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Invasive and Non-Invasive Stimulation in Parkinson's Disease

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1. Introduction

The ability of the brain to process information relies on its control of the conduction of electric currents. Brain diseases invariably affect this capability. One of the therapeutic approaches to a variety of neurological disorders therefore includes the application of electric currents and fields to the brain. A successful example of this strategy is the introduction of deep brain stimulation which has become a cornerstone of the therapy of advanced Parkinson's disease (PD), dystonia and essential tremor. Several studies have proven its effectiveness and often patients respond immediately to this therapy. Invasiveness and complexity of this treatment restrict its indication. On the other hand, there are techniques for the non-invasive modulation of cortical excitability namely transcranial magnetic stimulation (TMS) as well as transcranial direct current stimulation (tDCS). These techniques have been investigated in several studies including patients with PD. However results so far are heterogeneous and limit their therapeutic value. In the following chapter the basic principles of as well as therapeutic experiences with invasive and non-invasive electrical stimulation techniques and their applications in patients with PD will be discussed.

2. Electrical stimulation in Parkinson's disease

2.1 Invasive electrical stimulation in Parkinson's disease

In the modern era of medicine the modification of cerebral function by electrical stimulation for therapeutic purposes was considerably influenced by the introduction of stereotactic methods into neurosurgery in the middle of the 20th century (Hariz et al., 2010). The stereotactic induction of lesions in the medial nucleus of the thalamus (medial thalamotomy) was reported in a first series with psychiatric patients "in order to reduce the emotional reactivity by a procedure much less drastic than frontal lobotomy" (Spiegel et al., 1947). The frontal lobotomy which was a psychosurgical treatment for psychoses at that time was associated with significant irreversible cerebral destruction. Therefore, applying thermocoagulation with a wire or cannula inserted stereotactically through the intact dura to induce a defined lesion within a distinct cerebral structure in patients with psychiatric disorders revealed a significant therapeutic advancement. Simultaneously, the potential of this technique for the treatment of movement disorders or pain syndromes was suggested (Spiegel et al., 1947). Indeed, the first pallidotomies performed at that time

had morbidity rates of 45% and a mortality rate of 15% (Gildenberg P.L., 2003). Stereotactically implanted intracranial electrodes offered the opportunity not only to induce a structural lesion by thermocoagulation but also to identify the basal ganglia electrographically by its distinct pattern of recordable neuronal activity. A related approach without the use of stereotactic instruments but with a similar technique was named chemopallidectomy and consisted in the instillation of absolute alcohol in the globus pallidus with an intracranial cannula. Reduction of rigidity or tremor in several geriatric parkinsonian patients who were considered to old for the alternative and complex anterior choroidal artery occlusion provided evidence for the potential of surgically targeting the basal ganglia for the treatment of movement disorders (Cooper I.S., 1955). Intracranial intraoperative electrical stimulation of the inserted electrodes was conducted early on in order to thereby identify potential targets for the induction of a lesion. Stimulation was performed with low (~ <30 Hz) and high (~ >30 Hz) frequencies in different centers at that time and a significant therapeutic effect of high frequency stimulation at 100 Hz with intracranial stimulation has been described in the early phase of this new therapy (Gildenberg P.L., 2003). Still, even though electrodes were left in place intracranially up to several days electrical stimulation was applied for diagnostic and not for therapeutic purposes. With the introduction of levo-dopa for the treatment of PD its surgical therapy became infrequent. In the following years intracranial electrical stimulation was tested as experimental procedure for a variety of disorders e.g. as a treatment for refractory pain or with cerebellar implants for the treatment of epilepsy (Gol A., 1967; Shealy et al., 1967; Cooper et al., 1976). Devices for chronic subdural electrical stimulation were developed within the same time. The idea of chronically implanted subdural electrodes on the visual cortex working as "prosthesis" for the blind by inducing meaningful visual perceptions in blind patients by electrocortical stimulation was realized in a few patients (Brindley G.S. and Lewin W.S., 1968). Still, this method was not implemented in larger groups of patients for a variety of reasons. Also, early promising results of therapeutic deep brain stimulation in epilepsy or pain could not be reproduced by following studies leading to a subsequent decline of deep brain stimulation in epilepsy. In succession torticollis spasmodicus appears to be the first disorder of the motor system that has been treated with chronic electrical stimulation of the spinal cord (Gildenberg P.L., 1977). Then, in the 1980s the group of Benabid and colleagues rediscovered the beneficial therapeutic effect of intracranial electrical stimulation. Their report of the suppression of parkinsonian and non-parkinsonian tremor when stimulating the nucleus ventralis intermedius of the thalamus (VIM) intraoperatively before VIM thalamotomy as well as the first description of permanent implantation of deep brain stimulators into the VIM in four patients pioneered the surgical treatment of PD by deep brain stimulation as applied today (Benabid et al. 1987).

2.1.1 The object of invasive electrical stimulation in Parkinson's disease

The important role of the basal ganglia for movement control has probably been recognized in the 17th century (Lanska D.J., 2010). Modern concepts of function of the basal ganglia have lead to and benefit from the introduction of neurosurgical approaches in the therapy of movement disorders like PD. The basal ganglia include the striatum (putamen and caudate nucleus), the globus pallidus internus (GPi), the globus pallidus externus (GPe), the subthalamic nucleus (STN), the subtantia nigra pars reticularis (SNr) and the substantia nigra pars compacta (SNc). The basal ganglia receive their main

