Masaryk University, Brno

Faculty of Medicine

1st Department of Neurology

NEUROPSYCHOLOGICAL AND NON-MOTOR ASPECTS OF DEEP BRAIN STIMULATION OF SUBTHALAMIC NUCLEUS

Marek Baláž, MD, Ph.D.

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Summary

Subthalamic nucleus (STN) is an important glutamatergic structure within basal ganglia strongly influencing the activity of its major output channels.

STN has been involved in the pathophysiology of the parkinsonian symptoms, and the disruption of its pathological activity by deep brain stimulation (DBS) partially reverses some of the clinical, electrophysiological, and metabolic abnormalities related to Parkinson's disease (PD). STN is the most frequent subcortical structure used as a target of the neuromodulation surgery – DBS. Implantation of deep brain electrodes during DBS surgery offers unique access to deep brain structures and offers possibility to record electric brain activity directly from brain itself.

There has been an increase of reports regarding cognitive disorders and other non-motor impairments related to deep brain stimulation (DBS) surgery for Parkinson's disease recently. The impact of STN DBS on cognitive and behavioral functions is still not elucidated completely, but it is evident that at least in some patients it may have clinical importance. The mechanism by which STN regulates the motor functions in the neural circuitry is not yet fully understood and much less is known about its influence on cognitive networks.

The aim of our research work in the scope of last few years was to investigate the participation of STN in non-motor activities, namely the executive functions. We performed such experiments by the recording of intracranial cognitive potentials, specifically the late complex of evoked potentials – the P3 wave, and other electophysiological methods (oscillations, event related synchronization and desynchronisation). We also employed sophisticated survey methods such as disease-specific quality of life questionnaires.

In summary, results of our research indicate that STN actively participates in cognitive and non-motor activities. Its participation in these activities is conditioned by the difficulty of the task, i.e. it participates in more demanding cognitive tasks.

STN seems to cooperate directly with inferior frontal cortex in its cognitive-related performance. The connection of subthalamic nucleus with dorsolateral prefrontal cortex seems to be at best indirect. Modulation of STN activity by continuous DBS can influence wide array

of non-motor function in addition to its well described and usual effect on motor symptoms of PD.

The proof of participation of subthalamic nucleus in executive functioning underlines the need of meticulous selection of candidates for deep brain stimulation surgery of this target in PD.

Contents

1 List of frequently used abbreviations

DBS – deep brain stimulation

ERP – event related potentials

ERD/ERS –event related desynchronisation/synchronisation

IPD – Idiopathic Parkinson's disease

PD – Parkinson's disease

P300 – P300 wave (event-related potential elicited during the process of decision making)

P3 – P3 wave – another name for event. Related potential known as P300

QoL – quality of life

rTMS – repetitive transcranial magnetic stimulation

STN – subthalamic nucleus

2 Deep brain stimulation of subthalamic nucleus in Parkinson's disease

2.1 Introduction – subthalamic nucleus

Subthalamic nucleus (STN) is a small lens-shaped midbrain nucleus lying on the dorsomedial surface of internal capsule. Despite its relatively small size, STN is thought to play a prominent role in the pathophysiology of Parkinson's disease (PD) (Obeso et al, 1997). STN not only plays a key role in motor behavior, but also is a potent regulator in the limbic and associative circuits (Temel 2005).

As the only glutamatergic structure of BG, it is a major source of excitation. STN innervates mainly globus pallidus interna (GPi) and substantia nigra, but also globus pallidus externa (GPe), ventral pallidum, pedunculopontine nucleus, and, to a lesser extent, striatum, nucleus accumbens, and ventral tegmental area.

Major subcortical inputs to STN arise from ventral pallidum and GPe (the indirect pathway), thalamus, pedunculopontine nucleus, dorsal raphe, ventral tegmental area, and pars compacta of substantia nigra (Baunez et al, 2010).

Direct cortical projections to STN were described several decades ago (Monakow 1978), but they were considered to be sparse, and therefore regarded as less important. According to more recent views, STN occupies not only a crucial position in the indirect pathway of BG, but it also receives direct cortical projections, especially from frontal lobe, namely primary motor cortex, supplementary motor area, and dorsal and ventral divisions of premotor cortex, such as the hyperdirect pathway from inferior frontal cortex (IFC) (Nambu 1997, Baláž 2010).

In 2004, Strafella indicated that the role of cerebral cortex in regulating the activity of STN was not known in humans. Transcranial magnetic stimulation of motor cortex changes the neuronal activity of STN (Strafella et al, 2004).

Diffusion Weighted Imaging (DWI) tractography demonstrated a three-way white matter network between preSMA, IFC, and STN region in right hemisphere in tasks related to reversing initiated motor responses, as revealed by the stop-signal paradigm (Aron, 2007). The anatomic source of control over the putative cognitive function of STN is less well described, but it is clear that STN is involved not only in motor but also in associative and limbic cortico-BG-thalamocortical loops.

The direct connections to STN from prefrontal cortex and the relation of STN to structures such as nucleus accumbens and ventral pallidum (both well known for their involvement in

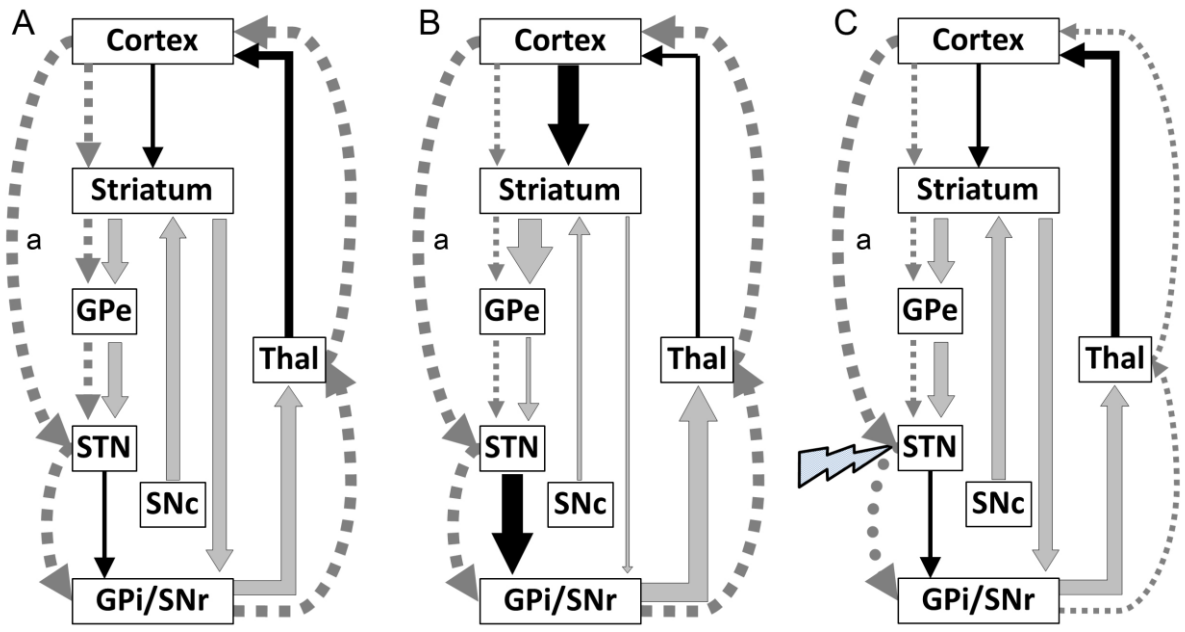
motivational processes) may explain why STN contributes to functions well beyond motor activities.

Subthalamic nucleus (STN) is an important glutamatergic structure within the basal ganglia strongly influencing the activity of its major output channels. The most important of those is the reciprocal connection of globus pallidus. It completes a loop with pallidum, since subthalamic nucleus gets inhibitory input from those areas of globus pallidus.STN has been involved in the pathophysiology of the parkinsonian state, and the disruption of its pathological activity partially reverses some of the clinical, electrophysiological, and metabolic abnormalities related to Parkinson's disease. STN is the most frequent target structure used for the neuromodulation surgery – deep brain stimulation (DBS).

Schematic position of STN in PD and in normal state is depicted in Figure 1.

Figure 1. Schematic view on position of STN in integration of information from basal ganglia and hyperdirect pathway

A. Situation in healthy individual; B. Parkinson´s disease (PD); C: Parkinson´s disease with DBS STN



Used from Rektor, Bočková, Rektorová, Chrastina, Baláž, Clinical neurophysiology

Symbols. Solid lines and boxes: Oversimplified scheme of basal ganglia-thalamocortical (BG) circuitry. Black lines: excitatory pathways; grey lines: inhibitory pathways, Dotted lines: cognitive loop; (a): the hyperdirect pathway, bolt: DBS stimulation. Adapted from: Rektor et al, 2014

Explanation. The cognitive loop remains relatively spared by the dysfunction of the motor BG circuitry in PD (A and B), the cognitive loop is down-regulated by DBS STN (C) despite the (relative) normalization of the motor part of the circuitry.

A unique feature of STN among basal ganglia nuclei is that it receives inputs directly from frontal cortex, bypassing pathways involving striatum (Monakow et al., 1978; Nambu et al., 1996), and that this hyperdirect fronto-subthalamic pathway is fast conducting (Nambu et al., 2000) compared with much slower striatal pathways (Yoshida and Precht, 1971; Hikosaka et al., 1993). This raises the possibility that STN is suitable for quick control of action (Isoda et al. 2008).

2.2 Treatment of advanced Parkinson's disease

PD is a progressive disorder of the central nervous system (CNS) with the annual incidence of about 20 per 100,000 persons in the fifth decade of life to about 90 per 100,000 persons in the seventh decade of life.

PD is traditionally considered to be a motor system disorder. The four primary symptoms are rest tremor, rigidity or stiffness of the limbs and trunk, bradykinesia and postural instability (usually appearing late in the course of the disease). With progression of the disease non-motor symptoms gain more clinical importance. However, some non-motor symptoms predate even the onset of typical motor symptomatology. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing simple tasks. Other symptoms include an expressionless face, reduced manual dexterity, handwriting difficulties, drooling, sleep problems, urination at night, depression and anxiety, constipation, and difficulty turning in bed at night.

The disease is chronic and progressive, but it does not affect everyone in the same way. PD may appear to be progressing faster in some patients than in others. Some patients become severely disabled; others experience only minor disruptions in motor functions.

The approximate age of PD onset is 60 years (Bower et al, 1999).There exists only symptomatic treatment for PD so far. This condition is of neurodegenerative nature and no neuroprotective treatment was convincingly showed to be effective.

Levodopa is currently the mainstay of treatment for Parkinson's disease (Olanow et al, 2001). However, long-term levodopa treatment is complicated by involuntary movements known as (choreatic) dyskinesia and motor fluctuations in which patients cycle between periods of good mobility ("on" periods) and impaired mobility ("off" periods) (Lang et al, 1999). These complications result in disability that cannot be satisfactorily controlled by medical therapy in the majority of patients.

Initially, changes of medication regime, addition of dopamine receptor agonist or inhibitors of COMT enzyme may improve motor fluctuations. With further progression of disease invasive treatment methods may be considered. Generally, medication therapies can improve quality of life in patients with PD for many years.

Three invasive methods for treatment of advanced PD available in Czech republic include apomorphine subcutaneous pump, intraduodenal Levodopa and deep brain stimulation (DBS).

Apomorphine HCl is a fast-acting dopaminergic agonist after it is injected subcutaneously. It has high affinity for D_4 receptors; moderate affinity for D_2, D_3, D_5, and adrenergic α1D, α2B, and α2C receptors; and low affinity for D_1 receptors. It is internationally approved as a therapy for the acute intermittent treatment of "off" episodes in patients with a fluctuating response to dopaminergic therapy (Goldenberg 2008). Via this modified insulin pump, a programmed infusion rate is dispensed in most cases using a 12–16 h regimen. If needed, the pump can administer apomorphine for 24 h and does not have to be discontinued overnight.

Duodopa and DBS are used more extensively than apomorphine pump.

Duodopa is a combination of Levodopa (20 mg/ml) and Carbidopa (5 mg/ml) applied in form of a gel into the duodenum. Preceding the permanent therapy, a test application period of Duodopa via a nasoduodenal catheter system is generally used. If this is well tolerated by the

patient and symptoms improve, a percutaneous, endoscopic gastrostomy (PEG) is performed and Duodopa is delivered via a portable pump and a duodenal catheter. If the retention period is 24 h, Duodopa is given as a monotherapy. If the Duodopa treatment is subject to a 16 h regimen, a prolonged release Levodopa tablet is often administered before bedtime. A number of studies have shown a significant reduction of time in “off” and a significant increase of time in “on”, as well as a reduction of dyskinesia (as reviewed by Ossig and Reichmann, 2013).

Advances in understanding of the pathophysiology of the basal ganglia have provided opportunities for neuromodulation strategies to manage these problems. Findings from animal models have led to the development of neuromodulatory surgical procedures for Parkinson's disease that target the subthalamic nucleus and pars interna of the globus pallidus (Olanow et al, 2000, The DBS for PD Study Group 2001).

The introduction of DBS was a major step forward for the treatment of Parkinson’s disease (PD) and other movement disorders. There have been over 100,000 DBS implants worldwide until the end of 2013. DBS improves the cardinal motor symptoms of PD and reduces motor fluctuations and dyskinesia. In addition, this procedure with only minimal lesionial effects, allows for modulation of the target region in an adjustable and reversible way. &the most frequently used target is STN.

The implanted neurostimulator enables the changes of voltage in patients electrodes and as such allows for adaptation of stimulation over time to the needs of the individual patients and reduction of possible side effects.

The good symptomatic benefit of DBS STN on tremor, rigidity, hypokinesia and the decrease in duration and severity of dyskinesia after the reduction of dopaminergic medication contributes to the spread of DBS STN procedure to the hundreds of centers worldwide.

DBS STN is not a curative treatment and does not prevent further course and development of new symptoms of PD and has no influence on the signs and symptoms of PD that do not respond to L DOPA.

The quadripolar intracranial electrodes are implanted in the target area and connected to the neurostimulator via subcutaneous connective cables. The principle of DBS STN function is the continuous high frequency stimulation of the target region.

The exact mechanism of DBS is not clear (Benabid et al. 2009). It is supposed that this mechanism is highly complex and includes the inhibition or activation of various neural structures. The overall effect depends mostly on stimulated structures (axons or neuronal bodies) and stimulation parameters. The DBS STN is probably based on depolarisation block of glutamatergic neurons in the STN (Koppel et al 2006). The overall effect of DBS is probably the neural inhibition. The effect of DBS STN is related to the frequency of the stimulation, which should be more than 100 Hz to reach the most robust symptomatic effect. Other stimulation parameters include the pulse width (usually in the range of 60 to 90 usec) and the amplitude. With increasing amplitude the volume of stimulated tissue (?) increases as well. The area of neuronal tissue involved by the monopolar stimulation spreads to 2 or 3 mm from the electrode if amplitude of stimulation in the region of 2 V are used (Pollak et al, 2002).

We consider necessary to stress the need to repeat that despite its successes DBS remains a symptomatic treatment and does not influence the course of the PD itself and very likely it has no influence on the neurodegeneration process itself.

As far as DBS STN is a symptomatic treatment that improves the quality of life (QoL) of patients, there appears to be an advantage if the stimulation is used earlier in the course of the disease (Deuschl 2012).

Currently the problems that remain unsolved are non-motor symptoms of PD. Especially gait problems, postural instability and cognitive problems belong to so far untackled problems of late stage PD. Even deep brain stimulation of pedunculopontine nucleus (PPN), a small cholinergic pontine area was not able to provide solution to any of these problems (Castrioto and Moro, 2013).

2.3 Indications of DBS STN

DBS is indicated for the treatment of drug-resistant complications of advanced PD. Higher baseline scores on section III (motor) of the unified PD rating scale (UPDRS) and higher baseline levodopa responsiveness are independent predictors of greater change in motor score after surgery (Benabid et al. 2009).

Numerous factors need to be taken into account in deciding whether a patient with PD is a candidate for DBS. Patient-related factors including age and the presence of other comorbid disorders need to be considered. Neuropsychological and neuropsychiatric concerns relate

both to the presurgical status of the patient and the potential for surgery to result in new problems postoperatively. Extremely important are factors related to the underlying PD, including the specific parkinsonian motor signs (tremor, bradykinesia, gait dysfunction), previous medical therapies, including benefits and adverse effects, and past surgical treatments (Lang et al, 2006).

Because of the strict inclusion criteria, the DBS is indicated in only relatively small part of patients with advanced PD, according to some authors it can be suggested only to about 4.5% of the patients (Morgante et al 2008). The inclusion and exclusion criteria for this procedure are summarized in the Tables 1 and 2.

