystonia [4] and PD [2], and the ventral intermediate nucleus of the thalamus (VIM) in essential tremor [5]. Other nuclei e.g. the pedunculopontine (PPN) [6, 7] and the centromedian-parafascicularis nucleus (CM-Pf) [8] are currently being explored for PD. DBS is also assessed in other indications e.g. treatment refractory Gilles de le Tourette syndrome [9] and depression [10].

STN-DBS is successful in the management of late stage Parkinson's disease (PD)[1-3]. However, in line with the progressive nature of PD, the therapeutic effect on motor signs decreases over time [11, 12], some patients have an unsatisfactory outcome despite proper electrode placement and side effects such as worsening speech, reduced verbal fluency and weight gain affect an important number of patients. Some of these side effects may result from current spread to remote structures. Techniques that restrain the volume of the tissue activated may therefore allow reducing or avoiding them. Another reason of current limitations may be that stimulation parameters of classical DBS are set according to empirical algorithms [13] which do not take advantage of the latest discoveries of PD pathophysiology such as abnormal oscillatory activity in the basal ganglia network [14]. Altogether, this underlines that continued efforts are needed to overcome current limitations with available DBS techniques.

Positive results on motor control in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primates have set the grounds for the successful translation of STN-DBS to PD patients in the early nineties [15]. Since then, this model has allowed gaining significant insights in the underlying mechanisms of action of DBS and is currently being used for the development of new stimulation techniques (cf. below). Altogether, this underpins the high potential of this preclinical model for future translation of DBS research in PD.

II. Technical considerations

A. The MPTP non-human primate model of parkinsonism

Following the observation that MPTP can induce parkinsonism in humans [16], different MPTP-treated models were established in non-human primates. They are based on the injection of the toxin either in the muscle, the carotid artery or intravenously. Depending on the procedure, lesioning of the nigrostriatal dopamine system occurs more or less quickly (for review see [17]). MPTP-treated non-human primates reproduce clinical hallmark features of PD, i.e. bradykinesia and rigidity, while only few species such as green monkeys display tremor.

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In recent years, we have proposed a progressive model of parkinsonism, where animals receive daily injections of small amounts of MPTP until developing motor symptoms [18, 19]. This model allows obtaining a more than 95 percent bilateral depletion of striatal dopamine.

B. Stimulation electrodes and devices

A scaled-down version of human DBS macroelectrodes (Model 3387, Medtronic Inc., Minneapolis, MN; four contacts with a diameter of 0.76 mm, a thickness of 0.50 mm and a separation between contacts of 0.50 mm, NuMED Inc, Hopkinton, NY) is commercially available. Contact thickness and the separation between contacts can be further customized upon request. Proper placement of the stimulation electrodes in the STN can be achieved under guidance by stereotactic ventriculography, intraoperative extracellular recordings and postoperative x-rays. Furthermore, a stereotaxic non-human primate atlas of the basal ganglia is available [20] allowing the preoperative calculation of the stereotaxical coordinates of the stimulation electrodes.

Once in place, the stimulation electrodes can be connected to the same implantable pulse generator that is used in the clinical setting. Another possibility is to perform stimulation with an external device while the animal is seated in a primate chair. A detailed description of the surgical procedure is provided elsewhere [21].

C. Clinical outcome measures

As in the clinic, the severity of PD motor symptoms can be monitored by a video-taped assessment of disability scores by experienced and blinded scorers. Ratings in MPTP-treated non-human primates are performed by using an established scale that is inspired by the human Unified Parkinson's Disease Rating Scale [22]. The scale assesses tremor, posture, general activity, vocalization, freezing, rigidity and slowness of arm movements. The maximum disability score is 25. A score of 0 corresponds to a normal animal and a score above 6 to a parkinsonian animal. During the progressive induction of parkinsonism, MPTP injections are usually stopped after the disability score reaches 8 points.

Another possibility is the use of an automatic assessment of locomotor activity as endpoint for preclinical studies [23].

III. VALUE OF THE MPTP MODEL FOR TRANSLATING DBS

A. Effect of DBS on basal ganglia activity

The overall mechanisms of action of DBS remain incompletely understood. Several studies in MPTP-treated non-human primates and PD patients have reported consistent changes in firing activity of STN and GPi neurons during STN-DBS [24-28]. According to these studies, firing rate of STN neurons decreases while those of GPi neurons increases during STN-DBS. In both, MPTP-treated non-human primates and PD patients, time-locked responses to STN stimulation pulses have been observed in pallidal neurons [27-29].