external input from the primary motor cortex (M1), premotor areas including the supplementary sensorimotor area (SSMA) and the cingulate motor area in the anterior cingulum. Additionally, the ventrolateral and the ventral anterior nuclei of the thalamus project to the basal ganglia. The striatum is the first relay and therefore the main gate for a majority of the afferents to the basal ganglia. Also the STN receives primary afferents from the aforementioned cortical areas (Table 1). Importantly, the projections to the basal ganglia are highly organized by means of their functional and topographic origin into three main groups of afferents (Parent A., 1990). First, afferents from M1 and premotor areas including the SSMA preferentially project to the postcommissural putamen; second, afferents from prefrontal cortex project to the precommissural putamen and the caudate nucleus; third, those afferents originating in limbic areas including the anterior cingulum and the orbitofrontal cortex project primarily to the ventral striatum. Additionally, afferents from the primary motor regions are organized somatotopically including distal limb projections (Bauswein et al., 1989). This organizational principle of afferents has been recognized in the striatum as well as in the STN whose dorsolateral part receives information from M1, while its ventrolateral part receives projections from the caudal cingulate motor area. The SSMA and the pre-SSMA as well as the rostral part of the cingulate motor area project to the dorsomedial part of the STN, while other premotor areas connect to its ventromedial part (Hartmann-von Monakow et al., 1978; Takada et al., 2001). Electrophysiological studies in non-human primates revealed that corticostriatal neurons differ in their neurophysiological properties from corticospinal neurons. The former show slower conduction velocities, lower discharge rates and a different response pattern to somatosensory input. Indeed, both systems appear to be supplied by completely different populations of cortical neurons (Turner and DeLong, 2000). Another important source of input to the striatum are mesencephalic nuclei with the dopamiergic projections of the SNc being the most significant. The SNc is itself influenced by feedback projections from the STN, the SNr and external afferent sources like the prefrontal and orbitofrontal cortex, the raphe nuclei, the superior colliculi. Functionally, a tonic firing pattern that can be modified by reward-learning has been recognized as a characteristic electrophysiological pattern of dopaminergic neurons of the SNc (Hollerman & Schultz, 1998, Wichmann and DeLong, 2007).

On a cellular level afferents to the striatum terminate almost exclusively on medium spiny neurons that represent 90-95% of all striatal neurons. The information processing within these GABAergic neurons is further modulated by intrinsic cholinergic and peptidergic interneurons (Wichmann and DeLong, 2007). The large majority of target-neurons in the STN is glutamatergic unlike all other nuclei of the basal ganglia and only few neurons in the human STN were found to be GABAergic (Levesque and Parent, 2005). The information is further processed via two different systems: the direct and indirect pathway. The former projects directly to the output nuclei of the basal ganglia, the GPi and the SNr. The indirect pathway is polysynaptic and its information is modulated in the GPe and STN from where it then projects to GPi and SNr as well. Medium spiny neurons forming the direct pathway preferentially exhibit dopamine D1-receptors and express substance P. Indirect pathway medium spiny neurons on the contrary do express predominantly D2-receptors and enkephalin (Gerfen et al., 1990). Therefore, both major classes of dopamine receptors - the D1-like family whose activation increases and the D2-like family whose activation decreases the concentration of the second messenger cyclic adenosine monophosphate (cAMP) - are represented in the striatofugal system. The dopaminergic projections from the SNc balance direct and indirect striatal projections within the basal ganglia, the net effect of which

promotes an inhibitory influence on the output of the basal ganglia to the thalamus leading to increased thalamocortical activity in case of the direct pathway and to an opposite effect in case of the indirect pathway (Wichman and DeLong, 2007). Loss of function of the neurons of the SNc in Parkinson's disease causes a functional imbalance of the output of the basal ganglia.

The output of the basal ganglia that arises mainly from the GPi and SNr is primarily directed towards the ventral anterior nucleus and the ventrolateral nucleus of the thalamus. From this nucleus the information is further transmitted to motor-, premotor- and prefrontal cortex (Hoover and Strick, 1993). As mentioned previously the relative topographic segregation between the three main functional input systems of the basal ganglia is maintained through the different stages of information processing including its output projections (Shink et al., 1996). Other neurons of the SNr project to the superior colliculus or the reticular formation.

While the aforementioned subcortical network maintains normal motor function in the healthy state its dysfunction in Parkinson's disease is correlate of the clinical symptoms like tremor, hypokinesia, rigidity. The depletion of dopamine in the striatum due to degeneration of the SNc is decisive in this pathophysiology and both the dysinhibition of the direct pathway as well as the increased inhibitory activity of the striatopallidal fibers of the indirect pathway finally lead to a reduced activity of thalamocortical projections to the various motor areas. Aside from the pure imbalance of inhibitory and excitatory mechanisms in PD recent research has recognized alterations in frequency and synchronization of basal ganglia circuits (Hammond et al., 2007). Some evidence suggests that increased synchronization of oscillations in the beta-frequency range between basal ganglia and cortical projection areas impair movement control and are a correlate of PD. This synchronization indeed can be suppressed by dopaminergic therapy. Further research on this subject is required.

Anatomical structure	Main transmitter
Striatum	GABA
STN	Glutamate
GPi	GABA
GPe	GABA
SNc	Dopamine
SNr	GABA

Table 1. This table lists the predominant neurotransmitters of substructures of the basal ganglia. STN = subthalamic nucleus, GPi = globus pallidus internus, GPe = globus pallidus externus, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata. GABA = gamma-amino-butyric acid.

2.1.2 The medium of invasive electrical stimulation in Parkinson's disease

Currently, the hardware implanted for deep brain stimulation includes the stimulation device or internal pulse generator, the stimulating electrode(s) and a connector between these elements. The battery driven stimulator is usually implanted subcutaneously in the subclavicular area. This device is connected to two or less often one deep brain electrode(s) by a stimulator cable that is tunneled through cervical, retroauricular and