Tab. 1. Indication criteria for DBS STN

PD with late motor complications resistant to medication changes
Good therapeutic response to L DOPA (positive L DOPA test – decrease of UPDRS motor score by 33 %)
No affective or cognitive disorder
Age less than 70 years
No atrophy or structural changes in brain MRI (magnetic resonance imaging)

Tab. 2. Exclusion criteria for DBS STN

Insufficient response of troublesome symptoms to L DOPA
Postsynatic dopaminergic lesion, Parkinson plus syndromes (multisystem atrophy, progressive supranuclear paralysis)
Disorders of cognitive functions, dementia
Depression
Psychotic symptoms
Diseases decreasing the life expectancy
Prominent late motor complications of PD not responsible to dopaminergic therapy (gait disorders, falls, speech disorders)
Medical complications that rule-out the total anesthesia

According to: *Rektor I, Baláž M: Hluboká mozková stimulace u Parkinsonovy nemoci. Parkinsonova nemoc: doporučené postupy diagnostiky a léčby, II. Pozdní stadium, Galen 2004*

2.4 Clinical outcomes of DBS STN

The main scale used to analyse the intensity of symptoms in PD is the Unified Parkinson's Disease Rating Scale (UPDRS), which is based on the rating of a series of symptoms for both sides of the body. In a meta-analysis of 37 cohorts comprising 921 patients (Kleiner-Fisman et al, 2006) the estimated decrease in absolute UPDRS II (activities of daily living) and III (motor) scores after surgery in the stimulation-on, medication-off state compared with the preoperative off -medication state was 50%. Its effect on the motor score of the Unified Parkinson's Disease Rating Scale (known as UPDRS III) with post-operative improvement in medicaton off state ranges from 28 to 71% according to various authors (for a review see - Benabid et al. 2009).

DBS STN decreases the motor fluctuations by 55 to 85%, duration of L-DOPA induced dyskinesia by about 50 to 80% and justifies the decrease of 40-80% of L DOPA equivalent dose compared to the pre-operative dose (Houeto et al. 2000 and 2003).

The quality of life after DBS STN (as assessed by the PDQ-39 – Parkinson's Disease Quality of Life Questionnaire) is improved by about 34% (Krack et al. 2003). This improvement is sustained after three years in several subscales of the Sickness Impact Profile questionnaire (Volkmann et al. 2009). The quality of life of caregivers is also improved (Lezcano et al, 2004).

2.5 Complications of DBS STN

DBS STN is generally to be considered quite a safe procedure with low incidence of side effects (Krack a kol. 2003). Implantation of the brain electrode carries a risk of intracranial bleeding or contusion. In a study of 526 consecutive patients (325 patients with STN-HFS, 138 with thalamic DBS, and 63 with DBS of the internal globus pallidus [GPi]), haemorrhages occurred in 8.4% (range 0.2–12.5%) of all DBS cases mostly at the entry point or subcortically, but rarely

in the target, and more often in hypertensive patients. 3.4% of this series of patients had asymptomatic haemorrhages, symptoms were transient in 4.4%, and permanent in only 0.6% of patients (Benabid et al, 2007).

Reported infection rates for DBS surgery vary widely, from less than 1% to more than 15% . Local hardware infections can arise even after several months postoperatively (Chrastina et al, 2008). Further possible surgical complications include the risk of subdural hematoma, pneumocefalus and skin erosion. Complications in general state, including aspiration pneumonia, pulmonary or urinary infection, thrombophlebitis, and pulmonary embolism, can occur in patients with severe PD (Benabid et al. 2009).

Side effect of stimulation itself are usually caused by the spread of stimulation current to neighboring neural structures. These include corticobulbar and corticospinal tract (tonic muscle contractions), third nerve fibers (monocular eye deviation), sensory track fibers (paresthesia) (Pollak et al. 2002).

Side effect of stimulation current itself tend to be only transient, and recede after switching off the stimulator, adjusting the stimulation settings or stimulating of the different electrode contacts. Stimulation-induced dyskinesias can be a sign of accurate placement of the electrodes, and are reversible. The side effects of the stimulation disappear usually within short period of time – second, minutes or hours at most, depending on the respective side effects. Most patients after DBS STN gain weight (Macia et al, 2004

2.6 Cognitive and neuropsychiatric changes after DBS STN

PD itself is a neurodegenerative disorder characterized not only by motor, by also by cognitive, neuropsychiatric, autonomic and other nonmotor symptoms. The efficacy of DBS STN for the motor symptoms is well described. However, the effects of DBS STN on cognitive and neuropsychiatric symptoms are less clear (Voon et al., 2006). A range of neuropsychiatric symptoms have been recognized in PD and are presumed to be caused by the underlying neurodegenerative process, dopaminergic medications, underlying vulnerabilities and psychosocial factors. These symptoms range from disorders of cognition, mood, anxiety, hallucinations, to apathy. More recently the dopamine dysregulation syndrome as the group of behaviours reslutling from the chronic administration of dopaminergic drugs have been

described (Evans 2004). Available data differ in the description of DBS STN effect on cognitive functions. According to systematic review (Temel et al. 2006) the cognitive problems were present in 41% of evaluated patients while the depression was present in 8%, hypomania or mania in 4% of subjects. Most of the cognitive changes after DBS STN are transient, mild and generally clinically insignifficant according to other paper (Voon et al. 2006).

The severity of cognitive changes is widely described from very mild, with no effect on activities of daily living (Witt et al. 2004) to serious complications with disruption of several cognitive domains (Saint-Cyr et al. 2000).

Data from observations and restrospective studies with low number of patient show either the presence of postoperative cognitive deterioration (Hariz et al. 2000) or, on the contrary, improvement in speed of information processing, verbal memory improvement, problem solving and generating of random numbers (Jahanshahi et al. 2000).

Also other authors describe improvement in certain cognitive parameters – ranging from mental flexibility (Witt et al. 2004) to overall cognitive improvement (Daniele et al. 2003).

Many published papers describe only minor changes in cognitive functions in patients well selected for the DBS STN (Morrison et al. 2004).

Most outcome paper suggest that negative outcomes of DBS STN include decline in verbal fluency (Gironell et al. 2003), declines in conditional associative learning (Koppel et al. 2006), decrease of processing speed (Hariz et al. 2000), and decline in selected measures of executive functions (Krack et al. 2003).

Specific patient subgroups such as older patients and patients with moderate cognitive impairment prior to surgery seem to be at greater risk of suffering cognitive and neurobehavioral deficits (Dujardin et al. 2001). The available data do not make clear if older age per se or other medical conditions associated with older age are responsible for the increased risk of cognitive changes following surgery.

According to most studies the dementia is an exclusionary criterion for DBS STN, thus there are no large-scale studies describing the influence of DBS STN on cognitive functions in demented patients (Voon et al. 2006). Krack and his coworkers document gradual onset of dementia in 3 of 49 patients who were followed for 5 years following implantation of deep electrodes in STN. None of these patients met diagnostic criteria for dementia prior to the

surgery. The authors attributed the development of dementia to ongoing neurodegenerative PD as no acute changes were present following surgery in these three patients.
The methodological issues have to be taken into account as well. Number of studies evaluating the cognitive and neurobehavioral effects of DBS included only small number of patients and only few of them have included the control patient group of PD patients who did not have the surgery. The absence of control groups makes it difficult to determine whether a change occurring after DBS in surgical group might have occurred also in non-operated patients, thus reflecting non-DBS factors (PD progression, medication effects).
(Gironell et al. 2003, Morrison et al. 2004).

Postoperative cognitive and neuropsychiatric changes can be caused by multiple factors (Table 3).

Tab. 3 Factors that could cause the neuropsychiatric complications after DBS STN.

Preoperative psychiatric state of the patient (psychiatric disorder)
Surgery related factors (duration of operation, electrode trajectory, site of definitive electrode implantation, number of microelectrodes used, possible surgery complications)
STN stimulation factors (placement of stimulation electrode, stimulation parameters)
Postoperative issues (adjustments of dopaminergic medication)
Psychosocial issues (patient adjustment to the postoperative state, neurobehavioral influence)
PD related factors (non-dopaminergic symptoms, neurodegeneration)

The cognitive functions can be influenced either by the surgical procedure connected with electrode implantation or the high frequency stimulation of target and neighboring structures. The adjustments of dopaminergic medication (e.g. decrease of L DOPA equivalent dose after DBS STN) could also have profound influence on neuropsychiatric performance.
The medication therapy changes have the indirect consequences, e.g. possibility of apathy and abulia occurrence caused by the very fast decrease of dopaminergic medication. Apathy and abulia could augment patient's performance in neuropsychiatric testing. Too slow decrease of medication, puts the patient to increased risk of neuropsychiatric changes (hypomania, mania, hypersexuality) (Houeto et al. 2003).

The effect of surgical procedure itself is connected either by non-specific perioperative factors (stress of the surgical procedure) or the specific factors related to selected trajectory in the basal ganglia. From the anatomical point of view it is very likely that the occurrence of cognitive and neuropsychiatric decline is related to the electrode placement into the vicinity of limbic and associative structures and tracts.

Recent evidence has implicated the stimulation parameters (amplitude, pulse width, stimulation frequency) as the intriguing factor influencing the cognitive and various non-motor symptoms of PD. The most important seem to be the amplitude and frequency. There seem to be some evidence that stimulation parameters that improve the motor symptoms of PD could, at least in some cases, worsen the cognitive performance of the patient (Koppel et al. 2006).

Several studies approached the lead location or lead trajectory as a possible variable in relation to neuropsychological effects of DBS STN. Chronic anteriorly located active contact stimulation within ventral STN was found out to be one such variable *(Tsai 2007)*. According to another study *(Witt et al, 2013)* patients with DBS STN who declined in semantic verbal fluency, Stroop task and the backward digit span task performance showed a position of the active electrode outside the volume built by the active electrodes of stable performers. Passage of the chronic stimulation lead through the head of the caudate increased the risk of global cognitive decline and working memory performance after DBS STN in group of 68 patients with advanced PD. Authors suggested that the electrode path should be planned outside the caudate nuclei, whenever possible. This study also stressed the importance of precise positioning of the active stimulating contact within the subthalamic volume to avoid adverse effects on semantic verbal fluency and response inhibition.

Other papers cited patient related factors as possible predictors of worsened neuropsychological outcomes after DBS STN in PD.

Umemura found out that high preoperative UPDRS III motor score in the medication-off period and a depressive state evaluated with BDI-II correlated significantly with decline in executive function (Umemura, 2013). There were 57 patients included in this study.

Also other patient inherent factors (such as age, attention, dose of anti-parkinsonian medication, scores on axial motor symptoms and a lower L-DOPA response before surgery) were reported as predictors of neuropsychological side effects (Daniels et al., 2010; Smeding et al., 2011).

Factors related to drug withdrawal factors (Thobois 2010) also have to be taken into account. Changes in dopaminergic medication after DBS STN should be gradual and slow.

The surgery and stimulation-related modulation of STN conveyed cognitive functions can be caused also by the relatively small size of STN. It may be impossible for electric current to avoid the parts of STN dedicated to cognitive functioning.

The behavioral changes after bilateral DBS STN have been analysed in already cited meta-analysis that included 1398 patients (Temel et al. 2006). There was no statistically significant relation between the clinical characteristics of operated subjects (gender, duration of PD before the operation, age), motor outcome of DBS and cognitive or neuropsychiatric changes. Only patients with preoperative clinically relevant behavioural alterations can be at risk for further deterioration after surgery.

Perriol and coworkers investigated the correlation patterns of the motor, cognitive and behavioural consequences of DBS STN with respect to positioning of active stimulation contact (Perriol et al. 2006). They have described the cognitive changes 12 months after surgery only in 3 patients with a history of pre-operative, dopaminergic psychosis or post-surgical confusion. Age and a distant history of depression were associated with occurrence of post-surgical depression. The cognitive or affective changes had no relation to the motor outcome.

There is a ongoing debate on exact frequency and severity of cognitive and/or neurobehavioural changes after DBS STN. However, from the available data it seems quite clear that the patients with preoperatively disordered cognitive functions, history of depression or behavioural problems carry increased risk of neuropsychiatric complication after the DBS surgery. This only confirms the role of neuropsychologist in DBS team. Meticulous neuropsychologic and neuropsychiatric examination is essential also in the time after the surgery for assessment of long-term effects of DBS STN on cognition (Fanfrdlová et al. 2006. Telecká et al.2010).

STN appears to be involved in complex cognitive behavioural functions and networks such as the network underlying the Theory of Mind (Péron et al., 2013). Moreover, neuropsychiatric problems such as depression (Voon et al., 2006, Thobois et al. 2010), apathy (Voon et al. 2006),

suicide ideation/attempt (Voon et al., 2008) were also reported after DBS STN surgery, and were reviewed recently by Rodriguez-Oroz et al., 2012. Behavioural complications were reported after DBS STN more frequently than after DBS Gpi. The etiology of these problems is multifactorial and except for reduction of dopaminergic medication (Thobois et al., 2010) and preoperative risk factors (Lim et al. 2009) includes also stimulation of contacts located in non-motor areas (Mallet et al., 2002, Mandat et al., 2006, Raucher-Chéné et al., 2008). The impulsivity and mania are thought to be related to diffusion of electric current to limbic parts of STN (Rodriguez-Oroz et al., 2012, Mallet et al., 2007, Krack et al., 2010). STN DBS might alter the coupling between prefrontal cortex and basal ganglia during decision-making processes (Cavanagh et al., 2011).

It is possible to outline the characteristics of a patient with increased risk of cognitive and neurobehavioural impairment post DBS STN surgery (Tab.4). It has to be stressed that with careful adherence to selection criteria the risk of neuropsychiatric side effects after DBS STN is low.

We have observed cognitive disorder related to surgery only in one patient from our group of about 45 patients after DBS STN. Transient postoperative confusion occurred in 4 patients. In three patients the hypomania or mania was observed immediately after the surgery. The 12 month observational neuropsychological data of our group were published earlier (Telecká et al. 2010).

Table 4.

Patient with increased risk of cognitive and neurobehavioural impairment after DBS STN surgery

Age above 70 years
Preoperative neuropsychiatric dysfunction (diagnosed dementia, depression, behavioural disorders)
DBS surgery complications (infection, intracranial bleeding)
Prolonged intraoperative microrecording with higher number of microelectrode trajectories.
Insufficient or overactive dopaminergic stimulation (depending on adjustments of dopaminergic therapy postoperatively)

From: Baláž M and Rektor I., 2008

3 Commented compilation of original journal articles

3.1 Participation of subthalamic nucleus in executive functions.

Published in: Movement Disorders 23(4):553-7, 2008, IF: 5.6

Commentary.

The following article was the first from our studies pertaining recording from subthalamic macroelectrodes. The aim of the study was to evaluate the P3 wave characteristic in STN with the use of deep brain electrodes. These recordings were unique as they were centered on event related potentials that evaluated cognitive functions.

We included ten patients with advanced PD who were treated by DBS. In the time interval between inserting deep brain electrodes and implantation of the final neurostimulator, the electrodes were available for recording via externalization device. This interoperation period is usually used clinically for so called external stimulation deemed for evaluation of stimulation effect. Altogether 14 electrodes were available for evaluation.

We evaluated P3 waves in all patients using two paradigms. One of the protocols was so called standard auditory oddball paradigm during which a patient was asked to silently count number of rarely occuring sounds. Recordings during this protocol did not reveal any signs of P3 potentials generation. Other paradigm was so called dual-task protocol during which a patient was asked to silently increase the ordinal and day of the date with each rarely occurring sound. Dual task has an increased demand on executive functions of patients with PD. The P3 evoked by this dual-task protocol was found to be significantly changed specially if examined in patients with Parkinson's disease by Garcia Larrea et al. Indeed, we were able to find the generators of P3 related to this dual task within vicinity of subthalamic nucleus in 8 out of 14 electrodes.

The P3 potentials related to the increased demand on executive functions were detected by STN contacts known to have the best effect on Parkinsonian motor signs. This could suggest that STN participates in the executive function processing. The neuronal pools involved in cognitive activities may be located in close vicinity to, or even overlapping with, the neurons active in motor functions.

Our study confirmed the participation of subthalamic nucleus in executive functions. However, surprisingly if compared to previous studies by our group there was no sign of generator for P3 standard oddball protocol that was otherwise present widely within subcortical structures as was published by our group earlier (Rektor et al, 2005).

Our results published in this paper suggested that STN stands out amongst other BG structures in that participation of this structure in executive functions was conveyed through other pathways than usual basal ganglia-thalamic-cortical circuitry. Overall, the findings from this study indicated that STN played an active role in processing executive functions in patients with the Parkinson's disease.

Participation of the subthalamic nucleus in executive functions:

An intracerebral recording study.

M. Baláž, I. Rektor, and J. Pulkrábek

[1] Movement Disorders Centre, Department of Neurology, St. Anne's University Hospital, Medical School of Masaryk University, Pekařská 53, 656 91 Brno, Czech Republic

Corresponding author:

Dr. Marek Baláž

Department of Neurology

St. Anne's University Hospital

Medical School of Masaryk University

Pekařská 53, Brno 656 91

telephone: +420 54318 2624

fax: +420 54318 2658

e-mail: marek.balaz@fnusa.cz.