Beyond these findings, data from MPTP-treated non-human primates have helped to model the contribution of STN projection neurons and fibers of GPi and internal capsule to overall pallidal activity changes during STN-DBS [29, 30]. Clinically effective STN-DBS activated STN projection neurons in both investigated animals, and GPi and internal capsule fibers in one animal. Time-locked responses to STN stimulation differed between animals according to the respective contribution of the involved neural elements, i.e. STN projection neurons and adjacent fibers of passage. An analysis of mean firing rate and firing pattern also showed differences between animals with significant changes in one although motor symptoms were improved in both [30]. Altogether, this suggests that disrupting abnormal basal ganglia activity is the most important action of STN-DBS which may be achieved via STN projection neurons or adjacent fibers of passage. Another possibility may be antidromic activation of cortical areas through stimulation of cortico-subthalamic fibers as has recently been suggested [31].

In recent years, abnormal synchronization in the basal ganglia network has been proposed as a key feature of PD. It has been found in MPTP-treated non-human primates and PD patients [14, 24, 32-38]. A few studies have assessed the effect of STN-DBS on synchronized activity in the basal ganglia. Findings were again consistent between PD patients and MPTP non-human primates showing that STN-DBS decreases abnormally synchronized activity [24, 39].

While recordings in patients are often limited by the short time that offers the surgical procedure, the MPTP-treated non-human primate model provides a unique opportunity to study the mechanisms of action of DBS. This in underpinned by previous studies that have allowed gaining significant insights in the mechanisms of action of DBS and the interplay between the different neural elements that are believed to mediate the beneficial effects of STN-DBS. Furthermore, in contrast to rodents, findings in MPTP-treated non-human primates can easily be related to clinical outcomes.

IV. NEW STIMULATION TECHNIQUES

A. Coordinated reset stimulation

Changes in synaptic connectivity in the dopamine depleted state may underlie the appearance of abnormal synchronized activity in the basal ganglia [40]. Based on a stochastic phase resetting theory [41], in a number of generic as well as physiology motivated theoretical models, we have shown that synaptic connectivity can be reshaped by using novel desynchronization techniques [42-44]. Accordingly, coordinated reset stimulation (CR), i.e. brief high-frequency pulse trains delivered via different sites at different times, enables the network to unlearn strong synaptic interactions. A brief high-frequency pulse train is a weak stimulus which does not block neuronal firing and which is unable to provide complete desynchronization during stimulus

delivery. It rather resets the phase of the stimulated neurons. Since brief high-frequency pulse trains are applied at different sites and times, the population splits into several subpopulations followed by desynchronization of the population activity. Moreover, desychronization continues even though stimulation is turned off.

According to theoretical considerations, CR stimulation is the most effective when (i) the stimulation frequency is close to the frequency of abnormal basal ganglia oscillations [42, 45] and (ii) the volume of tissue activated by the brief high-frequency pulse trains that are delivered through the different electrode contacts is not overlapping [46].

As yet, a clinical application of CR stimulation is limited. On the one hand there is no approved implantable CR device. On the other hand in a study in externalized patients the window between surgery and implantation is short (1 week), because of the risk of infection and ethical concerns.

Because of these limitations, we have assessed the effects of external CR (an implantable device is under development and will soon be tested *in vivo*) in three MPTP-treated non-human primates with a portable stimulator fulfilling all medical device requirements for a study in humans and capable of standard DBS and CR stimulation [47]. Three protocols were tested in each animal: (i) classical DBS, (ii) CR with "DBS-like intensity" and (iii) CR with low intensity.

CR consisted in the random application of brief high-frequency pulse trains (5 pulses with an intraburst frequency of 150 Hz, i.e. the duration of each train was 33.3 ms) through the 3 lower contacts of the scaled-down version of the human DBS macroelectrode. Pulse width was set at 120µs. The delay between subsequent brief high-frequency pulse trains was 47.6 ms corresponding to a CR stimulation frequency of 7 Hz which is close to the frequency of abnormal oscillations in MPTP treated non-human primates [24]. Each stimulation cycle included three brief high-frequency pulse trains that occurred with a delay of 47.6 ms, i.e. the total duration of each cycle was 142.8 ms. Three cycles of CR were followed by 2 cycles without stimulation.

In each protocol, stimulation was applied for 2 hours over 5 days. Locomotor activity was assessed the days of stimulation (after the end of external CR or DBS) and during the post-stimulation period as long as it was different from baseline. STN-DBS increased locomotor activity the days of stimulation corresponding to a transient after-effect as seen in PD patients. CR with "DBS-like intensity" had a small effect on locomotor activity the days of stimulation which became significant during the 5 days after the end of CR. CR with low intensity significantly improved locomotor activity the days of stimulation. A significant effect persisted for 35 days.

Altogether, our preliminary data suggest that CR, an innovative form of DBS, improves locomotor activity in MPTP treated non-human primates. As predicted [46], CR with low intensity seems to be more effective than those with "DBS-like intensity". Compared to classical DBS, CR had sustained effects on motor symptoms suggesting the induction of plastic network changes. An ongoing project in MPTP-treated non-human primates will allow assessing the effect of CR during stimulation.

In conclusion, the MPTP model of parkinsonism has proven its usefulness in translating DBS research to PD patients. New stimulation techniques are currently being explored in this model and will soon head to the clinic if preliminary preclinical results are confirmed.

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