cranial subcutaneous tissue. The deep brain electrodes have four electrode contacts at their tip counting from the most central electrode contact that is labeled as contact zero. The diameter of the lead body is 1.27 mm. The length of the electrode contact varies between 1.5 and 3 mm whereas the electrode spacing varies between 0.5 and 4 mm depending on the model of the lead. This system is controlled by an external telemetric programmer that allows to modify current intensity, pulse width, frequency of stimulation, polarity of the stimulus and electrode configuration. A typical type of deep brain stimulator offers a range of 0 - 25.5 mA in the current mode or 0 - 10.5 V in the voltage mode regarding adjustment of the stimulation intensity. The frequency of stimulation can be modified within a range of 2-250 Hz and the pulse width can be altered between 60 and 450 μs according to the manufacturer of deep brain stimulation devices (Medtronic; Minnesota, U.S.A.). However, the parameters stimulation frequency as well as pulse width are infrequently subject to changes and the fine tuning of the stimulator is commonly done by changing the stimulus intensity. Stimulation frequency is most often set at around 130 Hz providing a good ratio between efficiency and energy consumption (Volkmann et al., 2006). This is based on studies which demonstrated a high efficiency of electrical stimulation within a range of stimulation frequencies between 30 and 250 Hz when stimulation intensity is left constant (Mihailovic and Delgado, 1956). Similarly the range in which the pulse width can be varied closely reflects the most efficient and safest interval for neuronal excitation which is between 100 and 500 μs (Mihailovic and Delgado, 1956). In general and due to different time constants a shorter pulse width is more likely to excite axons or axon hillocks at least in the case of single pulse stimulation (Ranck, 1975; Nowak and Bullier, 1998). And commonly the pulse width of a deep brain stimulator is set at 60 μs (Perlmutter and Mink, 2006). In contrast to these parameters, the configuration and polarity of the electrodes are typically modified in the course of the treatment. A monopolar montage with a single "active" cathodal electrode contact on the deep brain electrode referenced to the "inactive" anodal pulse generator or a bipolar montage between two of the four electrode contacts with one serving as cathode and one as anode can be chosen. The monopolar configuration with an inactive reference is often preferred since it improves the ability to relate a therapeutic effect to a specific electrode contact. Nonetheless, monopolar as well as bipolar stimulation should both be regarded as being relatively focal. The preference of the cathodal polarity for monopolar stimulation results from its higher efficiency in stimulating neurons compared to anodal pulses regarding intracerebral application of electrical stimulation. Indeed, threshold currents for the induction of action potentials in pyramidal tract cells can differ up to more than factor ten between cathodal and anodal current (Stoney et al., 1968). Neuroanatomically electrical stimulation preferentially activates structures parallel to the electrical field (Ranck, 1975). Knowledge of this factor may help to interpret the effects of DBS. DBS in PD is continuous and therefore energy consuming. Optimal parameters of DBS account for this factor increasing the interval for exchange of the battery. In fact, modern devices are advertised with having a longevity of 9 years (Medtronic; Minnesota, U.S.A.). However, patients need to be aware of the potential necessity of a second surgical intervention for battery changes. Also the existence of intracranial metallic material as well as the stimulation device impose vigilance on the possible hazards and restrict use of magnetic resonance imaging (MRI), transcranial magnetic stimulation (TMS), diathermia or other external electromagnetic sources in patients with DBS.

2.1.3 The mechanism of action of invasive stimulation in Parkinson's disease

The choice of the target to be stimulated in order to reduce symptoms of PD has been decisively influenced by previous experiences with lesional surgery for the therapy of PD. In fact Benabid et al. (2009) stated that "DBS mimics the effects of ablation in all targets used to date." However, dependence on active stimulation of the electrode contacts clearly indicates a dynamic neurophysiologic mechanism of action of DBS which has not been fully elucidated so far (Perlmutter and Mink, 2006). The similarities between the effects of a lesion and stimulation of particular neuroanatomical targets supported the theory that high-frequency deep brain stimulation of the STN and other targets acts in general inhibitory on the neuron and hence on the functional output of the stimulated structure i.e. of the STN. In accordance with that hypothesis a study using single neuron patch-clamp-technique in prepared slices of the STN of Wistar rats has shown that electrical high-frequency stimulation (stimulation frequency = 100-250 Hz, pulse width = 100 μs, duration of stimulation = 60 seconds) is able to block single-spiking or bursting activity of STN-neurons for about six minutes after stimulation an effect that can be evoked repeatedly (Beurrier et al., 2001). This effect did neither depend on Ca2+ mediated transmitter release nor was it the consequence of membrane hyperpolarization. In another study using in-vivo records of patients undergoing surgery for advanced PD single pulses with an intensity of 50 μA induced short-lasting inhibition of tonically firing neurons of the GPi within a radius of up to more than 600 μm. In this study however, a transmitter-dependent mechanism was proposed (Dostrovsky et al., 2000). Moreover, it was demonstrated in a Positron-emission-tomography (PET)-study that the regional cerebral blood flow (rCBF) of the SSMA, the cingulate motor cortex and the dorsolateral prefrontal cortex (DLPFC) during active stimulation of the STN is significantly increased compared to inactive stimulation. These findings resembled the results of studies which compared changes of rCBF before and after pallidotomy (Grafton et al., 1995; Limousin et al., 1997). Also, it was shown by PET that the pathophysiological hypoactivity of the SSMA as found in PD is reversed by active DBS of the STN as well as pallidotomy (Ceballos-Bauman A.O., 2003). Nevertheless, the view of a predominant inhibitory action of DBS has been challenged for several reasons (Vitek J.L., 2002). Importantly, other studies focused on the effects that DBS of the STN exerts on related nuclei of the basal ganglia. Supporting increased excitatory action of the STN elevated levels of glutamate were found in SNr and GP of normal rats after DBS of the STN with intracerebral microdialysis (Windels et al., 2003). This effect depended strongly on the frequency of stimulation with a maximum increase of glutamate in the GP and SNr at 130 Hz, weaker increases at either 60 or 350 Hz and no effect at 10 Hz being concordant with the well-known frequency dependence of the clinical effect of DBS of the STN in humans. Studies that demonstrated an increased activity of neurons in the SNr after DBS of the STN are in line with these results. Nonetheless, effects were depending on stimulation intensity and while high intensities of high-frequency DBS induced the aforementioned increase in neuronal activity, low-stimulation intensity reversed this effect (Maurice et al., 2003). In light of the evidence suggesting blocking of activity of STN neurons it is likely that the excitation measured in related nuclei is due to activation of efferent fibers from the STN rather than the neurons themselves. Experimental evidence suggest that the threshold for activation by intracranial electrical stimulation is lowest at axons and their initial segments and in fact much higher at the neuronal cell body (Nowak and Bullier, 1998). Another effect of intracerebral brain stimulation may be relevant for the efficacy of this treatment which is the "anodal surround" effect. With increasing intensity of cathodal DBS the depolarizing

outward current induced by the stimulation around the electrode is compensated by an increasing hyperpolarizing inward current which is highest in relative proximity to the current source hence resembling the effect of anodal stimulation. Therefore, conduction of action potentials of an excited axon may be blocked completely in orhodromic and antidromic direction. With greater distance from the electrode contact the anodal-like effect decreases and action potentials will not be interrupted (Ranck, 1975). Consequently, action potentials of those elements centered closest around the stimulating electrode contact may not leave this zone around the contact further supporting a theory of central inhibition and peripheral excitation. An influence of DBS on oscillations and firing patterns in the basal ganglia has been proposed as relevant correlate of its therapeutic efficiency more recently (Welter et al., 2004).