Abstract:

Objective:

The objective of our work was to find whether the subthalamic nucleus (STN) is directly involved in cognitive activities, specifically in executive functions.

Patients and methods:

Ten patients with idiopathic Parkinson's disease had P3 potentials recorded by externalized deep brain electrodes that were implanted in the STN or in its immediate vicinity. Two contacts of each electrode were positioned inside the STN according to clinical effect, perioperative microrecording, and stimulation. The P3 waves were recorded following the auditory stimulus in a standard oddball paradigm. They were compared to the P3 waves elicited from a protocol modified by a dual task with an increased demand on executive functions.

Results:

The P3 potentials with a steep amplitude gradient evoked by the modified protocol were detected by the contacts in 8 out of the 14 available electrodes, located either inside the STN or in its immediate vicinity. The modified protocol led to an increased latency of the P3 potential in 8 of 14 electrodes. No local field potentials of the standard P3 potentials were recorded.

Conclusion:

The P3 potentials related to the increased demand on executive functions were detected by the STN contacts known to have the best effect on Parkinsonian motor signs. This could suggest that the STN takes part in the executive function processing.

Introduction

In recent years, there has been a steady increase in the number of reports regarding cognitive disorders and other non-motor disorders related to deep brain stimulation (DBS) surgery for Parkinson's disease (PD) (1). According to the current practice, DBS of the subthalamic nucleus (STN) should not produce any major adverse cognitive or behavioral effects in properly selected patients.

The mechanism by which the STN regulates motor functions in the neural circuitry is not fully understood, and little is known about its influence on cognitive networks**.**

In this study, P3 cognitive event-related potentials in the STN were recorded. The late positive complex of event-related potentials (ERP) - the P300 or P3 wave - may represent various functions, such as the closure of sensory analysis, the update of working memory, the attention and decision processes, and the facilitation of motor pathways in motor tasks. An earlier study showed that P3-like potentials are generated throughout the basal ganglia,

notably in the putamen (2). The present study measured the amplitudes and latencies of P3 waves using a dual task protocol in order to evaluate the involvement of the STN in executive functions.

Garcia-Larrea and Cezanne-Bert elaborated a dual task P3 paradigm that proved to be suitable for the study of executive functions in PD (3,4). Parkinsonian patients examined with a dual-task paradigm showed significantly greater P3 attenuation than age-matched controls, even in tasks not requiring any motor response (4). This suggests that the executive load imposed by the dual task is pathologically increased in PD independently of motor impairment.

In this study, we raise the question of whether the STN generates the brain potentials linked with an oddball protocol on one hand, and the potentials evoked by cognitive processes linked with executive functions (modified protocol) on the other hand. The impairment of executive functions is a well-known sign of PD.

Methods and material

Patients

The present study included ten patients with L DOPA-induced motor complications of Parkinson's disease (6 men and 4 women with a mean age of 55.8; SD 9.61 years), indicated for DBS surgery by the Commission for Neuromodulation Surgery of the Brno Movement Disorders Centre. The mean preoperative UPDRS III (Unified Parkinson's Disease Rating Scale) was 43.6, SD 6.9 off medication; and 22.3, SD 4.1 in on-medication state. The mean duration of the disease was 13.5 years, SD 3.2 years. All patients freely gave their informed consent to participate in the study. The hospital ethics committee endorsed the study.

Surgical procedure

The sterotaxic frame used was the Leibinger open frame with the Praezis plus software and the Talairach diagram. The STN coordinates used were in respect to the AC-PC (anterior commissure – posterior commissure) line: 11.0 mm laterally, 5.0 mm below and 3.0 mm behind the midpoint of AC-PC line. The implantation procedure was performed in two steps. First, the stimulation leads (Medtronic, Inc.) were implanted bilaterally into the targeted structure by a stereotaxic MRI-guided technique under local anesthesia. The lead placement was confirmed by microelectrode recordings, which served as the reference for ascertaining the position of each contact (electrode pole) within the STN and in relation to the adjoining

structures. We used the standard tungsten microelectrode 291 A (Medtronic, Denmark) with impedance of 0.5–1.5 MΩ for microrecording.

The motor part of the STN was identified by recording the pattern of neuronal activity, background activity, and motor responsiveness (changes in neuronal firing in response to passive and active manipulation of contralateral limbs during the perioperative microrecording). We determined the dorsolateral border of the STN by microelectrode recording of cellular firing patterns. We also assessed the lead location by evaluating the symptom response to the intraoperative microstimulation. Once the final target coordinates were determined, a permanent quadripolar DBS electrode (model 3389 with 0.5 mm intercontact distance) was implanted, and the intraoperative test stimulation was performed to optimize clinical effect**s.** The electrode position was verified by the intraoperative use of fluoroscopy to compare the position of the trajectories of the microrecording electrodes with the definitive trajectory of the quadripolar macroelectorode.

In all but two patients, the best response of the Parkinsonian motor signs (tremor, rigidity, and akinesia) to the postoperative stimulation was observed in the two central contacts of the quadripolar electrode. In the two other patients, the best effect on motor signs was present on the two most distal contacts.

In the second part of the operation, the electrode cables were internalized and a neurostimulation device (Itrel III or Kinetra, Medtronic Inc., Minneapolis, USA) was implanted.

The period between the two steps of the operation ranged from 3 to 7 days. This period served for functional assessment and testing of efficacy during the external stimulation. We also used this period of time for measuring Event-Related Potentials (ERP) (see below).

ERP measurements

The recordings of ERP (P3) were performed during the interoperative period from the externalized DBS electrodes. The recordings were performed on the third day after the electrode implantation in all patients included in the study. All patients were in an on-medication state during the ERP recording.

ERP recordings were performed using the 8-channel Nihon Kohden Neuropack 4200EP/EMG device (Nihon Kohden Electronics, Osaka, Japan) or the 32 channel EEG system TruScan (Deymed Diagnostic, Alien Technic, Czech Republic). Time base ranged from 0 to 1200

milliseconds (ms); filter range: 1 hertz (Hz) – 200 Hz; sensitivity gain: 200 microvolts (uV); sampling 256 Hz. We used a biauricular reference electrode.

The P3 waves evoked by an auditory stimulus in the standard oddball paradigm (7) were recorded and compared to the P3 waves elicited by the modified protocol with increased involvement of executive and cognitive resources (4).

The auditory oddball paradigm was used with no motor activity during the test (3). Tones were delivered through earphones at a 2 Hz frequency: frequent tones were delivered at 1000 Hz and 70 decibel (dB) for 0.1 second (s) duration; rare (target) tones were delivered at 2000 Hz and 70 dB for 0.1 s duration. The tones were randomly generated at 5:1 ratio.

In the first test, the subjects were instructed to recognize the target tones and to silently count them in the standard protocol. They were asked to report the total number of target tones at the end of each recording session.

The second test used a modified auditory oddball paradigm involving increased demands on executive functions. The target and frequent tones were delivered with identical parameters to those of the standard protocol described above. The tasks in this condition consisted of silently changing the date upon each target presentation. Immediately prior to the recording, the subjects were given a two-item date that included the day of the week and the ordinal date (e.g. Monday**,** the 19th). The date had to be updated after each target stimulus. The final outcome had to be presented at the end of the recording session (4).

Only target data were further analyzed. The main ERP component of a P3 wave was identified visually and quantified by its latency and amplitude parameters. The peak latencies were measured from the stimulus onset. We evaluated the first distinctive potential to appear in the 250-600 ms window. Only the P3-like potentials with a steep voltage change were considered to suggest nearby generators (we did not find any phase reversal pattern in our patients) (8). Significantly larger amplitude recorded from the lead contacts within the STN, compared to the neighboring contacts outside of the STN, particularly a steep voltage gradient, implied a local generation of the P3-like potentials (9).

The processing steps included a statistical evaluation of quantitative data (values of amplitudes and latencies of the P3) and a qualitative analysis (assessment of presence or absence of steep voltage change, e.g. rise of amplitude in the contacts located within the STN

compared to the contacts outside of this structure). The statistical analysis of recorded potentials was performed by comparing the number of electrodes with the presence of ERP with an amplitude gradient within the STN to electrodes with the P3 waves but without the amplitude gradient in the STN in each protocol.

We also compared the latencies of the P3 peaks in standard versus modified paradigms.

The Wilcoxon matched pairs test was used for the analysis of latencies, while a test of homogeneity of binomial distribution was used to assess the presence of P3 generators.

Results

Amplitudes

The recordings were taken from 20 electrodes. In 6 electrodes, either no P3-like potentials were present (in 3 electrodes), or only artifacts were found (in the other 3 electrodes).

We found a voltage change – a steep rise in amplitude – in the P3 potential recorded during the modified protocol (dual task) within the STN in 8 of the 14 electrodes available for the generator potential evaluation (Fig.1). In the remaining 6 electrodes, there were no generators of P3-like potentials present. There were no differences regarding the age, medication, motor state, or electrode positioning in patients where the P3 was absent from ERP recordings.

We also observed intracerebral P3 with negative polarity (such as the one depicted in Fig.2) due to the nature of intracerebral recording, when even a slight shift in the mutual position of a lead and a generating structure can influence the resulting curve.

A statistical evaluation proved the occurrence of generator activity to be statistically significant $p < 0.0001$ (test of homogeneity of binomial distribution). We did not observe such a voltage change in the P3 recorded during the standard protocol.

Latencies

We observed that the modified paradigm led to an increased latency of P3 in 8 out of 14 tested electrodes (16 out of 28 contacts) in the contacts located within the STN (contacts with the best motor effect) (Fig.2). The mean latency of P3 from the contacts presumed to be within the STN in the standard protocol reached 261.9 ms, SD $\pm$ 40.3. The mean latency was 294.8 ms $\pm$ 51.31 in the modified protocol. The differences between the latencies in the standard and modified paradigms were statistically significant with $p < 0.0001$ (Wilcoxon matched pairs

test). Latencies for the contacts outside of the STN reached 252.25 ms ± 29.28 in the standard protocol, compared to 259.5 ms ± 30.17 in the modified protocol. The difference between these latency values was not statistically significant.

Discussion

In this study, we recorded cognitive event related potentials (P3) using standard and modified auditory oddball protocols, where the latter was modified by an increased demand on executive functions. We evaluated potentials that displayed an amplitude gradient in adjacent contacts. A significantly larger amplitude in one contact than in a neighboring contact, particularly a steep voltage gradient over a short distance, implied a local generation of ERP. The "steep voltage changes" were considered to be generators because of their significance as the accepted signs of proximity to a generating structure (7).

One limitation of the present study is the determination of an exact location for the recording contacts within the STN. The absence of a phase reversal could mean that a recording contact was positioned in the immediate vicinity of neuronal population generating the P3 rather than in the STN itself. Due to the small volume of the STN, we cannot fully exclude the possibility that some potentials were generated adjacent to the STN and not directly in the nucleus. On the other hand, as the P3 local fields were recorded on the contacts with the best motor effect, it is highly probable that the actual STN activity was recorded. The characteristics of the electrodes used, especially the relatively small lead volume and short intercontact interval, enabled a relatively precise localization of the signal source. A slight shift in the mutual position of a lead and a generating structure (dipole generator) can dramatically influence the recording.

In our recordings, no generators of the standard oddball P3 could be recorded in the STN. On the contrary, the modified protocol with a dual task elicited a local field P3 potential within the STN. This could indicate a specific, task-related involvement of the STN in the cognitive processing of information. In this case, only a task with an increased demand on executive functions produced the possible P3 local fields. These findings are more intriguing when we consider that our target was either directly in the motor part of the STN (dorsolateral) or in its immediate vicinity, according to the perioperation microrecording results and the effect of DBS procedure on the motor performance of the patients. The neuronal pools involved in the cognitive activities may be located in close vicinity to, or even overlapping with, the neurons

active in motor functions. The cognitively active neurons might be affected by DBS in some cases, especially if the small size of the STN is taken into account.

The latencies of P3 in the two paradigms also differed. The P3 latency is considered to be a measure of stimulus classification speed during memory updating. Also, there is a link between P3 latency and the timing of attention processes. (8). We propose that the presence of the difference in the P3 latency between the standard and modified paradigms in the contacts with the best motor response (presumably the ones within the STN) and the absence of these changes in the contacts outside of the STN support the role of the contacts with the best motor response in cognitive processing of executive functions.

The basal ganglia participate in various cognitive activities. It has been suggested that the basal ganglia system is the generator of the cognitive patterns (9,10). P3 like potentials have been recorded in the caudate, putamen, and pallidum (2,11,12,13). The basal ganglia are also involved in the attention processes (10). Nevertheless, the involvement of the STN in these functions is still largely unknown. The generating of cognitive potentials related to executive functions in the STN may indicate that the STN has an active role in processing executive functions.

It is probable that the STN participates in the executive functions as a part of a cortico-basal ganglia-thalamocortical loop. The existence of direct anatomical pathways linking the STN to the prefrontal areas of the brain has been reported recently. When a voluntary movement is about to be initiated by the cortical mechanisms, a corollary signal conveyed through the cortico-subthalamo-pallidal “hyperdirect” pathway first inhibits the large areas of the thalamus and cerebral cortex that are related to both the selected motor program and other competing programs. This direct connection between the STN and the cortex could perhaps explain the role of the STN in influencing the cognitive and executive functions (14). Our findings may therefore suggest that a certain effect of DBS surgery on cognitive performance could be connected to the direct influence of the operation procedure and/or stimulation on the “cognitive” parts of the STN.

The majority of studies on cognitive function changes related to DBS for PD suggest that the DBS-STN results in a relatively small cognitive morbidity in well-selected patients.

The most robust findings across various studies appear to be a decline in word fluency, verbal memory, conditional associative learning, visuospatial memory, processing speed, and

selected measures of executive functions (15,16). However, multiple reports exist about patients, who sustained significant cognitive decline following surgery (17,18).

Some studies have also examined the role of stimulation on neuropsychological performance. These reports demonstrated either no significant cognitive effects, or improvements in processing speed, working memory, and other functions with stimulation (19). Therefore, the effect of an electrical current on the cognitive parts of the STN cannot be excluded.

As we recorded in the early postoperative phase, it is possible that this effect is transitory and does not occur later or occurs only in patients with postoperative cognitive impairment.

Recordings of ERP have been performed in patients treated for Parkinson's disease for many years.There have been no examinations performed in healthy controls. As has been shown by Garcia-Larrea, Parkinson's disease itself influences P3 recordings. The impact of long-term L-DOPA therapy on P3 recordings cannot be excluded, and the results of our study have to be viewed from this perspective.

Overall, the findings from this study indicate that the STN plays an active role in processing executive functions in patients with the Parkinson disease. However, further data are needed to understand the clinical implications of our results.

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Fig. 1. Amplitude changes suggesting the vicinity of P3 generators.

A. Steep rise of voltage suggesting the generator activity after testing with modified protocol. P3 recorded from STN (channels 2 and 3) compared to activity recorded outside of STN (channels 1 and 4).