2.1.4 The indication for invasive electrical stimulation in Parkinson's disease

Despite its invasive nature, the perioperative risk and the highly specialized therapy DBS offers some advantages over the classical pharmacological treatment of PD that hold true regardless of the stage of the disease. DBS acts continuously reducing fluctuation of symptoms that often are due to variable serum levels of antiparkinsonian drugs. Therefore, if implantation succeeded DBS has a good therapeutic predictability. Also, psychiatric side-effects like hallucinations due to levo-dopa administration or use of dopaminergic drugs are less common with DBS. However, the therapeutic value of DBS depends to a significant extent on the correct identification of appropriate patients for this therapy. Since other parkinsonian syndromes do not respond sufficiently to DBS the diagnosis of an idiopathic Parkinson syndrome (IPS) or PD must be firm. Criteria for the adequacy of the diagnosis of PD have to be checked before indicating a surgical approach in the treatment of PD. An asymmetric onset of the disease and early and satisfying response to levo-dopa are typical and crucial features of PD. Also tremor is typical of PD whereas it is infrequent in other parkinsonian syndromes. On the other hand early existence of significant postural instability, autonomic dysfunction or cognitive decline point to an atypical Parkinson syndrome. In any case the presurgical evaluation must include the performance of a levo-dopa-test (Charles et al., 2002). A single high-dose application of levo-dopa e.g. 250 mg 12 hours after discontinuation of antiparkinsonian treatment is sufficient. The motor symptoms of PD then should be evaluated in the state off medication and in the best on-state or 1 hour after application of the single test-dose of l-dopa. Part III of the Unified Parkinson's disease rating scale (UPDRS) is the preferred tool to asses the outcome of this test and an improvement of 30% in this part of the UPDRS is regarded as significant and typical of PD. However, some centers demand an even better presurgical response to this test (Welter et al., 2002). Since dementia should preclude surgery for DBS a neuropsychological testing is part of the presurgical evaluation. As a screening tool for surgery the mini-mental state examination (MMSE) is useful and a result of less than 24 points would omit further testing. However, it has to be taken into considerations that often candidate patients are not unfamiliar with this test and results may incorporate training effects. Age is negatively correlated with a favourable outcome of the procedure. Often an age of 75 is regarded as upper limit for performing an implantation of deep brain electrodes. Still, this guideline is not exclusive. A recent cranial MRI is essential for the presurgical evaluation and should rule out leukoencephalopathy, atrophy or other functionally relevant abnormalities. Also a preexisting psychiatric disorders will preclude a patient from surgery for DBS. Therefore patients will need to be assessed by a psychiatrist presurgically. A multidisciplinary setting

is required for taking the decision for implantation of a deep brain stimulator. Today, DBS is a treatment choice for advanced PD that is not manageable by pharmacotherapy e.g. due to motor fluctuations, dyskinesias or psychiatric side effects of medication. Currently, a multicentre randomized, open-label clinical trial is investigating a potential role of STN-DBS compared to best medical treatment on quality of life for earlier stages of the disease (NCT00354133).

2.1.5 The outcome of invasive electrical stimulation in Parkinson's disease

According to the manufacturer of the medical devices for deep brain stimulation (DBS), the healthcare company Medtronic (Minnesota, U.S.A.), more than 80.000 patients have received deep brain stimulators since 1995 as of March 2011. DBS first was approved for the therapy of essential tremor in Europe in 1995 and in the U.S.A. in 1997. In 1998 it was licensed for therapy of advanced Parkinson's disease in Europe, Canada and Australia while the approval of the food and drug administration (FDA) in the U.S.A. followed in 2002. An approval for the treatment of dystonia in the U.S.A. came in 2003. Additionally, DBS can now be applied for severe obsessive compulsive disorders (OCD) and focal epilepsy refractory to pharmaceutical treatment in Europe.

Three structures are currently targeted for invasive therapy of PD: the nucleus ventralis intermedius of the thalamus (VIM), the globus pallidus internus (GPi) and the nucleus subthalamicus (STN). The effectiveness of electrical deep brain stimulation of these intracerebral structures for the therapy of PD has each been proven by several clinical outcome studies. Among the aforementioned target structures the VIM was the first which was investigated for therapy of PD (Benabid et al., 1987). Today it is the target least often chosen for DBS in PD. However, it remains a particularly effective therapy for resting or postural tremor in PD, both of which are less well controlled by the alternative strategies of DBS of the GPi or STN. Conversely, improvement of akinesia and rigidity is less satisfying with DBS of the VIM compared to DBS of STN or GPi. Hence, DBS of the VIM is a valuable therapeutic choice in patients with tremor dominant forms of PD and is effective in about 90% of these patients (Tarsy et al., 2008). Also, the results of a prospective randomized study indicate that DBS of the VIM is superior to thalamotomy regarding clinical outcome with significantly higher effectiveness concerning activities of daily living and upper extremity mobility as well as a more favorable benefit risk ratio (Schuurman et al., 2000). The second most frequently targeted structure for DBS for PD is the GPi. The motor score of the UPDRS improves by 30-40% on average with results ranging from 10-70% after uni- or bilateral DBS of the GPi as measured 3 to 12 months after surgery in most studies (Weaver et al., 2008). In two studies the clinical benefit of bilateral DBS of the GPi remained relatively stable in a long-term perspective after two and three to four years compared to short-term results after six and twelve months respectively indicating a long-term benefit of this treatment (Ghika et al., 1998; Rodriguez-Oroz et al., 2005). This improvement in motor function is reflected by patients self-reporting a significant increase of daily time in an on-state from 26 to 69% following bilateral electrode implantation in the GPi (Rodriguez-Oroz et al., 2005). The main target of DBS for PD today is the STN. A reduction of the motor part of the UPDRS of 50% on average can be expected after implantation of depth electrodes into the STN. Also, STN DBS is effective regarding bradykinesia, rigidity as well as tremor. Additionally, dyskinesias and motor fluctuations are likely to be reduced significantly. On the other hand, postural stability more often does not improve satisfactorily following DBS of the STN and may even worsen in some cases. Regarding non-motor consequences of this therapy it has been

suggested that a decline in cognitive abilities may be related to DBS of the STN. However, from current data it is not clear to which extent this finding is the consequence of the natural course of the disease. A decisive advantage of STN DBS is the potential postsurgical reduction in the levo-dopa dosis which may in a subgroup of patients even lead to a temporary cessation of pharmacotherapy (Merello, 2008). In general, the procedure results in a better quality of life for patients on average. One study compared DBS of the STN in addition to medication against best pharmacotherapy alone in patients with advanced PD. Significant superiority of the former treatment was demonstrated in both the UPDRS as well as in a PD quality of life scale after six month in patients under 75 years of age (Deuschl et al., 2006). Even though DBS does not exceed the overall effectiveness of levo-dopa therapy off states are less frequent with DBS. Comparison between DBS of the STN and the GPi based on the literature suggests that both procedures are equally effective regarding motor outcome and self-reported function (Follett et al., 2010). Due to different parameters of stimulation battery life of stimulators of the GPi may be shorter compared to devices implanted for stimulation of the STN. Also, patients undergoing STN DBS require a lower dose of dopaminergic treatment compared to patients after GPi DBS. In contrast, neuropsychological complications may be less frequent with stimulation of the GPi (Weaver et al., 2008; Follett et al., 2010). Aside from the potential benefits of any type of DBS patients need to be made aware of the perioperative risks including implantation site infection or intracranial hemorrhage and long-term risks like breakage of material, dislocation of the electrodes or an immunological reaction. Finally it must be clarified to the patient that the procedure occasionally may fail to improve the symptoms of PD.

2.2 Non-invasive stimulation in Parkinson's disease

There is good evidence from basic research that application of rTMS and tDCS can have a lasting impact on cortical plasticity and several studies suggest that these techniques may offer a new therapeutic approach to a variety of neurological disorders. Still, compared to DBS the therapeutic effects of transcranial stimulation in Parkinson's disease so far appear to be rather small and variable. This may in part be due to a heterogeneity of study protocols regarding several parameters of stimulation. Representing innovative mechanisms exploration of the therapeutic potential of these techniques deserves further attention.

2.2.1 Technical aspects of non-invasive electrical stimulation

Transcranial magnetic stimulation: Current flow in an iron coil will induce a magnetic field perpendicular to the electric current flow. The magnetic field again induces an electric field perpendicular to itself. In consequence, this electric field is parallel and in opposite direction to the inducing current flow. When applied on the scalp above the cortex brief currents of an electric coil are able to produce direct excitation of neurons. While single pulse transcranial magnetic stimulation (TMS) is used to induce a neuronal action potential which then may produce a motor evoked potential the single pulses of repetitive TMS (rTMS) usually do not reach the threshold for inducing action potentials. Several parameters that can be determined with single pulse TMS reflect different aspects of cortical excitability: 1) the resting motor threshold (RMT) or active motor threshold (AMT) probably reflect membrane properties, 2) the silent period (SP) which is a quiescent phase in the electromyogram (EMG) is partially of cortical origin and is related to the function of GABA-B receptors. 3) short intracortical inhibition (SICI) and short intracortical facilitation (SICF) occur when a subthreshold stimulus precedes a suprathreshold stimulus by less than 5 ms or 8-30 ms

respectively. SICI likely depends on GABAergic function while mechanisms of the SICF are less clear and probably involve function of GABA receptors as well as N-methyl-D-aspartate (NMDA)-receptors (Hallett, 2007; Ziemann, 2004).

On the other hand, rTMS has the potential to alter the cortical excitability depending on duration and mode of stimulation (Hallett, 2007). rTMS frequencies of around 1 Hz induce an inhibitory effect on cortical excitability (Chen et al., 1997) and rates of more than 5 Hz generate facilitation (Pascual-Leone et al., 1994; Hallett, 2007). Huang et al. (2005) developed a different high-frequency transcranial magnetic stimulation (TMS) - called Theta-burst stimulation (TBS) - with excitability modulating after effects of up to 60 minutes in healthy volunteers. Here the repetition rate of the rTMS is irregular with three pulses with an inter-pulse interval of 20 ms (50 Hz) repeated every 200 ms (5 Hz) applied either continuously for 40 seconds as continuous TBS (cTBS) or for two seconds repeated 20 times every 10 seconds then named intermittent TBS (iTBS). cTBS produces a short-lasting inhibitory effect on cortical excitability and iTBS induces a short-lasting cortical facilitation. This induction of cortical plasticity or metaplasticity resembles the effects of repetitive electrical stimuli of single neurons which lead to either long-term potentiation (LTP) or long-term depression (LTD). Hence, the effects of rTMS are often referred to as LTP-like facilitation and LTD-like inhibition, respectively. Therapeutic applications of rTMS is based on these facilitatory or inhibitory effects that outlast the stimulation procedure itself and are aimed to modulate excitability of the cortex at least transiently.

Several substances were found to alter the effects of TMS on cortical excitability or rTMS on cortical plasticity. Based on a review by Ziemann (2004) carbamazapine, phenytoin and lamotrigine which all are blocking sodium-channels reduce the motor threshold. Lorazepam and diazepam increase the SICI while they reduce the SICF. The NMDA-receptor antagonists dextrometorphan and memantine also reduce the ICF while SICI is enhanced. This pattern is also observed in a dose-dependent manner for ethanol. And D2-agonists like bromocriptine or cabergoline as well as the combined D1-/D2-agonist pergolid are enhancers of the SICI as well while an opposite effect is observed for the dopamine-antagonist haloperidol. Therefore dopamine receptor agonists or antagonists have been termed "inverse modulators of motor cortex excitability" (Ziemann et al., 1997). LTP-like cortical plasticity as studied mainly with paired associative stimulation (PAS) is increased during treatment with D2-agonist cabergoline as well as methylphenidate and decreased under treatment with NMDA-receptor antagonist dextrometorphan as well as haloperidol, lamotrigine, lorazepam and biperiden (Ziemann et al., 2006).