B. No difference in amplitudes between contacts inside versus outside of STN after testing with standard protocol.

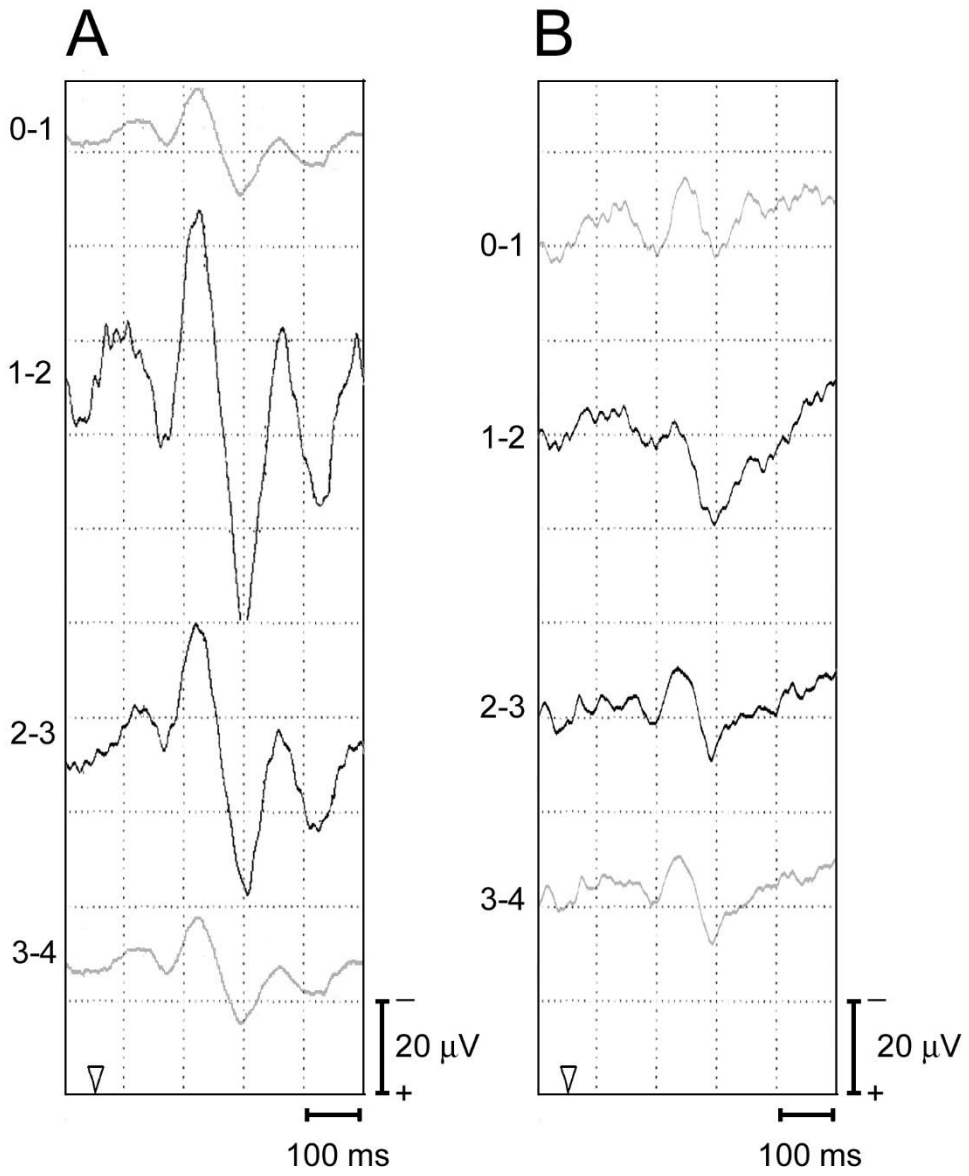
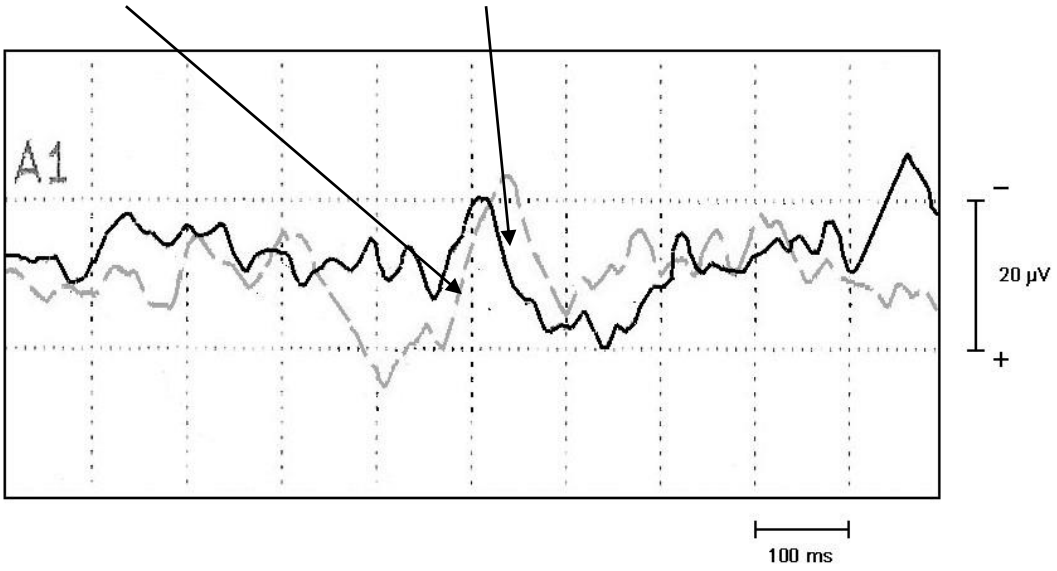


Fig. 2: Differences of P3 latencies of standard and modified protocols.

Diference in latency of P 3 in standard (bold black line) and modified protocols (dotted line). This graph depicts the P3 recording of patient KG from a single contact pair within the STN (there is no difference between P3 amplitudes present in this figure). Thick black arrow marks the stimulus onset (0 milliseconds).

P3 P3



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3.2 The effect of cortical repetitive transcranial magnetic stimulation on cognitive event-related potentials recorded in the subthalamic nucleus in patients with Parkinson's disease

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Commentary

In this paper we corroborated our previous research regarding the position of STN in cognitive and executive functions. The aim of the work was to find out whether the use of repetitive transcranial magnetic stimulation (rTMS) over two distinct cortical structures may modulate the electrophysiological properties of intracranial P3 waves. We again used two P3 auditory protocols – standard auditory oddball and dual-task modified protocol that were described in detail in previous commentary and article (2.1). Also the procedure with the recordings from deep brain electrodes was similar to previous study. Additionally, we applied rTMS over either dorsolateral prefrontal cortex (DPLPFC) or inferior frontal cortex between first and second recordings of P3 waves. We planned to modulate the cortical activity of two previously mentioned cortical areas and to follow the resulting changes in P3 waves. rTMS is presumed to represent a suitable tool to investigate plasticity within a functional network and opens the possibility of intervening directly with the mechanisms of cortical plasticity in the human cortex (Siebner and Rothwell 2003). Altogether 18 patients after DBS STN were included in the study. 1 Hz rTMS over the right IFC led to shortening of ERP latencies in both protocols. The correlation between neuropsychological test performance and P300 latency from earlier papers indicated that individual latency variability was related to mental processing speed, with peak timing affected by cognitive operations specific to perceptual and attentional processing (Polich and Herbst 2000). The speed of executive processing is thus reflected by the latency duration. It seemed that the 1 Hz rTMS over the IFC facilitated the executive processing. These changes were not present after the stimulation of DLPFC. The involvement of STN in cognitive activities is selective and specific. As we stated in our earlier paper, the standard oddball protocol did not generate ERP waves in STN, in contrast to a protocol modified by an increased load of executive functions. Overall, the findings from this and earlier studies indicate that STN plays an active role in processing executive functions in patients with Parkinson's disease, probably outside of the classical cortical-basal ganglia-thalamic circuits.

Direct cortico-STN connections bypassing these circuitries could explain the modulation of STN.

This paper showed that there exists a direct functional link between IFC and STN which is active during executive functions. No similar link was observed between DLPFC and STN.

The effect of cortical repetitive transcranial magnetic stimulation on cognitive event-related potentials recorded in the subthalamic nucleus

M. Baláž, H. Srovnalová, I. Rektorová, I. Rektor

Department of Neurology, St. Anne's University Hospital, Medical School of Masaryk University, Pekařská 53, 656 91 Brno, Czech Republic

Corresponding author: rTMS and cognitive event related potentials in STN

Marek Baláž, MD

Department of Neurology

St. Anne's University Hospital, Masaryk University

Pekařská 53, Brno 656 91, Czech Republic

Telephone: +420 543 182 624, fax: +420 543 182 658

E-mail: marek.balaz@fnusa.cz

Keywords: inferior frontal cortex; subthalamic nucleus; executive functions; ERP; P3; hyperdirect pathway

Abstract:

We studied whether the cognitive event-related potentials (ERP) in the subthalamic nucleus (STN) are modified by the modulation of the inferior frontal cortex (IFC) and the dorsolateral prefrontal cortex (DLPFC) with repetitive transcranial magnetic stimulation (rTMS). Eighteen patients with Parkinson's disease who had been implanted with a deep brain stimulation (DBS) electrode were included in the study. The ERPs were recorded from the DBS electrode before and after the rTMS (1 Hz, 600 pulses) over either the right IFC (10 patients) or right DLPFC (8 patients). The ERPs were generated by auditory stimuli. rTMS over the right IFC led to a shortening of ERP latencies from 277 ± 14 ms (SD) to 252 ± 19 ms in the standard protocol and

from 296 ±17 ms to 270 ±20 ms in the protocol modified by a higher load of executive functions (both $p < 0.01$). The application of rTMS over the DLPFC and the sham stimulation over the IFC showed no significant changes. The shortening of ERP latency after rTMS over the right IFC reflected the increase in the speed of the cognitive process. The rTMS modulation of activity of the DLPFC did not influence the ERP. Connections (the IFC-STN hyperdirect pathway) with the cortex that bypass the BG-thalamocortical circuitries could explain the position of the STN in the processing of executive functions.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective long-term treatment for motor symptoms in advanced Parkinson's disease (PD) (Krack et al. 2003). The STN itself is involved in the pathophysiology of PD, and the disruption (e.g. by DBS) of its pathological overactivity partially reverses some of the clinical, electrophysiological, and metabolic abnormalities related to PD (Hamani et al. 2004).

There are controversial opinions on the impact of STN-DBS on cognitive and behavioral functions. It appears that the STN has anatomically a central position within the basal ganglia-thalamocortical associative and limbic circuits and is functionally a potent regulator of these pathways. From a clinical point of view, STN-DBS modulates not only motor but also cognitive and affective functions (Temel et al. 2005). According to some authors, DBS causes only minor changes, related perhaps more to the effect of surgery than the stimulation itself (Okun et al. 2009). A randomized multi-center study showed that STN-DBS does not reduce overall cognition or affectivity, although there was a selective decrease in frontal cognitive functions and a decrease in patient anxiety after the treatment (Witt et al. 2008). According to the meta-analysis, cognitive problems were faced by up to 41% of patients (Temel et al. 2006). A review article underlined certain methodological differences between papers related to neuropsychological and cognitive disorders connected with this procedure (Voon et al. 2006). Overall, it is evident that at least in some patients the change in cognitive functions after STN-DBS may have a clinical importance.

The connections of the STN have been well characterized in both rodents and primates. Both the subcortical and cortical connections were extensively studied with diffusion tractography

(Aravamuthan et al. 2007), which proved that the STN connections in humans largely matched those found in primates. The major connections of the STN are with the globus pallidus and substantia nigra pars reticularis. The STN receives the excitatory outputs from various parts of the cerebral cortex, including the motor cortex, supplementary motor area, and dorsal and ventral premotor cortex (Hamani et al. 2004).

Apart from the striatum, the subthalamic nucleus (STN) is the only structure in the basal ganglia to receive a direct cortical projection (Albin et al. 1989; Parent and Hazrati 1995). This independent corticosubthalamic projection originates from the motor and premotor areas (Afsharpour 1985, Canteras et al. 1990; Bolam et al. 2002) as well as the medial prefrontal cortex, which includes the prelimbic and ventromedial prefrontal areas (Kitai and Deniau 1981; Berendse and Groenewegen 1991; Maurice et al. 1998). This direct interaction between the frontal cortex and the STN implicates its participation not only in sensorimotor functions but also in higher-order cognitive processing (Chudasama et al. 2003).

In this study, we attempt to further clarify the position of the STN in cognitive function processing. In contrast to the striatum and pallidum (Rektor et al. 2004 and 2005; Bareš et al. 2003), no cognitive ERP was generated in the STN area in our recent studies (Baláž et al. 2008; Bočková et al. 2008) using a standard oddball protocol (see Methods). On the other hand, the generators of P3-like potentials within the area of the STN had been elicited only after a task with an increased demand on executive functions. This could mean that the STN is involved only in more “difficult” tasks that can be corroborated by a circuitry possibly different from the basal ganglia-thalamus-cortical loop (Baláž et al. 2008). The question arises whether this role of the STN is conveyed in the cortico-basal ganglia-thalamocortical circuits or by a different pathway.

We therefore sought to learn whether either the cortico-basal ganglia-thalamus dorsolateral prefrontal cortex (DLPFC) loop or perhaps a pathway between the inferior frontal cortex (IFC) and the STN (see below) modifies the cognitive performance of the STN.

The DLPFC (Brodmann areas 9, 46) has been associated with executive functions and with higher cognitive functions (Hoshi 2006). It has been proposed that the indirect projection from the STN to the DLPFC via the connection to the substantia nigra pars reticulata may explain the effect of STN-DBS on cognitive functions (Jahanshahi et al. 2000).

The right IFC (Brodmann area 44) has been shown to participate in executive processing, e.g. in resolving dual task interference at the perceptual attention stage. The suppression of a proponent response and the response selection have been attributed to the IFC (Jiang 2004). Even more intriguing, a direct connection between the IFC and the STN - the "hyperdirect" pathway and its influence on motor aspects of STN activity - has been described (Nambu et al. 2002). The fiber-tracking studies of non-human primates show that the ventral premotor cortex projects directly to the ipsilateral STN (Croxson et al. 2005). An fMRI paper pointed out that the STN and the IFC were coactivated in the right hemisphere for response inhibition (Aron and Poldrack 2006).

We used repetitive transcranial magnetic stimulation (rTMS) to influence the activity of selected cortical structures. rTMS is presumed to represent a suitable tool to investigate plasticity within a functional network and opens the possibility of intervening directly with the mechanisms of cortical plasticity in the human cortex (Siebner and Rothwell 2003). The effect of a single-pulse transcranial magnetic stimulation (TMS) over the motor cortex on STN neuronal activity has been studied (Strafella et al. 2004). TMS of the motor cortex was shown to modulate the neuronal activity of STN in subjects with PD, supporting the important role played by the corticosubthalamic circuit in the modulation of the basal ganglia output. This first study opened up new avenues for in vivo studies of corticosubthalamic interactions in humans.

We utilized the ERPs and their parameters as a tool to observe the impact of rTMS of cortical structures on the executive functioning of the STN and to determine the context of putative cognitive networks comprising the STN. We measured amplitudes and latencies of the P3-like wave. The late positive complex of event-related potentials (ERPs) - the P300 or P3 wave - may represent various functions, including the closure of sensory analysis, the update of working memory, the attention and decisional processes, and in a motor task the facilitation of motor pathways (Brunia et al. 1988). It is not the intent of this paper to enter in the very complex ongoing discussion about the exact meaning of ERP in the 300 ms range.

García-Larrea and Cézanne-Bert elaborated a dual task P300 paradigm that is suitable for the study of executive functions. Parkinsonian patients examined with a dual-task paradigm show significantly greater ERP attenuation than age-matched controls, even in tasks not requiring any motor response (García-Larrea et al. 1997, García-Larrea and Cézanne-Bert, 1998). This

suggests that the executive load imposed by the dual task is increased in Parkinson's disease independently of motor impairment. Our previous results have shown that, in contrast to the other structures of the basal ganglia, the STN participates in the generation of P3 potentials with a modified, but not a standard oddball, protocol (Baláž et al. 2008).

To the best of our knowledge, rTMS over the IFC has not been tested in PD patients or with the oddball P3 protocols.

Methods

Patients

18 patients with L-DOPA-induced motor complications of Parkinson's disease (12 men and 6 women with a mean age of 55.8 ± 6.52 years), indicated for DBS surgery by the Commission for Neuromodulation Surgery of the Brno Movement Disorders Center, participated in the study. The mean preoperative Unified Parkinson's Disease Rating Scale (UPDRS) III was 43.6 ± 6.9 off medication, and 22.3 ± 4.1 in the on-medication state. The mean duration of the Parkinson's disease before the operation was 13.5 ± 2.3 years. All patients freely gave their informed consent to participate in the study. The hospital ethics committee endorsed the study. The patients were divided into two groups according to the area of rTMS stimulation (8 patients with DLPFC stimulation; 10 patients with IFC stimulation). No difference between the groups regarding age, duration of disease, or the dose of dopaminergic treatment was present (Table 1). There was no significant difference in neuropsychological status between these two groups. All of the patients were assessed by a neuropsychologist before their inclusion on a waiting list for the DBS surgery. No patients with psychiatric disorders, dementia, or behavioral problems were included in the study.

Surgical procedure (STN-DBS)

The stereotactic procedure was performed using the Leibinger open frame with the Praezis Plus software and the Talairach diagram. The STN coordinates used were in respect to the anterior commissure-posterior commissure (AC-PC) line: typically 12.0 mm laterally, 5.0 mm below and 3.0 mm behind the midpoint of AC-PC line (Lanotte et al. 2002). The implantation procedure was performed in two steps. First, the stimulation leads (Medtronic Inc., Denmark)

were implanted bilaterally into the targeted structure by a stereotactic MRI-guided technique under local anesthesia. The lead placement was established by microelectrode recordings, which served as the reference for ascertaining the position of each contact (electrode pole) within the STN and in relation to the adjoining structures. We used the standard tungsten microelectrode 291 A (Medtronic, Inc., Denmark) with an impedance of 0.5–1.5 M for the intraoperative microrecording and microstimulation. The two most distal contacts were usually placed within the STN, as established by a microelectrode recording.

The motor part of the STN was identified by recording the pattern of neuronal activity, background activity, and motor responsiveness (changes in neuronal firing in response to passive and active manipulation of contralateral limbs during the perioperative microrecording). We determined the dorsolateral border of the STN by microelectrode recording of cellular firing patterns (Benazzouz et al. 2002). We also assessed the planned lead position by evaluating the symptom response to the intraoperative microstimulation. Once the final target coordinates were determined, a permanent quadripolar DBS electrode (Medtronic, model 3389 with 0.5 mm intercontact distance and 1.5 mm electrode contact width) was implanted. The electrode position was verified by the intraoperative use of fluoroscopy to compare the position of the trajectories of the microrecording electrodes with the definitive trajectory of the quadripolar macroelectrode. This procedure was repeated for the other side.