Aside from medical drugs the duration of stimulation may decisively affect the result of rTMS. Whereas 40 seconds of continuous TBS decreases cortical excitability, halving the same stimulation to 20 seconds induces facilitatory effects (Gentner et al., 2008). A similar reversal of the impact of a stimulation has been reported by others (Gamboa et al., 2010). An additional influence on the effect of cortical stimulation may results from the state of pre-activation of target muscles during a stimulation. As an example, effects of iTBS can be abolished when the muscle of interest is contracted with approximately 10% of maximal power (Huang et al., 2008). It is important to note that in PD rigidity may be more often present at rest in contrast to situations in most studies which are performed with healthy individuals. Pre-activation of a muscle e.g. due to rigidity or tremor in these patients may shift intracortical homeostasis, which then may influence MEP-amplitudes and neuronal recruitment.

Transcranial direct current stimulation: In 1980 it was demonstrated that a high-voltage shock applied transcranially over the primary motor cortex is able to produce a motor-

evoked potential (Merton and Morton, 1980). Despite being non-invasive the application of this transcranial electric stimulation (TES) is painful which limits its applicability. A well-tolerated technique of transcranial electric stimulation has been introduced into research on neuroplasticity in the recent past (Nitsche and Paulus, 2000). Here instead of directly inducing action potentials a weak direct current is applied on the scalp and is able to gradually modulate cortical excitability in humans. An "active" electrode placed on the scalp above a cortical target region to be stimulated – e.g. above the primary motor cortex – and a distant reference electrode that is usually placed supraorbitally and contralaterally to the active electrode are both connected to a battery-driven stimulator forming an electric circuit. In healthy young individuals the cerebral cortex beneath a cathodal electrode can be hyperpolarized whereas the cortex beneath an anodal electrode can be depolarized as shown by decrease or increase of the amplitude of motor evoked potentials (MEPs). This effect can last up to 60 minutes after stimulation and even longer under circumstances (Nitsche et al., 2007). More recently, Terney et al. (2008) similarly showed that alternating current stimulation with random amplitude and frequency variation - transcranial random noise stimulation (tRNS) – is able to produce a significant increase in regional motor-cortical excitability in healthy subjects for up to 60 minutes after the end of stimulation. Studies have demonstrated a relevance of different neuronal transmitter systems for the mediation of this effect. For example, the NMDA-receptor antagonist dextrometorphan is able to completely abolish the effect of either anodal or cathodal tDCS (Liebetanz et al., 2002). It has been shown that the decreased cortical excitability following cathodal tDCS can be prolonged by administration of pergolide, a combined D1/D2 agonist, and can be diminished by sulpiride, a D2-antagonist. Additionally, co-administration of pergolide and sulpiride abolishes effects of cathodal as well as anodal tDCS with a tendency of reversing effects of anodal stimulation (Nitsche et al., 2006). Confirmatory, it has been reported more recently that the facilitating effect of anodal tDCS in healthy volunteers can be reversed under the influence of l-dopa and may lead to a significant decrease in cortical excitability (Kuo et al., 2008). Indeed, a complex U-shaped or inversely U-shaped dose-dependent effect of D2-receptor stimulation on MEP-amplitudes in healthy individuals after cathodal or anodal tDCS respectively has been proposed (Monte-Silva et al., 2009). These results highlight especially the role of dopamine in cortical plasticity affecting strategies on the application of this technique in patients with Parkinson's disease.

2.2.2 Neurophysiology of non-invasive electrical stimulation in Parkinson's disease

Transcranial magnetic stimulation: Some of the basic parameters measured by single pulse or paired pulse TMS are affected by PD and medication for the disease. Typically, there is no change in motor threshold in patients with PD compared to healthy individuals. The silent period as well as the SICI are decreased and can be normalized by application of parkinsonian medication in patients with PD (Priori et al., 1994; Lefaucheur et al., 2004; Hallett, 2007). Most studies do not report a significant effect of PD on ICF (Cantello et al., 2002). However, results regarding the effect on this parameter are heterogeneous (Bareš et al., 2003).

The effects of rTMS on neurophysiologic parameters in patients with PD can significantly differ from those in healthy persons. Gilio et al. (2002) already described a lack of MEP-changes after 5-Hz rTMS in patients with PD in contrast to healthy subjects. Moreover, they found that voluntary contraction of the target-muscle during 5 Hz rTMS did abolish changes in cortical excitability. Accordingly, a recent study showed that iTBS does not induce

cortical plasticity in patients with PD under dopaminergic medication (Stephani et al., 2011). Despite findings of Ueki et al. (2006) who reported a restored cortical plasticity in patients with PD after administration of dopaminergic drugs in response to interventional paired associative stimulation (iPAS) this may not be the case in response to iTBS. And in a placebo-controlled, double-blind, randomized trial on iTBS in patients with PD there was no improvement of the UPDRS after 8 sessions of stimulation over the motor cortex and dorsolateral prefrontal cortex (Benninger et al., 2011; table 2). Comparably, no change in cortical excitability after application of an inhibitory continuous TBS (cTBS) protocol could be found in a recent report (Eggers et al., 2010).

Transcranial direct current stimulation: Within the few studies published on tDCS in patients with PD there is only one that also reports on the effects of stimulation on a neurophysiological parameter (Fregni et al., 2006). This study demonstrated a 70%-increase of the MEP-amplitude at a single time-point directly after 20 minutes of anodal tDCS over the primary motor cortex with an intensity of 1 mA. The same protocol with cathodal stimulation over the primary motor cortex induced a significant decrease of the MEP-amplitude of around 20%. These results are analogue to those of healthy persons and interestingly, antiparkinsonian drugs in these patients were held for approximately 12 hours prior to the experiment. In a recent study a new technique of transcranial alternating current stimulation (tACS) termed transcranial random noise stimulation (tRNS) was applied. This technique uses randomly alternating currents of ± 500 μA. Patients with PD showed a decrease in cortical excitability in contrast to results on healthy subjects whose cortical excitability increased after 10 minutes of tRNS (Stephani et al., 2011; Terney et al., 2008). Continued dopaminergic therapy may have contributed to this paradoxic effect.

2.2.3 Therapeutic use of non-invasive electrical stimulation in Parkinson's disease

Both, rTMS and tDCS offer the possibility of non-invasively altering cortical excitability and inducing cortical plasticity in humans (Pascual-Leone et al., 1994, Nitsche and Paulus, 2000). However, they share the disadvantage of not being able to directly modulate subcortical structures like the basal ganglia due to a restricted operating distance. Hence, their therapeutic potential depends on disease processes that directly or indirectly affect cortical function. A pathological decrease or increase in excitability of cortical areas like the supplementary motor area (SMA), the dorsolateral prefrontal cortex (DLPFC) and the primary motor cortex (M1) has been demonstrated in various stages of Parkinson's disease thus providing potential targets for therapeutic applications of non-invasive stimulation in PD (Lefaucheur, 2005).

Transcranial magnetic stimulation: Based on these concepts rTMS has been applied in patients with PD in several studies with a variety of different stimulation protocols (Table 2 and Table 3). A meta-analysis of studies that reported on effects of rTMS on the UPDRS between 1985 and 2007 included 10 sufficient prospective trials with control groups on different sham conditions. Whereas in 6 trials high-frequency rTMS was used 3 trials applied low-frequency rTMS and in one trial both techniques were used. A significant effect size of 0.58 was only found for high-frequency rTMS whereas meta-analysis of low-frequency rTMS revealed no therapeutic effect (Elahi et al., 2008). In the one study that tested 10 Hz as well as 0.5 Hz real rTMS in patients with Parkinson's disease both were shown to improve motor performance 20 minutes after their application. However, their effects on parameters of excitability were reversed compared to healthy individuals indicating an altered motor cortex excitability in these patients (Lefaucheur et al., 2004).

Improvement in the UPDRS has been reported after low and high-frequency rTMS of varying duration and location by others (Wu et al., 2008). However, the largest study of rTMS in PD so far had 85 participants that were assigned to three different groups. Applying very low frequency rTMS (0.2 Hz) there was no improvement of UPDRS III (Okabe et al., 2003). In an early study Siebner et al. (2000) e.g. detected a significantly improved mobility of the arm one hour after 5 Hz rTMS over the contralateral M1 area of the hand. Favouring the effectiveness of high-frequency rTMS, Strafella et al. (2001) could show that 10 Hz rTMS for one second every 10 seconds for 15 times which then was repeated three times every ten minutes over the prefrontal cortex conditions a dopamine release in the striatum. Still, in a series with 22 patients who each underwent single sessions of 0.5 Hz rTMS, 10 Hz rTMS, iTBS, cTBS and sham stimulation no significant effect of either stimulation was found on the UPDRS III while training effects may have masked any possible therapeutic effect of the TMS (Rothkegel et al, 2009). In accordance with this result, the most recent studies evaluating the clinical effectiveness of cTBS or iTBS both of which are powerful techniques for the modulation of cortical plasticity in healthy individuals did fail to demonstrate a significant therapeutic benefit further suggesting a lack of change in cortical excitability in patients with PD (Eggers et al., 2010; Benninger et al., 2011).

Authors	Year	Verum	Sham	No. Of ses.	Coil	Hz	Sec	dd	RMT	n	Method	Results
Shimamoto et al.	2001	Bilateral frontal cortex	Acoustic sham	8 (once a week)	Round	0.2	300	On	100 ±10%	9	1(150s left+150s right)	Mild but significant improvement of UPDRS III after 2 months. No improvement after 1 month. Significant effect on activities of daily living.
Ikeguchi et al.	2003	F3 (clockwise) or F4 (counterclockwise)	Occipital stimulation between inion and auditory meatus (clockwise on the left, counterclockwise on the right)	6 in 2 weeks	Round	0.2	600	On	70% of max. output	12	1(150s left+300s Pause(?) +150s right)	Mild but significant decrease of UPDRS III in up to 7 days after rTMS
Okabe et al.	2003	Motor cortex	Sham condition + occipital lobe	8 (once a week)	Round	0.2	500	On	110% AMT	85	1(250s clockwise-250s anticlockwise)	No sigificant effect on UPDRS
Lefaucheur et al.	2004	M1(hand)	Sham coil	1	F8	0.5	1200	Off	80%	12	continuous	Significant decrease in UPDRS equal to 28-32% of the l-dopa effect
Arias et al.	2010	Vertex	Two coils (inactive coils beneath an active coil	10	Round	1	100	On	90%	9	1(50s clockwise-5min pause-50s anticlockwise)	No significant effects on any signs compared to placebo stimulation
Eggers et al.	2010	M1(hand)	Same coil placed 90° in angulation over M1	1	F8	50/5	40	Off	80%AMT	8	1(40s)	No significant effect on UPDRS III nor measures of cortical excitability

Table 2. Studies on the therapeutic use of low-frequency rTMS in patients with PD. Study-results reported here mainly refer to the UPDRS while other measures of motor excitability are mainly neglected. M1 = primary motor cortex, no. of ses. = number of sessions, F8 = figure of eight, Hz = Hertz, dd = dopaminergic drugs during stimulation, RMT = resting motor threshold, AMT = active motor threshold, DLPFC = dorsolateral prefrontal cortex, mA = milli Ampere, UPDRS = unified Parkinson's disease rating scale.