In the second step of the surgery, the electrode cables were internalized and a neurostimulation device (Kinetra, Medtronic Inc., Minneapolis, USA) was implanted.

The period between these two steps of the operation ranged from 3 to 4 days. This period served for functional assessment and testing of DBS efficacy during the external stimulation. We used this period for our measuring of the event-related potentials (ERP) and for the rTMS study as well. No stimulation of the STN was initiated during the days that were used for our recordings.

Event related potentials (ERPs) measurements

The recording sessions were performed on the third day after the electrode implantation in all the patients included in the study. The sessions were carried out in the same quiet room

during the morning hours. All patients were in an on-medication state during the ERP recordings.

ERP recordings were performed using the TruScan amplifier system (Deymed Diagnostic, Alien Technic, Czech Republic) with 32-channel capability. The time base ranged from 0 to 1200 milliseconds (ms); filter range: 0.2 hertz (Hz) – 70 Hz; sensitivity gain: 200 microvolts (uV); sampling rate 256 Hz. We used a biauricular reference electrode and a silver grounding electrode mounted to the skin in the left clavicle region.

We measured the amplitudes and latencies of ERPs elicited in two protocols.

The ERPs evoked by an auditory stimulus in the standard oddball protocol (Squires et al., 1975) were recorded first, followed by the modified protocol with an increased involvement of executive resources.

The auditory presentation of stimuli was identical for both protocols. Tones were delivered through earphones with an interstimulus interval of 2 seconds: frequent tones were delivered at 1000 Hz and 70 decibel (dB) for 0.1-second (s) duration; rare (target) tones were delivered at 2000 Hz and 70 dB for 0.1 s duration. The tones were randomly generated at a 5:1 ratio (standard-target). There were approximately 30 (29 to 32) target tones presented in each protocol. We changed the number of tones between the protocols in order to maintain the patient concentration on the task, as there were altogether 4 tests presented to patients during the study (standard and modified protocol pre-rTMS and again post-rTMS).

In the first test, the subjects were instructed to recognize the target tones and to silently count them in the standard protocol. They were asked to report the total number of target tones at the end of recording session.

The second test used a modified auditory oddball paradigm involving increased demand on the executive functions. García-Larrea and Cézanne-Bert elaborated this dual task for the P3 paradigm that proved to be suitable specifically for the study of executive functions in Parkinson's disease (García-Larrea et al. 1997, García-Larrea and Cézanne-Bert 1998). The task in this condition consisted of silently changing two parameters of the date upon each target presentation. Immediately prior to the recording, the subjects were given a two-item date that included the day of the week and the ordinal date (e.g. Monday the 19th). The date had to be updated after each target stimulus. The final outcome had to be presented at the end of the recording session (García-Larrea et al. 1997).

The protocols were explained to the patients before the first performance, and patients were briefly reminded before each respective recording with an identical set of instructions.
For technical reasons (the presence of externalized electrodes and their cables on the scalp and time limitations due to the necessity of performing the ERP measurement immediately after the rTMS) we did not perform any ERP recordings from the scalp. After the recording of standard and modified protocol the rTMS was applied. After rTMS the recordings of both protocols were repeated immediately.

rTMS

rTMS was applied using the Magstim Super Rapid stimulator (Magstim Company, Whitland, UK) and a figure-of-eight air-cooled coil (7 cm mean diameter). For the sham stimulation, we used the same stimulator and a sham coil with an identical shape, but without the air cooling and with minimum output.
Each patient had a brain magnetic resonance image (MRI) completed prior to the rTMS study. The brain image was acquired and transformed into the standard (Montreal Neurological Institute) stereotactic space using affine transformations (Jenkinson and Smith, 2001). Using a frameless optically guided stereotactic system, the coil was placed over the appropriate location over the scalp as marked on the MRI. During the stimulation, the coil was held tangentially to the scalp with the handle pointing back and inducing a current flow in the postero-anterior direction.
The coil was well fixed at the stimulation site and the position of center of the coil in relation to the target was constantly monitored on the computer screen. The coil could be adjusted if necessary to maintain the constant alignment of coil and targeted area to within 1 mm. The examined patient's chin was leaning over the holder fixed to same aluminum frame as the coil. Frameless stereotaxy (Brainsight Frameless 1.5; Magstim Company, Whitland, UK) was used to target the optimal position of the stimulated site and to ensure the same cortical area stimulation in all patients. The coordinates for the IFC [X = 42, Y =26, Z = 16] were used based on a study of inhibition in a go-no-go paradigm (Aron and Poldrack, 2006). The coordinates for the DLPFC [X = 39, Y =26, Z = 47] were selected in accordance with previous studies (Vanderhasselt et al. 2006; Kaffenberger et al. 2008).

The coil was kept at the appropriate stimulation site with only negligible deviations during the stimulation. The position of the coil, the recording electrodes, and the areas that were stimulated by rTMS is shown in Figure 1.

The part of the cortex modulated by the rTMS was probably limited to the stimulated area, as a frameless stereotactic system was used for coil focusing and a low-intensity stimulation (80% of motor threshold) was used. A spread to dispersed interconnected areas has been reported only at higher intensities (Siebner et al. 2003). The area of spherical 8-cm-radius surface defined by the half-maximum of the induced electric field, i.e. the quarter-maximum of power, was approximately 20cm² for our coil, as calculated according to previous data (Hallett and Chokroverty 2005). The distance between the peak of this surface and a point located at its border defined above is approximately 25mm. The IFC and PFC can be treated as two points on this surface. As the distance between them is more than 30mm, the stimulation power at the non-target point will be less than a quarter of the stimulation power. at the target point.

One rTMS session (600 pulses) of 1 Hz stimulation was delivered to each patient over the area of the right inferior frontal cortex (Brodmann area 44) or over the right DLPFC (Brodmann area 9, 46). The right side was selected for technical reasons – the externalized outlets of deep brain electrodes were located over the left parietal part of the skull. No patient had the stimulation applied over both the DLPFC and the IFC. In four patients who were stimulated over the IFC, sham stimulation was also applied. The time difference between the sham and active stimulations was approximately 24 hours in order to avoid any possible prolonged rTMS effect on the intracranial recordings. The reason for using the sham stimulation only in some of the patients was purely technical. At the beginning of our study, we had no sham coil available.

rTMS was given with an intensity corresponding to 80% of the resting motor threshold (MT). The MT was measured as the lowest intensity capable of producing motor evoked potentials (MEPs) in the right first dorsal interosseus muscle. The threshold was determined for relaxed muscle.

In summary, the stimulation parameters were: 1 Hz rTMS frequency, one block of 600 pulses comprised of 60 pulses in 10 trains; 80% resting motor threshold intensity; the total number of stimuli did not exceed 600 pulses per day.

One study reports that the influence of rTMS on cognitive functions can last up to 60 minutes and depends on the site and the frequency of the stimulation (Evers et al. 2001). Another report finds that the effect of 1 Hz stimulation with an intensity of 90% of motor threshold on the cortex lasts about 15 minutes (Gerschlager et al. 2001). We performed all post-rTMS measurements within 15 minutes (a single protocol lasted about 5-6 minutes).

Data analysis

The data related to target (rare) stimuli were further analyzed. The segments with artificial signals (artifacts - such as ones caused by the movement of the patient - were removed). The main ERP cognitive component was identified visually, off-line) and quantified by its latency and amplitude parameters. The peak latencies were measured from the stimulus onset. We evaluated the first distinctive potential, regardless of polarity, to appear approximately in the 200-600 ms window as the cognitive ERP.

The processing steps included a statistical evaluation of the qualitative data (an assessment of clearly visible changes of latencies) and a quantitative data analysis (a comparison of values of the amplitudes and latencies of the ERPs in respective paradigms). The ANOVA and Tukey post-hoc test was used for the analysis of latencies. The latencies of the ERP peaks in both standard and modified paradigms in both conditions (before and after rTMS was applied) were compared.

Results

rTMS with 1 Hz frequency over the right IFC caused a statistically significant shortening of latencies of ERPs in both standard and modified protocols. These changes were observed invariably in all patients. No such changes were observable either after the sham rTMS of IFC or after the active rTMS of the DLPFC area.

We found a voltage change – a steep rise in amplitude – in the ERPs recorded during the modified protocol (dual task) compared to the standard protocol within the STN in 34 of the 36 electrodes available for the generator potential evaluation. These amplitude changes were described earlier (Baláž et al. 2008). There were no changes of motor symptoms observed after the rTMS of DLPFC or IFC in any of the patients.

1. IFC active stimulation

The rTMS led to a shortening of latencies in both protocols in all patients (Tables 2, 3). Overall, the mean latencies of ERP in the standard protocol were 277 ± 14 ms before the rTMS and 252 ± 19 ms after the rTMS. In the modified protocol, the mean latency changed from 296 ±17 ms to 270 ± 20 ms. The statistical significance of both latency changes reached $p<0.000001$. (ANOVA - $F(3, 267)=30,167$) and $p=0.000017$ according to the post-hoc Tukey test. A typical latency change in a single patient is shown in Figure 2.

The changes of latencies were statistically significant on both occasions and there was no statistical difference between the ERP latency of the standard protocol and the modified protocol.

Amplitudes of ERPs were only slightly changed after the 1 Hz rTMS. The amplitudes were slightly decreased in both the standard and modified protocols. The decrease was however not statistically significant (Table 4).

2. IFC sham stimulation

In four patients (FK, JH, BK, RZ), sham rTMS stimulation was also used. There were no changes in either the latencies or the amplitudes after the sham stimulation. The waveforms of ERPs before and after rTMS in both protocols were almost identical, with no difference in latencies (277 ± 1 ms before rTMS and 276 ± 1 ms after rTMS in the standard protocol, and 299 ± 1 ms and 299 ± 1 ms in the modified protocol).

3. DLPFC active stimulation

There was no statistically significant change in latencies after the stimulation of DLPFC (Figure 3). We found only a minimal change in the latencies (Table 3). In the group of 8 patients, the mean ERP latency changed from 274 ± 5 ms to 280 ± 5 ms after the rTMS in the standard protocol, and from 289 ± 3 ms to 299 ± 4 ms after the rTMS in the modified protocol. This latency difference was not found to be statistically significant ($p=0.2649$ - post-hoc Tukey test). The amplitude changes were not present.

There were no noted effects of the rTMS of either area or of the sham stimulation on the test performance of the patients. The number of errors in the counting of target signals (standard

protocol) or the reporting of the date and the day of the week (modified protocol) were not statistically different between the two groups.

Discussion

In this study, we recorded cognitive ERPs using standard and modified auditory oddball paradigms, where the latter was modified by an increased demand on executive functions. The main component of the ERP appeared in the P3 time window. The P3, as the late positive complex of event-related potentials, is the most conspicuous and widely used of the cognitive ERPs. An ERP in the 300 ms range may represent various functions, such as the closure of sensory analysis, the update of working memory, the attention and decision processes, and the facilitation of motor pathways in motor tasks (Brunia and Damen, 1988, García-Larrea and Cézanne-Bert 1998, Verleger 1997). The shape of intracerebral potentials frequently varies, and it is often difficult to identify the equivalents of individual components recorded on the scalp (Rektor et al. 2003 and 2004). We prefer to state that a cognitive process that shares critical common features with the P3 wave very probably elicited the ERP in this study.

We applied the rTMS over the IFC or DLPFC in an attempt to study the impact of modulation of the cortical excitability on ERP potentials recorded from the area of the STN.

1 Hz rTMS over the right IFC led to shortening of ERP latencies in both protocols. The correlation between neuropsychological test performance and P300 latency from earlier papers indicates that individual latency variability is related to mental processing speed, with peak timing affected by cognitive operations specific to perceptual and attentional processing (Polich and Herbst 2000). The speed of executive processing is thus reflected by the latency duration. It seems that the 1 Hz rTMS over the IFC might have facilitated the executive processing.

In contrast to the DLPFC, the IFC is linked with the STN via direct anatomical pathways , namely the hyperdirect pathway (Nambu 2004). This cortico-subthalamo-pallidal “hyperdirect” pathway inhibits the large areas of the thalamus and cerebral cortex that are related to both the selected motor program and other competing programs (Nambu, 2002).

The IFC itself is proposed to have an inhibitory effect on cognition and executive control (Aron et al. 2004). It was also suggested that the IFC excites the STN and so suppresses basal-ganglia thalamocortical output (Aron and Poldrack 2006). This is in line with our results, because if

we assume that the 1-Hz rTMS had an inhibitory effect on the IFC, the overall result could be a facilitation (by the release of the downstream structures from the IFC-STN control) of the cognitive function reflected by the shortening of P3 latencies. We also found the P3 shortening both in the standard and modified protocols, making an inhibitory effect on executive control very likely.

The observed effect of the rTMS of IFC on P3 latency can be interpreted as disinhibition of IFC-STN influence on the structures further downstream. The rTMS of IFC might have interfered with the normal ability of the STN to slow some cognitive processes (Frank et al. 2007).

It is of interest that the P3 was also shortened not only in modified but also in the standard protocol, which was deemed not to be generated within the STN. We assume that the P3 generation recorded from the STN area might have also included other structures. The candidates for such structures include the thalamus, and there are several areas very close to the STN that might produce a standard P3-like potential, i.e. the zona incerta or substantia nigra. It has been shown that there are some thalamic nuclei that generate P3 potentials, namely the posterolateral nucleus, while some other do not, i.e. the ventroposterolateral nucleus (Rektor et al. 2001).

According to our results, rTMS over the DLPFC had no effect on ERPs recorded from the STN. The DLPFC is part of the prefrontal cortico-basal ganglia-thalamocortical circuits and is a cortical region with major involvement in executive functions. Some authors presume the existence of an indirect communication between the DLPFC and the STN via the substantia nigra pars reticularis (Ilinsky et al. 1985, Barbas et al. 1991). It may be assumed that the STN could participate in the executive functions as a part of a cortico-basal ganglia-thalamocortical loop in close cooperation with DLPFC (Fig.4 A). Our data do not exclude the cooperation between the DLPFC and STN. We have taken into account that there exists a quite important segregation of information from various cortical areas to STN (Kolomiets et al. 2001, Strafella et al. 2004). Therefore our study do not by any means exclude the cooperation between the DLPFC and STN in other domains.

An interesting point is the influence that the various frequencies of rTMS can have over various cortical regions. It is well known that a 1Hz-rTMS over the motor cortex has an inhibitory effect on the motor function, but we lack consistent data regarding its effect on the IFC. The rTMS of cortical areas has been shown to influence the P3 wave recorded on the scalp by earlier studies. The 10 Hz rTMS over the frontal area in non-PD patients led to a delay of

the P3 component and thus presumably prolonged the cognitive processing (Jing et al. 2001). The 10 Hz rTMS over the DLPFC was shown to have no significant effect on motor status in PD (Olmo et al. 2007), while the 15 Hz rTMS over the left DLPFC has the potential to improve cognitive functions in PD patients (Boggio et al. 2005) or patients with cerebrovascular disease (Rektorová et al. 2005).

One limitation of the present study is the determination of an exact location for the recording contacts within the STN. Due to the small volume of the STN and the absence of phase reversals, we cannot fully exclude the possibility that some potentials were generated adjacent to the STN and not directly within the nucleus. The presence of the cognitive ERP in the motor part of STN could be explained by the overlap of neuronal populations in this structure. The electrophysiological data indicate that the overlap in the STN may well be present, as the segregation of cortical information flow that exists in the striatum is only partly maintained in the STN (Kolomiets et al. 2001).

The characteristics of the electrodes used, especially the relatively small lead volume and short intercontact interval, enabled a relatively precise localization of the signal source.

As we recorded in the early postoperative phase, it is possible that the microlesion effect might have been present. However, we do not expect that a microlesion effect could have influenced the changes in ERP latencies that we observed after the rTMS of IFC.

Recordings of ERP have been performed in patients treated for Parkinson's disease for many years. As has been shown by García-Larrea and others (Tachibana et al. 1997), Parkinson's disease itself influences P3 recordings.

The on-medication state was selected to ensure the best comfort and concentration for the patients during the recording-stimulation-recording session. However, from the available literature it is possible to assume that the L-DOPA itself could improve the P300 latency (Oshi et al. 1996). Also according to the work of Stanzione (Stanzione et al. 1991) the P3 latency is decreased in PD subjects after L-DOPA administration. On the other hand, only an insignificant shortening of P300 latency after L DOPA was described in patients who had been newly diagnosed with PD (Prabhakar et al. 2000). It seems that central cognitive processing is only weakly linked to the motor functions, and thus we did not expect any major changes in overall results if the patients would be examined in the off-L-DOPA condition.

Simultaneous DBS external stimulation was not contemplated due to time reasons (possible limited duration of post-rTMS modulation of activity of DLPFC and/or IFC) and also due to

possible artifact generation. Furthermore, as has been shown, DBS does not improve the P3 recorded from the scalp (Gerschalger et al. 2001).