Authors	Year	Verum	Sham	No. Of ses.	Coil	Hz	Sec	dd	RMT	n	Method	Results
Siebner et al.	2000	M1(hand)	Midfrontal	1	F8	5	600	Off	90%	10	15(30 s stimulation + 10 s pause)	Significant decrease in UPDRS III 1 h after stimulation
Khedr et al.	2003	Lower limbs+M1(hand l+r)	Same condition, elevated+angled away from head	10 (consecutive days)	F8	5	400	Off	120%	36	200 s over lower limbs + 100s each over left and right hand	Significant decrease in UPDRS 1h after 1th, 5th, 10th stimulation and after one month
Lefaucheur et al.	2004	M1(hand)	Sham coil	1	F8	10	1200	Off	80%	12	20(10s stimulation+50s pause)	Significant decrease in UPDRS equal to 28-32% of the l-dopa effect
Lomarev et al.	2006	M1(hand) + DLPFC each left and right	Verum coil turned around 180°	8 (within 4 weeks)	Solid core coil	25	1200	On	100%	8+8	4(12s) each on left+right M1, left+right DLPFC	No significant effect on UPDRS; Significant improvement in other motor tests.
Del Olmo et al.	2007	DLPFC	Verum coil 7 cm rostrally to the vertex	10	F8	10	1800	On	90%	8+5	3(15(1s stimulation +10s pause)) separated by 10 min.	No significant change in UPDRS after stimulation. Significant improvement of other motor tests.
Benninger et al.	2011	M1(hand) + DLPFC each left and right	Sham coil	8	Solid core	50/5	190	On	80%AMT	13+13	20(2s TBS+8s pause)	No significant effect on UPDRS III; significant effect on mood

Table 3. Studies on the therapeutic use of high-frequency rTMS in patients with PD. Study-results reported here mainly refer to the UPDRS while other measures of motor excitability are mainly neglected.M1 = primary motor cortex, no. of ses. = number of sessions, F8 = figure of eight, Hz = Hertz, dd = dopaminergic drugs during stimulation, RMT = resting motor threshold, AMT = active motor threshold, TBS = theta burst stimulation, DLPFC = dorsolateral prefrontal cortex, mA = milli Ampere, UPDRS = unified Parkinson's disease rating scale.

Transcranial direct current stimulation:

There are few studies in which the therapeutic efficiency of tDCS in PD was investigated (Table 4). An improvement of motor function in patients with PD measured by the UPDRS after 20 minutes anodal but not cathodal tDCS over the M1 region has been reported (Fregni et al., 2006). Boggio et al. (2006) demonstrated that patients with PD performed better in a memory and alertness test during a left prefrontal tDCS than during sham-stimulation. In another study the technique of rTMS was combined with tDCS in order to improve bradykinesia in PD (Grüner et al., 2010). In this study low frequency rTMS over the primary motor cortex contralateral to the more effected upper extremity was preceded by either sham, cathodal or anodal tDCS. Whereas the results in different tests of movement control (frequency of finger and hand tapping, horizontal pointing movements) improved significantly after performing rTMS preceded by either sham or

anodal tDCS the beneficial effect of 1 Hz rTMS on bradykinesia was reduced when preconditioning was performed with cathodal tDCS. Patients were tested while they were on dopaminergic drugs in this study as well. In the most recent study 25 participants with PD received 20 minutes of 2 mA anodal tDCS over the (pre)motor or prefrontal cortex on 8 days within 2.5 weeks each while on parkinsonian medication. A significant clinical improvement of the mobility of the upper extremity in the on- and off-state one day after the last stimulation was the main result in this study. But neither the velocity of gait nor the overall UPDRS score differed between sham and verum stimulation (Benninger et al., 2010). Also, there was a significant placebo effect in most conditions. However, size and montage of the electrodes used in this study differed from previous attempts possibly confounding the comparability of these results to earlier approaches and studies in healthy individuals. Finally, techniques of transcranial electrical stimulation may be able to improve symptoms of PD even though current data indicate that the effect size may be moderate. Development of new stimulation protocols may improve understanding of pathophysiological concepts of PD and increase therapeutic efficacy (Pogosyan et al., 2009; Moliadze et al., 2010).

Authors	Year	Location	Conditions	mA	Min	dd	n	Object	Results
Fregni et al.	2006	M1 DLPFC	Anodal/cathodal	1	20	Off	8/9	Motor performance	Significant improvement of UPDRS III (about 22% reduction) only after anodal stimulation of M1
Boggio et al.	2006	LDLPFC M1	Anodal/Sham Anodal/Sham	1 vs. 2	20	Off	9	Working memory	Significant improvement of working memory only with 2mA anodal stimulation of the LDLPFC
Grüner et al.	2010	M1	Anodal/Cathodal/ Sham	1	10	On	15	Motor performance	Significant improvement of motor performance (hand tapping and horizontal pointing frequency) after 1 Hz rTMS preconditioned by anodal or sham tDCS
Benninger et al.	2010	M1/M2 + Prefront. cortex	Anodal/Sham	2	20	On	25	Gait + hand and arm movements	Improvement of upper extremity bradykinesia 1 day after anodal stimulation

Table 4. Summary of the therapeutic studies of transcranial direct current stimulation (tDCS) in Parkinson's disease. M1 = primary motor cortex, M2 = premotor cortex, LDLPFC = left dorsolateral prefrontal cortex, mA = milli Ampere, UPDRS = unified Parkinson's disease rating scale.

3. Conclusion

Electrical or magnetic stimulation techniques amend the therapeutic tools for the treatment of PD. Among them, deep brain stimulation is the only approved treatment. It's positive effect on tremor and bradykinesia is significant and immediate in patients with advanced PD. In contrast, rTMS and tDCS are experimental techniques and their therapeutic effects, if present, are comparably small. Still, these techniques are relatively new and future protocols may improve their efficacy.

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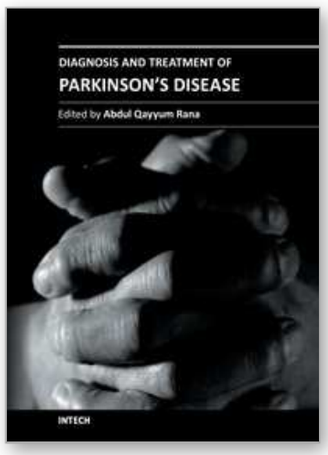

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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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