The behavioural tests following the TMS were not performed due to the paucity of time and due to the demands of the experimental protocol on the patients themselves. Patients had to perform each task altogether four times in the experimental design (twice for the standard protocol and twice for the modified protocol). The overall appearance of tiredness in the patients was assessed by the examiners as unsuitable for further testing. Furthermore, the evaluation of interpatient behavioural data would be quite difficult (e.g. due to different patients who were included into the groups of either DLPFC or IFC stimulation, the uncertainty regarding the duration of rTMS effect and possible changes in behavioral results caused by this effect).

Based on our data we cannot rule out the possibility that the rTMS of cortical structure could facilitate parallel cortical-subcortical processing within the basal ganglia-thalamo-cortical loop. However, we find very intersting, that such change was not present by the direct stimulation of the DLPFC.

The cortical recordings of the evoked potentials were not performed mainly due to various technical reasons. Therefore the conduction latency between cortical and subcortical potentials could not be ascertained and this shortcoming can limit the impact of our study. Experiments concerning the measurement of this latency can be performed in the future.

Conclusion

The cognitive processing of information in the BG appears not to follow the generally accepted model of cortico-BG-thalamocortical circuits. The involvement of the STN in cognitive activities is selective and specific. As we stated in our earlier paper, the standard oddball protocol did not generate ERP waves in the STN, in contrast to a protocol modified by an increased load of executive functions. Overall, the findings from this and earlier studies indicate that the STN plays an active role in processing executive functions in patients with Parkinson's disease, probably outside of the classical cortical-basal ganglia-thalamic circuits. Direct cortico-STN connections bypassing these circuitries could explain the modulation of the STN. A candidate for such connection is the "hyperdirect" pathway between the inferior frontal cortex and the STN pathways. In summary, rTMS of IFC and not of DLPFC influenced

the P3 recorded in the STN area, indicating that an important role is played by the IFC-STN pathway in executive functioning.

Our findings may suggest that a certain effect of DBS on cognitive performance could be caused by the modulation of the "cognitive" neuronal pools in the STN by surgery and/or stimulation. Determining the exact role of the STN in cognition remains an important and interesting challenge for future research, and further data are needed to understand the direct clinical implications of our results.

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Table 1:

Demographic and clinical characteristics of the two study groups.

Group variables	DLPFC stimulation group	IFC stimulation group
Age (years)	56.8 ±5.4	55.1 ± 7.0
Male-female ratio	4:4	4:6
Disease duration before the operation (years)	13.0 ±1.85	13.2 ±2.0
Dose of dopaminergic medication (in milligrams of L-DOPA equivalent)	1100 ± 380	1000 ± 240

Table 2:

Latencies (ms) of the ERPs before and after rTMS over IFC, in milliseconds (the average from the STN contacts ± SD)

	Modified protocol		Standard protocol	
Patient initials	Before rTMS	After rTMS	Before rTMS	After rTMS
OJ	297 ± 0	284 ± 1	268 ± 1	252 ± 2
MS	289 ± 1	253 ± 1	275 ± 1	233 ± 1
OV	318 ± 2	288 ± 1	248 ± 0	241 ± 1
LS	272 ± 3	246 ± 3	270 ± 2	219 ± 1
VN	297 ± 2	276 ± 2	280 ± 1	256 ± 1
JM	282 ± 0	266 ± 0	292 ± 1	255 ± 1
FK	323 ± 1	316 ± 1	293 ± 2	266 ± 2
JH	305 ± 0	292 ± 0	286 ± 2	265 ± 1
BK	315 ± 2	291 ± 2	297 ± 1	287 ± 1
RZ	298 ± 1	282 ± 0	275 ± 1	253 ± 1

Table 3:

Latencies (ms) of the ERPs before and after rTMS of DLPFC, in milliseconds (the average from the STN contacts ± SD)

	Modified protocol		Standard protocol	
Patient initials	Before rTMS	After rTMS	Before rTMS	After rTMS
BP	311 ± 1	312 ± 1	280 ± 1	283 ± 1
JZ	322 ± 2	321 ± 1	266 ± 1	267 ± 1
VM	290 ± 0	288 ± 0	277 ± 0	280 ± 1

DK	297 ± 1	296 ± 1	284 ± 1	284 ± 1
IT	368 ± 1	369 ± 2	302 ± 1.8	302 ± 2
JD	301 ± 1	311± 1	269 ± 1	274 ± 1
OS	381 ± 0	377 ± 1	314 ± 2	316 ± 0
AK	313 ± 0	318 ± 0	297 ± 1	299 ± 1

Table 4.

Amplitudes (μV) of modified ERPs before and after the 1 Hz rTMS of IFC (the average of all measured amplitudes ± SD)

	Before rTMS	After rTMS	p-value
Amplitude in the STN contacts	13.78 ± 6.84	12.23 ± 2.80	$p < 0.18$
Amplitude outside of the STN	12.80 ± 6.34	11.58 ± 3.96	$p < 0.22$

Figure legends:

Fig. 1. The relative position of recording electrodes, rTMS coil and stimulated regions. Green line depicts the electrode trajectory, with cross denoting the tip of the recording electrode), red dot covers the stimulated area. Blue coil is depicted schematically over the respective stimulated region.

MR scans are from the individual patients from respective groups (A - DLPFC, B - IFC).
The anterioposterior difference between slices is 20 mm (A) or 19 mm (B) respectively.

Fig.2. Intracranial P3 recorded from the deep brain electrodes before (bold black line) and after (bold grey line) the 1Hz-rTMS of IFC in the individual patient. Note the shortening of

latency after the 1Hz-rTMS is present (292ms versus 255 ms), highlighted by the arrows. Depicted lines represent the target signal recordings from respective contacts of quadripolar electrodes in modified protocol only. Recording electrode contacts are marked on the left (l1 to l4 – left side; p1 to p4 – right side). Contacts p1, p2 and l1, l2 are located within the STN itself.

Fig.3. Intracranial P3 recorded from the deep brain electrodes before (bold black line) and after (bold grey line) the 1Hz-rTMS of DLPFC in the individual patient. The shortening of latency after the 1Hz-rTMS is insignificant (382ms versus 375 ms). Depicted lines represent the target signal recordings from respective contacts of quadripolar electrodes in modified protocol only. Recording electrode contacts are marked on the left (l1 to l4 – left side; p1 to p4 – right side). Contacts p1, p2 and l1, l2 are located within the STN itself.

Figure 1

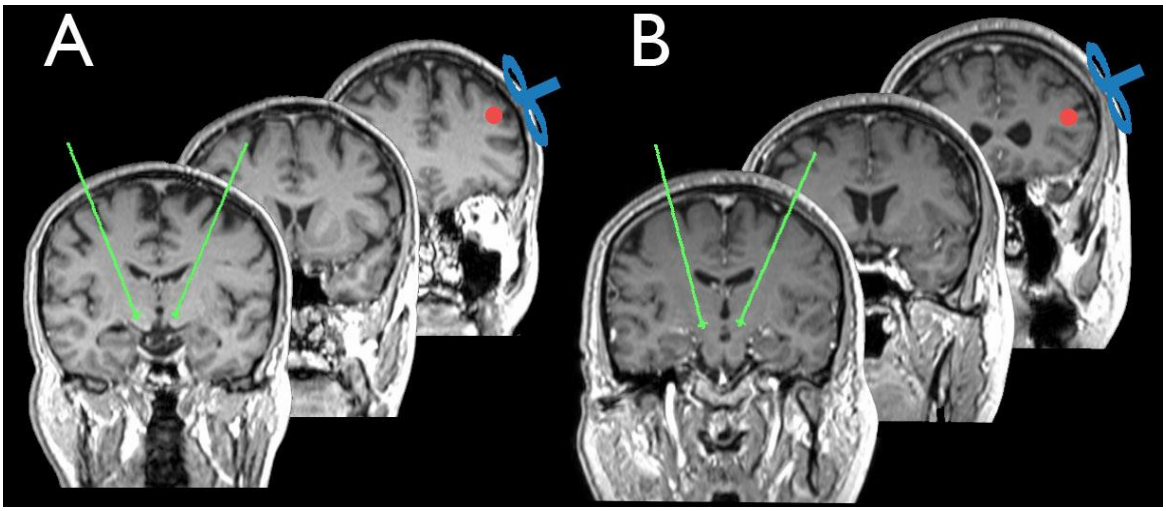
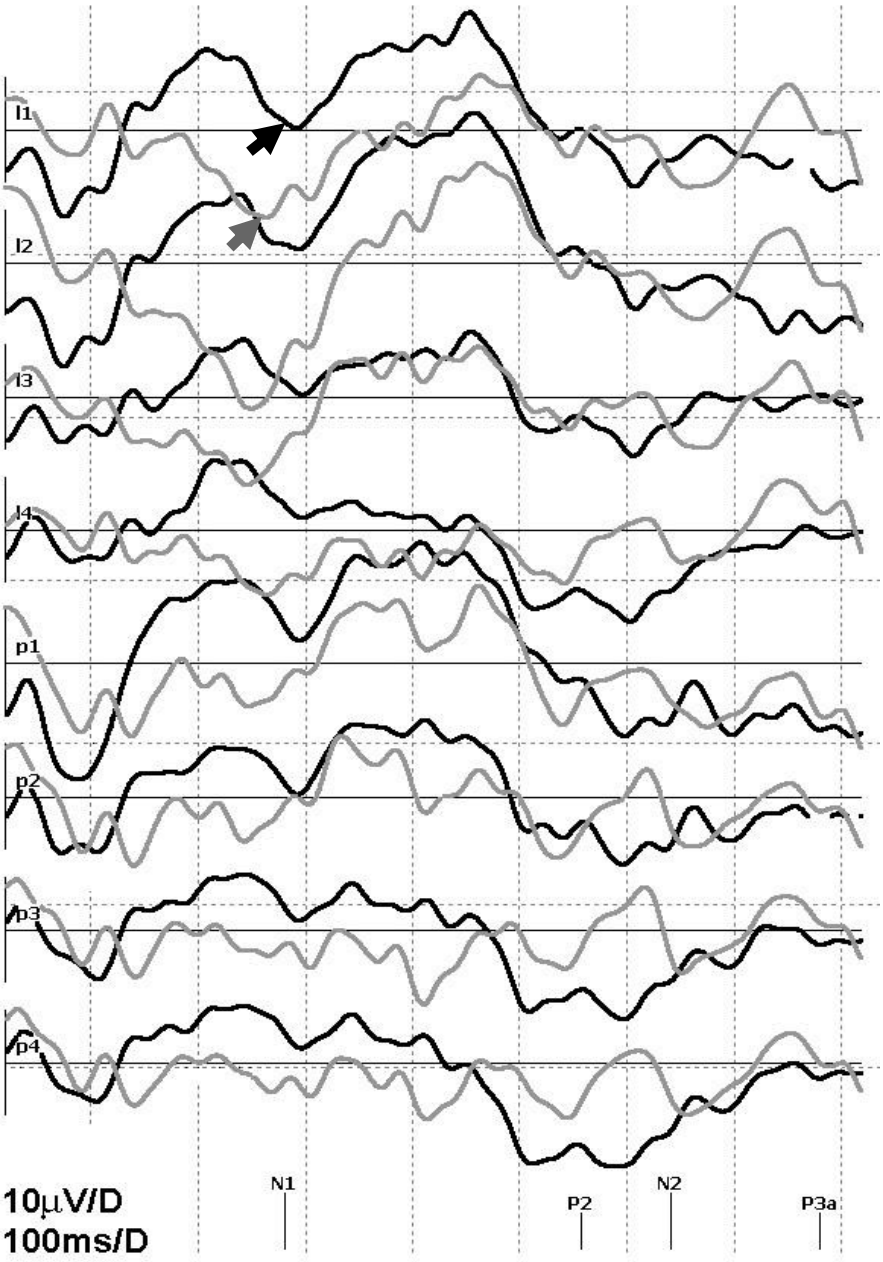


Figure 2


l1
l2
l3
l4
p1
p2
p3
p4
10μV/D
100ms/D
N1
P2
N2
P3a

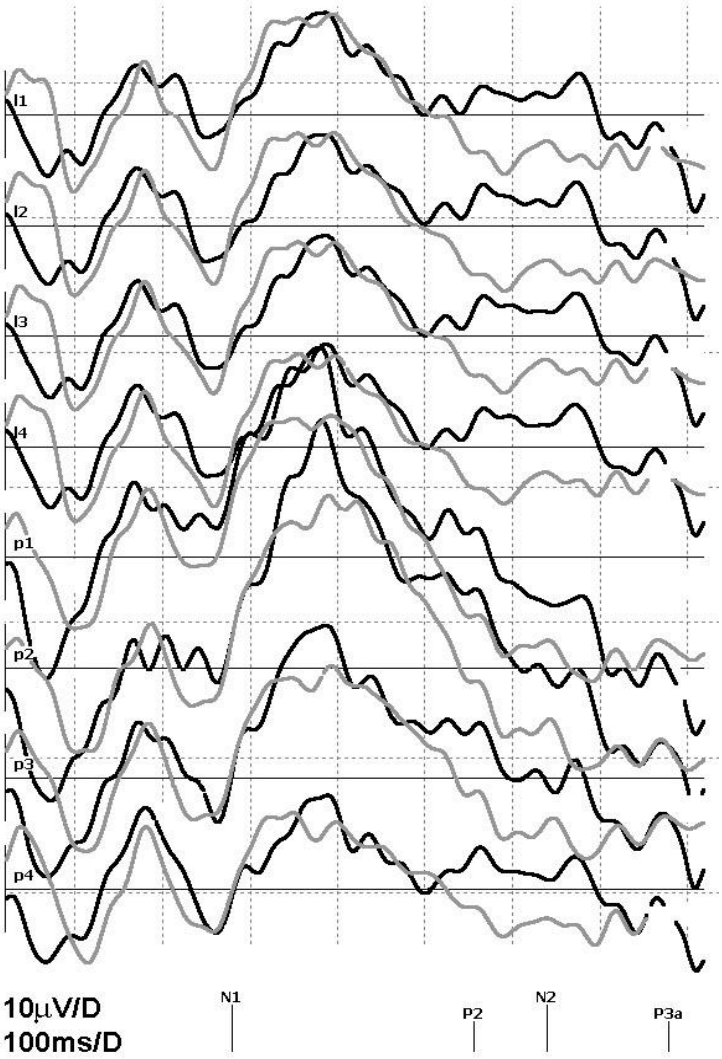


Figure 3

3.3 DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease

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Commentary.

In this paper we have reported various aspects of stimulation parameters and their influence on quality of life. DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease (PD). DBS stimulation parameters are usually aimed on improvement of motor symptoms of PD, such as tremor, rigidity, hypokinesia. Improvements in these aspects brought along by DBS then lead to decrease of dyskinesia – involuntary momevements often present in advanced stages of PD. Some effects of stimulation parameters on non-motor symptoms of PD has been described earlier (Spottke et al, 2002). Correct stimulation setting is a challenge for clinicians involved in DBS treatment. Major improvement of quality of life is a goal of this non-curative, symptomatic invasive treatment.

24 patients with advanced PD who were treated by DBS STN were included in the study. Setting of DBS parameters was thought to be optimal by investigators. However we have noticed that a certain sub-group of patients requests further increase of stimulation parameters, despite the significant improvement of their motor functions after DBS STN.

We decided to comply with patients' wishes, increase the stimulation and observe whether it has any effect on their QoL. We used sham stimulation increase as a suitable way that would enable us to assess whether the real stimulation increase was not related to possible placebo effect. We believe that without using this approach we would be unable to compare the benefit gained from the stimulation increase in selected group of patients.

We used disease-specific questionnaire, a PDQ-39 for assesment of patients quality of life before and after stimulation parameter changes. We found out that after the further amplitude increase in subgroup of patients (mean increase of amplitude of 0.35 V), there was a statistically significant additional improvement of total PDQ-39 score by another 22.9 %. In this group the emotions, stigma and communication subscales improved after the stimulation increase, without further change of UPDRS III. These increases of stimulation thus did not lead

to further changes in motor functions but in improvement of certain non-motor functions. We were able to demonstrate that the increase of stimulation parameters (amplitude) has a potential to improve some non-motor functions and aspects of QoL and thus has an additional effect on quality of life in certain subset of PD patients.

Meticulous observation of stimulation effects on various aspects of PD symptoms is warranted.

Quality of life scales such as the PDQ-39 and questionnaires should become an integral part of the clinical protocol for patients admitted to a Parkinson's disease surgical program. This may help to identify factors that affect the patient's quality of life other than the motor activity.

DBS amplitude setting can improve aspects of quality of life in patients with Parkinson's disease.

Marek Baláž [1,2], Martina Bočková [1,2] and Ivan Rektor [1,2]

[1] 1st Department of Neurology, St. Anne's University Hospital, Faculty of Medicine, Masaryk University, Brno, Czech Republic

[2] CEITEC - Central European Institute of Technology, Masaryk University, Brno, Czech Republic

Corresponding author:
Ivan Rektor, MD, PhD
1st Department of Neurology, St. Anne's University Hospital, Faculty of Medicine, Masaryk University
Pekarska 53, 656 91 Brno, Czech Republic
e-mail: ivan.rektor@fnusa.cz, telephone: + 420 603 864 046

Key words: Deep brain stimulation (DBS); Subthalamic nucleus (STN); Non-motor symptoms; Quality of life.

Abstract:

Objective:

The DBS STN is a non-curative treatment, its effect on the patient's quality of life (QoL) determines the therapeutic success of this procedure. We aimed to assess whether stimulation parameters setting may influence also some of the non-motor aspects of QoL.

Methods:

The QoL was assessed by PDQ - 39 questionnaire. The questionnaire was administered to patients before and after the DBS surgery. A sham change of stimulation amplitude was performed before the actual increase.

Results:

After the further amplitude increase in subgroup of patients (mean increase of amplitude of 0.35 V), there was a statistically significant additional improvement of total PDQ-39 score by another 22.9 %.

In this group the emotions, stigma and communication subscales improved after the stimulation increase, without further change of UPDRS III.

Conclusion

We were able to demonstrate that the increase of stimulation parameters (amplitude) has a potential to improve some non-motor functions and aspects of QoL and thus has an additional effect on quality of life in certain subset of PD patients. The meticulous observation of QoL should be a routine part of assessments before and after the DBS STN surgery, and can even aid during the parameter setting.

Introduction:

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a preferred surgical treatment for motor symptoms of advanced Parkinson’s disease (PD). As the DBS STN is a non-curative treatment, its effect on the patient's quality of life (QoL) determines its therapeutic success. Several studies have shown that this procedure indeed improves QoL in PD (Deuschl et al, 2006);(Weaver et al, 2009).

The non-motor symptoms are prevalent in PD. In many patients the QoL appears to be impaired more by the non-motor symptoms of PD than the motor ones (Schrag et al, 2003; Volkmann et al, 2009) .
Non-motor factors may reasonably be included in the selection of surgical target for deep-brain stimulation (Follett et al, 2010).

Quality of life in PD patients is influenced by motor and several non-motor aspects of the disease. The most prominent non-motor symptoms are depression, sleep problems and pain (Schrag et al, 2003; Schrag et al, 2000). Social aspects, such as communication, social support and disease burden impair the quality of life as well. Progression of PD and disease severity is associated with a decline in quality of life, but the exact longitudinal course and the contributing factors are not well established.

Sufficient voltage is required to achieve desired clinical effects of the stimulation, however the likelihood of side effects increases (Kuncel et al, 2004). The change of stimulation parameters is usually reflected by the improvement of motor symptoms of the PD.

We have noticed that a certain sub-group of patients requests further increase of stimulation parameters, despite the significant improvement of their motor functions after the DBS STN.
We decided to comply with patients wishes, increase the stimulation and observe whether it has any effect on the QoL. We decided to use sham stimulation increase as a suitable way that would enable us to assess whether the real stimulation increase was not related to possible placebo effect. We believe that without using this approach we would be unable to compare the benefit gained from the stimulation increase in selected group of patients.
We specifically aimed to assess whether stimulation parameters setting may influence also some of the non-motor aspects of QoL.

Methods:

We compared stimulation amplitude and its relation to QoL measured by PDQ-39 scale and NMS-Q, Non-motor symptoms questionnaire (Chaudhuri et al, 2006).To our study we included two groups of patients with PD, 36 months after the DBS STN surgery.

Patients

Each group consisted of 12 patients with similar clinical profile (duration of disease, timing of DBS surgery in course of PD, L DOPA dose, age, stimulation amplitude). Group A consisted of 12 patients (8 men, 4 women). These patients requested further increase of stimulation parameters, despite clinically significant improvement of their motor functions after the DBS as judged by experienced clinician (by rating of UPDRS III subscale). Average duration of the disease at the time of the operation was 11.4 ± 3.5 years. Average age was 59.6 ± 7.8 years.

Group B consisted of 12 matched patients (7 men, 5 women) who were satisfied with their overall clinical condition 3 years after the surgery. The characteristics of both patients groups are presented in Table 1.

There were no neuropsychological disturbances, including the impulsivity change in either group A or B. no neuropsychological disturbances, including the impulsivity change were presemt in either of the groups.

Procedure:

The initial coordinates for the STN (dorsolateral part) were determined in reference to AC - PC line (defined on the primary registration series) using indirect technique, typically 11-12 mm lateral to and 3 mm posterior to and 5 mm ventral to intercommisural point. The final target coordinates and electrode position were then modified with respect to direct visualisation of STN on T2 fat sat scans and relationship of the STN to red nucleus anterior margin and largest red nucleus crossectional area. The intraoperational microrecording and timulation were used. There was no difference in final electrode position between the groups of patients reported in this paper.

Assessments

The QoL was assessed by PDQ - 39 questionnaire (Jenkinson et al, 1997). The questionnaire was administered to patients before the DBS surgery, and at 36 months after the surgery. In both groups the assessment of QoL was repeated again, 2 months after the change of stimulation parameter settings (performed in group A only).

The NMS-Q was filled in by the patients in Group A before the stimulation parameters were increased and then again after two months. The effect of stimulation increase on individual items of NMS-Q was recorded. The NMS-Q assessment was based on patient response with “yes” and “no” in. An item was considered to be improved, as long as there was a change in answer from “yes“ to “no“ in statistically significant number of patients.

Stimulation settings change

The stimulation parameters change in this preliminary study was an increase of stimulation amplitude by 0.3 V to 0.5 V. Average amplitude increase was 0.35 V (± 0.1). The frequency (130Hz) and pulse width (90us) were not adjusted. The stimulation increase did not lead to dyskinesia or any other side effects in these selected patients.

A sham change of stimulation amplitude was performed before the actual increase. During the sham stimulation change the patients were informed about the parameter increase, which, in fact, did not occur. After two months of sham stimulation change, the actual stimulation increase described below was performed. The sham stimulation increase was performed in both group A and B. After the real change of stimulation amplitude settings (performed in group A only) the assessment of QoL was performed again.

The stimulation increase did not lead either to dyskinesia or any other side effects in these selected patients. The UPDRS III did not change either.

Statistical analysis

The ANOVA and Tukey test were used to evaluate differences between respective subscales and the groups of patients.

Table 1:

Patient groups data before and 36 months after the DBS

Average values (± SD) of UPDRS II and III scores and PDQ-39 score. LDOPA equivalent daily dose equivalent (LEDD) is shown in mg of the average daily dose. There were no statistically significant differences in the overall improvement between the two groups. Group A – patient with subsequent stimulation increase, B – control group.

	Before DBS (medication off)		36 months after DBS (medication off/stimulation on)		p value average of both groups (difference 36 months vs. Before DBS)
	GROUP A	GROUP B	GROUP A	GROUP B	GROUP A/B
UPDRS II	21 ± 4	20 ± 5	18 ± 3	17 ± 3	0.032/0.034
UPDRS III	43 ± 8	42 ± 7	26 ± 5	24 ± 5	<0.0001 both
LEDD (mg)	1002 ± 305	1012 ± 274	600 ± 280	580 ± 240	<0.0001 both
Stimulation amplitude* (V)	_____	_____	2.8 V ± 0.4V	2.7 V ± 0.4V	-
PDQ-39 (overall score)	74 ± 12	71 ± 10	48 ± 10	40 ± 12	0.00123/0.00142

* The frequency and pulse width were 130 Hz and 90 us in all these cases.

Results:

The quality of life significantly improved after the DBS in both groups of patients as shown by the improvement in UPDRS III score. However, group A (patients demanding the stimulation increase) showed less pronounced improvement of QoL (especially in emotions subscale) compared to group B (Table 2, Table 3). After the further amplitude increase in group A (mean increase of amplitude of 0.35 V), there was statistically significant additional improvement of total PDQ-39 score by another 22.9 % (Fig. 1). In group A the emotions, stigma and communication subscales improved after the stimulation increase. The UPDRS III did not improve further, however.

After the sham stimulation increase in group B, there was no further improvement of either motor or non-motor function present (Table 3).

A sham stimulation increase did not cause any change in PDQ-39 scale or NMS-Q.

The motor improvement observed in our study (UPDRS III improvement of 40 % or 43 % in our groups) is in line with outcomes reported in several studies (Rodriguez-Oroz et al, 2005; Simuni et al, 2002).

Table 2:

QoL subscale changes in both groups. Note the statistically significant improvements in Emotions, Stigma, Social support and Communication subscales

PDQ - 39	Before DBS		36 months after DBS		p values, 36 months versus before the DBS	
	GROUP A	GROUP B	GROUP A	GROUP B	GROUP A	GROUP B
Mobility	64	66	27	32	<0.0001	<0.0001
Activity of daily living	35	37	26	28	0.11	0.27
Emotions	40	42	25	26	0.017	0.015
Stigma	50	48	27	21	0.0007	0.0002
Social support	30	28	16	17	0.014	0.021
Cognition	33	32	30	31	0.24	0.23
Communication	39	42	21	22	0.001	0.001
Body dyscomfort	25	24	17	16	0.1120	0.1230

Table 3 Significantly improved subscales in individual patients of Group A (after the actual stimulation parameter increase compared to sham stimulation change). No change in non-motor scales were present in group B after the sham stimulation change.

	Group A	*Group B*

	At 36 months	*After the actual increase*	*After the sham increase*	*At 36 months*	*After the sham increase*
PDQ - 39 Overall score	48±12	37±10	47±13	38±10	39±10
Mobility	30±11	26±9	*31*±10	32±12	33±12
Emotions	25±8	19±10	*25*±8	26±9	25±9
Stigma	19±6	16±8	*19*±7	21±10	21±10
Communication	22±7	18±6	*21*±6	22±10	24±10
UPDRS III (med off/stim on)	24 ± 5	23±4	*24*±5	26 ± 5	25 ± 5

Discussion:

We report improvement in PDQ-39 score of approximately 32 % after three years of DBS STN. This result is in line with previous observation. As was noted in recently published metaanalysis (Martinez-Martin et al, 2012) ,considering four class I studies on bilateral STN published to date (Deuschl et al, 2006; Esselink et al, 2004; Follett et al, 2010; Williams et al, 2010) with a total of 855 patients (mean: 214; 34–366) and mean follow up of 12 months, the average improvement in HRQoL using the PDQ-39 was 15.4 %. These results are lower than those reported in reviews dating 4 or 5 years ago, where published trials on bilateral subthalamic DBS showed a HRQoL improvement of 60.5% in generic measures (Martinez-Martin et al, 2007) and 33.8–34.5 % in disease-specific scales (Kleiner-Fisman et al, 2006; Martinez-Martin et al, 2007).

Our observations suggest that the DBS may have a certain beneficial effect on non-motor features and social aspects of the disease and also on patient's evaluation of the disease stigma, at least in some patients.

In our study the emotions, stigma and communication as evaluated by the PDQ-39 improved after the stimulation increase.

The overall NMS Q score showed no further improvement after two months of stimulation increase. However, there was a significant improvement – i.e. significant number of patients reported improvement in questions 13 (loss of interest), 22 and 23 (daytime sleepiness, difficulty getting to sleep).
Both PDQ-39 scale and NMS-Q showed a partial amelioration of non-motor signs and non-motor aspects of QoL.

The selection of stimulation parameters for these patients may be insufficient if based only on the purely motor assessment.

Several open studies found marked improvements in physical and psychosocial aspects of HrQoL after STN stimulation, using generic or PD-specific scales (Spottke et al, 2002).
In general, non-motor symptoms of PD, such as mood disturbances, drive problems, pain or sleep disorders, have an impact on HrQoL, which may equal or exceed the influence of motor impairment (Volkmann et al, 2009). Well-known motor problems after STN-DBS, such as poor gait, balance, or speech, had surprisingly little impact on HrQoL in this study.
A recent large short-term randomized controlled multicenter study compared HrQoL in a group of 156 patients with severe motor symptoms of Parkinson's disease, who were randomly assigned in pairs to receive either bilateral DBS of the STN in combination with medical treatment or best medical therapy alone (Deuschl et al, 2006).
At 6 months, an improvement of HrQoL (PDQ-39 score) by about 25 % was found only in the surgically treated group, indicating that the symptomatic benefits of STN-DBS outlast the inherent surgical risks and lead to more effective reduction of the burden of disease than optimal drug therapy. An extended observational period, however, is necessary to assess the stability of these results along the chronic course of PD.
The prospective study of Volkmann et al. (2009) found out sustained improvements in HrQoL at 3 to 4 years in a relatively large proportion of parkinsonian patients that suffered from substantial disability at baseline despite best medical treatment.
On the other hand, the work of Drapier et al.(Drapier et al, 2005) using patient's self-assessment scales showed the clinical benefit of STN DBS on non-motor signs was quite subtle; physical items of QoL significantly improved, whereas mental items such as emotional well-being, social support, cognition and communication showed no improvement. The

authors suggest a dissociation of motor and non-motor symptoms control after bilateral STN DBS in PD patients.

In a study by Witjas and colleagues, patients implanted with bilateral STN DBS experienced significant benefits with sensory/painful fluctuations, dysautonomia (excessive sweating), and cognitive fluctuations (Witjas et al, 2007). In another study by Zibetti et al. (2007), sleep and constipation were the only symptoms that improved following bilateral STN DBS surgery in 36 PD patients.

Quality of life scales such as the PDQ-39 (Jenkinson et al, 1997) and questionnaires (NMS-Q - (Chaudhuri et al, 2008)) should become an integral part of the clinical protocol for patients admitted to a Parkinson's disease surgical program. This may help to identify factors that affect the patient's quality of life other than the motor activity.

Conclusions:

We have been able to demonstrate that the increase of stimulation parameters (amplitude) has a potential to improve some non-motor functions and aspects of QoL and thus has an additional effect on quality of life in certain subset of PD patients. The meticulous observation of QoL should be a routine part of assessments before and after the DBS STN surgery, and can even aid during the parameter setting. Certain effect of DBS STN on non-motor functions and social aspects of QoL (such as stigma, emotion, communications) can explain the further improvement of overall QoL after the stimulation amplitude increase.

Possible explanations for benefit of stimulation increase could be one or more of the following:

1. influence of non-motor symptoms of PD that are difficult to ascertain during regular visits on QoL
2. psychological aspect related to stimulation change
3. improvement of apathy, which is sometimes observed after the DBS STN

Further study with random design and larger number of subjects is warranted.

Especially important will be to describe the subjects who may benefit from an increase of the stimulation parameters beyond the values that improve the usual motor symptoms of PD.

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Conflict of interest: The authors declare that they have no conflict of interest.

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3.4 The modulatory role of subthalamic nucleus in cognitive functions – a viewpoint

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Commentary:

In the following paper our group formulated a viewpoint on the modulatory role of subthalamic nucleus in cognitive functioning by thorough review of several previous papers by ourselves and by other prominent authors in the field.
This paper was recently accepted for publication in Clinical Neurophysiology, after minor revision recieving excellent reviews.

I was a corresponding author for this article and contirbuted to whole process of article preparation from conception of idea to literature review, authored several articles that were reviewed in this paper and also played a prominent role in manuscript wiriting.

The modifications of electrophysiological activities of subthalamic nucleus (STN) by non-motor tasks, i.e. movement observation, emotional stimuli and impulse control, were reported repeatedly.
Despite being a small structure, STN is apparently involved in a variety of functions.
Based on our own electrophysiological recordings and results of other groups we believe that it acts as an indirect modulator which may be involved in tuning the functional systems. STN may modulate specific cognitive activities via contextual modulation of certain cortical areas. Our findings support the hypothesis of a cortical-STN bypass (via hyperdirect pathway) of a “classical” basal ganglia-thalamocortical circuitry, at least during the processing of certain cognitive functions. The modulation of cognitive functions appears to be selective, probably determined by the involvement of cortical neuronal populations interconnected with STN. There could also exist a spatial overlap of areas within STN regulating various functions. That may explain the fact that some non-motor symptoms of Parkinson's disease may improve after deep brain stimulation of STN. These improvements are likely to be caused by

combination of direct stimulation effect on non-motor function and overall beneficial effect of motor improvement on quality of life.

The modulatory role of subthalamic nucleus in cognitive functions – a viewpoint

Ivan Rektor[1], Martina Bočková[1], Jan Chrastina[2], Irena Rektorová[1], Marek Baláž[1]

Central European Institute of Technology – CEITEC, Masaryk University, Brno
and Movement Disorders Centre, Departments of Neurology[1] and Neurosurgery[2], St. Anne's Hospital, Medical School of Masaryk University, Brno, Czech Republic

Address correspondence to:
Marek Baláž MD, PhD
Movement Disorders Centre, First Department of Neurology, and CEITEC, Masaryk University
St. Anne's University Hospital, Pekarska 53
656 91 Brno
Czech Republic
phone: +420 543-182-637
fax: +420 543-182-624
e-mail: marek.balaz@fnusa.cz

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Highlights:

- reviewed findings support the idea that STN may play a unique role that differs from the role of other structures chained in the BG-thalamocortical circuitries
- it seems that at least a partial overlap of cognitive (and other specific non-motor) functions and motor functions exists within STN.
- subthalamic nucleus could serve as a nexus that integrates motor, cognitive, emotional, and reward-based components of behaviour

Abstract

The modifications of electrophysiological activities of subthalamic nucleus (STN) by non-motor tasks, i.e. movement observation, emotional stimuli and impulse control, were reported repeatedly.

Despite being a small structure, STN is apparently involved in a variety of functions.

Based on our own electrophysiological recordings and results of other groups we believe that it acts as an indirect modulator which may be involved in tuning the functional systems. STN may modulate specific cognitive activities via contextual modulation of certain cortical areas. Our findings support the hypothesis of a cortical-STN bypass (via hyperdirect pathway) of "classical" basal ganglia-thalamocortical circuitry, at least during the processing of certain cognitive functions. The modulation of cognitive functions appears to be selective, probably determined by the involvement of cortical neuronal populations interconnected with STN. There could also exist a spatial overlap of areas within STN regulating various functions. That may explain the fact that some non-motor symptoms of Parkinson's disease may improve after deep brain stimulation of STN. These improvements are likely caused by combination of direct stimulation effect on non-motor function and overall beneficial effect of motor improvement on quality of life.

Key words: electrophysiology; non-motor functions; cognitive functions; DBS; subthalamic nucleus

Introduction

A direct way of studying the function of subthalamic nucleus (STN) is a neurophysiological recording of event related electrical activities, i.e. the evoked potentials and oscillations, via intracranial deep brain electrodes (Kühn et al., 2005a; Rektor et al., 2009). The modifications of electrophysiological activities of STN by non-motor tasks, i.e. movement observation, emotional stimuli and impulse control, were observed and reported (Kühn et al., 2005b; Marceglia et al., 2009; Rodriguez-Oroz et al., 2011). STN recordings related to cognitive tasks performed by our group contributed largely to formulation of this review (Baláz et al., 2008; Baláz et al., 2010; Bočková et al., 2011; Rektor et al., 2009, Aulická et al., 2014).

STN function captivated researchers' interest by motor as well as non-motor effects of deep brain stimulation (DBS) on this structure. The involvement of STN in a broad spectrum of various non-motor functions was reported – attention (Bočková et al., 2011, Mallet et al. 2007), executive functions (Baláz et al., 2008, Voon et al., 2006), verbal learning and memory (Coulthard et al. , 2012), control of impulses (Rodriguez-Oroz et al., 2011), verbal abstract reasoning, conflict resolution (Brittain et al., 2012), facial emotion recognition (Le Jeune et al., 2008) and emotions (Kühn et al., 2005a, for review see Baunez et al., 2011). STN appears to be involved in complex cognitive behavioural functions and networks such as the network underlying the Theory of Mind (Péron et al., 2013). Moreover, neuropsychiatric problems such as depression (Voon et al., 2006, Thobois et al. 2010), apathy (Voon et al. 2006), suicide ideation/attempt (Voon et al., 2008) were also reported after DBS STN surgery, and were reviewed recently by Rodriguez-Oroz et al., 2012. Behavioural complications were reported after DBS STN more frequently than after DBS Gpi. The etiology of these problems is multifactorial and except for reduction of dopaminergic medication (Thobois et al., 2010) and preoperative risk factors (Lim et al. 2009) includes also stimulation of contacts located in non-motor areas (Mallet et al., 2002, Mandat et al., 2006, Raucher-Chéné et al., 2008). The impulsivity and mania are thought to be related to diffusion of electric current to limbic parts of STN (Rodriguez-Oroz et al., 2012, Mallet et al., 2007, Krack et al., 2010). STN DBS might alter the coupling between prefrontal cortex and basal ganglia during decision-making processes (Cavanagh et al., 2011).

Neuroimaging studies further support engagement of STN in performance cognitive tasks and other non-motor functions (e.g. Aron et al., 2007, Coxon et al., 2012, Haegelen et al., 2010, Herz et al., 2014, Kalbe et al., 2009, Le Jeune et al., 2008, Le Jeune et al., 2009, Le Jeune et al., 2010, Manes et al., 2014, Mansfield et al., 2011, Mathys et al., 2014, Lambert et al., 2012, Schroeder et al. 2002, Ballanger et al., 2009b).

In line with observations made in humans, the encoding of cognitive (Baunez and Lardeux, 2011), behavioural (Teagarden and Rebec, 2007), and reward-based (Lardeux et al., 2009) tasks in STN was found in rats.

Animal models brought relevant data on non-motor effects of STN manipulation well before it was shown in humans (reviewed by Baunez and Gubellini 2010). Study by Baunez in 1995 for the first time revealed possible side effects that might be related to the involvement of STN in non-motor behaviour. Generally, the evidence gained from animal models (Darbaky et

al., 2003; Temel et al., 2005) seem to confirm that STN high frequency stimulation (HFS) at parameters inducing beneficial effects on motor functions does not always correlate with beneficial cognitive effects reported in human patients (Perriol et al., 2006).With only few existing works describing STN stimulation in monkeys it appears that STN neurons respond to reward (Darbaky et al., 2005), suggesting that STN manipulations may affect motivation.

The studies in rats have raised the issue of non-motor involvement of STN and lead to a better consideration of these aspects in clinical studies and patients' management: the current interest for motivational and emotional effects of STN DBS in PD patients reflects also the recent interest for these processes in animal models.

When it comes to cognitive and motivational processes, mainly rat data are available. These studies highlighted the integrative function of STN, placing it at the interface between motivation and action. There was often a parallel to these findings in clinical observations of PD patients with STN DBS, but it would be important to perform further studies on monkeys, especially because of the fact that they could allow specific investigation of the sub-territories within STN (limbic, associative and motor areas) that are impossible to perform in the rat given the small size of STN in this species.

Results of fMRI pig study also suggested that STN DBS may have modulatory effects not only on circuits that facilitate motor function but also on those involved in higher cognitive and emotional processing (Min et al 2012).

The overlap of processing of motor and non-motor activities within STN

Neurophysiological recordings from STN

We have shown (Balaz et al., 2008; Baláz et al., 2010; Bočková et al., 2011, Rektor et al., 2009, Aulická et al. 2014) that there is a spatial overlap of parts regulating certain cognitive and motor functions in STN in patients with Parkinson's disease (PD). The local fields of cognitive related potentials were recorded through the electrode contact located in STN sites with the best motor effect. We studied event related potentials and oscillations while performing various cognitive tasks including the oddball paradigm, (both standard and one modified by a dual task), a three-stimulus paradigm, Ericsson´s flanker task and a protocol with writing letters in an executive function task. A deep electrode contact was submerged in the neuronal

tissue, and thus the potentials were recorded from its immediate vicinity. This means that the neuronal pools generating activities related to motor and cognitive tasks were either very close to each other or that some neurons were active in both tasks.

Of note, similarly to STN, we also observed a spatial overlap of several cognitive and motor control functions in pallidum and striatum. We recorded event related potentials evoked during various auditory, somatosensory and visual cognitive tasks, in motor as well as non-motor paradigms, and the Bereitschaftspotential on contacts of the same electrode (Rektor et al., 2005). These data were obtained in patients with epilepsy. To our knowledge, recordings of cognitive event related activities in pallidum and striatum have not yet been reported in patients with PD.

To sum it up, it seems that at least a partial overlap of cognitive (and other specific non-motor) and motor functions exists within STN. This notion may also support the view of an integrative role of STN.

The integration model of STN function

STN is apparently involved in a variety of functions, both motor (Benabid et al., 2009) and non-motor (Fasano et al., 2012), although it is a small structure (Parent et al., 2001, Yelnik, 2008). It is hard to imagine how the limited number of STN neurons could process all these functions separately despite certain distribution of motor and non-motor functions along the dorsoventral axis of STN (Rodriguez-Oroz et al., 2011). Functional imaging (FDG-PET, SPECT and fMRI) showed that stimulation of STN induced modifications of the pattern of brain activation not only within the nucleus itself, but it involved large-scale cerebral networks (Sestini et al., 2009, Ballanger et al., 2009a; Kalbe et al., 2009, Péron et al., 2010, Le Jeune et al., 2010, Ray et al., 2011). The functional linkage of the nucleus with other subcortical and cortical structures may be conveyed by separated cortico-basal ganglia-thalamocortical circuits.

According to “classical models” the functionally segregated sections of STN subserve motor, emotion, and cognitive processing (Parent and Hazrati, 1995, Alexander et al., 1990, Hamani et al., 2004). A recent probabilistic tractography study further supported the existence of three distinct sub-regions within the human STN (Lambert et al. 2012). The authors claimed that there are unique limbic and motor STN zones, and the associative zone might represent

an overlapping, somatotopically arranged transition between the two, thus providing an anatomical substrate for communication between two distinctive closed networks. Conversely, Alkemade and Forstmann (2014) used ultra-high resolution 7T MRI in an attempt to distinguish subregions of STN but their preliminary results rather point towards delineated subdivisions, or an organization without strict anatomical boundaries or septa. The authors assume that there is at least partial overlap between putative functional zones within STN.

An integrative model was proposed in which emotional, cognitive, behavioural, and motor functional modalities were not processed in a segregated manner but were all modified within the small volume of the nucleus. This nucleus could serve as a nexus that integrates motor, cognitive, emotional, and reward-based components of behaviour (Kalbe et al., 2009, Mallet et al., 2007).

This "integrative model" differs from that of Haber *et al.* (Haber et al., 2006) in which integration was based on the reciprocal striato-nigro-striatal and cortico-thalamo-cortical circuits and from that of Temel and colleagues (Temel et al., Tan et al., 2006) in which STN was a regulator of associative and limbic circuits, but not an integrator.

Integrative model of STN thus shows that its individual functions at least partially overlap and are integrated within this structure and therefore various effects of STN stimulation (such as effect on the array of above metioned non-motor functions) can be explained by this model.

STN modulates the cortico-subcortical circuitry when processing cognitive activities

We suggest that STN is engaged in tuning of the cognitive functional networks. Our findings support the idea that STN may play a unique role that differs from the role of other structures chained in the BG-thalamocortical circuitries. For example, in contrast to our results from striatum/pallidum mentioned above (Rektor et al., 2005; Rektor et al., 2004) the standard oddball cognitive potentials (P3) were not generated in STN (Balaz et al., 2008; Bočková et al., 2011). In patients with epilepsy, the epileptic spikes were recorded in STN but not in other BG structures (Rektor et al., 2002; Urrestarazu et al., 2009).

Classical hypotheses of segregated connection of STN in cortico-basal ganglia-thalamocortical circuits were described above. Indeed, other hypotheses (Joel, 2001; Parent et al., 2001) have also been proposed with respect to STN functional connectivity, including the "hyperdirect"

pathways between STN and cortex that bypass the well-known BG circuitries (Obeso et al., 2007) and might underlie the processing of at least some of the cognitive functions (Nambu et al., 2002). From experimental data in rats it appears that STN is involved in attentional processes possibly via this hyperdirect pathway (Baunez and Lardeux, 2011). Using viral tracers in prefrontal cortical sites in monkeys Haynes and Haber (Haynes and Haber, 2013) revealed presence of massive hyperdirect parallel projections between prefrontal cortex and STN. These data support the idea of strategic position of STN in the control of non-motor behaviour. The authors also demonstrated significant overlap of functional territories within STN. This overlap may enable the hyperdirect pathway to combine movement with both emotions and cognition – an association which is constant in involuntary behaviours (Martinez-Fernandez et al., 2013).

In humans, results of previous studies suggested that the hyperdirect pathway enables STN to use performance-monitoring signals to adjust motor behaviour (Frank et al., 2007). We reported that repetitive transcranial magnetic stimulation (rTMS) of inferior frontal cortex (IFC), but not of dorsolateral prefrontal cortex (DLPFC), increased the speed of processing executive functions (shortening of latencies of event-related potentials) in STN during a dual task performance (Baláz et al., 2010). IFC is a source of the hyperdirect pathway to STN (Nambu et al., 2002), while DLPFC is included in the cortico-thalamocortical circuitry. Our findings supported the role of a "hyperdirect" cortico-STN bypass of the usual BG-thalamocortical circuitry in processing of cognitive functions. Of note, we were able to replicate our pilot results and we improved attention and enhanced cognitive speed by rTMS applied over the same IFC coordinate in another PD cohort (Srovnalova et al., 2011) and also in subjects with mild cognitive impairment due to Alzheimer's disease (Eliasova et al. 2014).

As STN is the only BG structure, except for striatum, that receives a direct cortical projection (Nambu et al., 2002), it is in a position to receive information directly from cortex earlier than from BG - thalamocortical circuitry. Consequently, STN may have a modulatory influence on processing activities in the rest of the circuitry. The number of STN neurons is known to be small and STN may be targeted by the direct as well the hyperdirect pathway. Therefore, the information processed by the two pathways is very probably integrated within STN and it may play a central role in regulation of cortical areas via and the modulation of cortico - subcortical circuits (Figure 1). As it was shown by FDG-PET study STN DBS modifies metabolic activity in large cortical distributed networks (Le Jeune et al 2010).

The multifunctional and task-specific involvement of STN in cognitive activities

The involvement of STN in cognitive functions is documented less than its role in motor function regulation.

STN is a structure that takes part in multiple functions with respect to cognition. It can be assumed that STN is implicated in executive functions (Baláz et al., 2008; Baláz et al., 2010; Rektor et al., 2009, Aulická et al. 2014), attentional and orientation responses (Bočková et al., 2011), as well as in impulse control (Rodriguez-Oroz et al., 2011). Both STN DBS in PD patients and lesional experiments in rats showed impairment of response inhibition in go/no go tasks (Ballanger et al., 2009b; Baunez and Lardeux, 2011), suggesting that STN could play a critical role in "holding a response" (Frank et al., 2007). It has been documented using both PET and MRI techniques, that STN modulates non-motor basal ganglia-thalamocortical circuitry during conflict tasks requiring response inhibition (Schroeder et al. 2002, Aron et al. 2007). STN DBS selectively interferes with the normal ability to slow down when faced with decision conflict and can therefore produce impulsitivity in behaviour/impusive behaviour. Increased response conservativeness is associated with activation of STN (Frank et al. 2007, Mansfield et al. 2011). Cognitive action control is thought to rely on an interconnected network consisting of right inferior frontal cortex (r-IFC), pre-supplementary motor area (preSMA), and STN (Coxon et al. 2012, Herz et al. 2014).

STN has also critical importance in successful decision making when multiple pieces of information must be combined (Coulthard et al. 2012). Furthermore, the data from FDG-PET study of fear recognition confirm the role of STN in limbic functions (Le Jeune et al., 2008). The role of STN in associative and limbic circuitry suggests that it is a key basal ganglia structure for motivation (Le Jeune et al. 2009).

STN seems to play role also in language functions. It was found to have connectivity with regions involved in cognitive linguistic processes (Manes et al., 2014). Relationship between changes in the left frontal (dorsolateral prefrontal cortex and Broca area) PET activity and changes in cognitive outcome after deep brain stimulation of STN were observed (Kalbe et al. 2009).

De-coupling of brain areas involved in self-relevant but motor-unrelated cognitive processing (i.e. precuneus and posterior cingulate cortex) from STN motor network may represent a

potential mechanism behind the age-dependent decline in motor performance (Mathys et al. 2014).

A central role of STN in motor as well as associative, limbic, and cerebellar basal ganglia circuits was suggested (Hilker et al., 2004).

To sum it up, STN might modulate selective cognitive functions. Thanks to the central position and the integration of various functions STN may be a substrate for contextual modulation of targeted cortical areas.

STN appears to be involved in the modulation of only certain cognitive activities. We observed the involvement of STN in tasks with increased cognitive load but not in simpler cognitive tasks. Simple oddball evoked P3 like potentials were recorded only as a far field potential in STN while the dual task evoked local field of P3-like potentials directly in the nucleus (Baláz et al., 2008). Similarly, oscillatory activities in STN were evoked by writing letters in an executive task paradigm (where subjects were asked to write a letter different from the letter on a screen), but not by simple letter copying (Rektor et al., 2009). In a three stimulus paradigm the distractor stimulus evoked an early potential with a latency around 200 ms in STN that has not been observed in the scalp recordings. This demonstrated the engagement of STN in attentional and orienting responses (Bočková et al., 2011). The involvement of STN in processes controlling human behaviour, e.g. selection and inhibition of competing alternatives, was demonstrated by the Ericsson´s flanker task -related activation of the STN. Both conditions, i.e. congruent and incongruent, induced oscillatory changes in STN with significantly higher activation during incongruent trial. When compared with the activity recorded in anterior cingulate in epileptic patients, in STN not only ERD beta but also ERD alpha activity was significantly more activated by the incongruent condition (Aulicka et al., 2014).

In line with our results, task-specific effects on attentional performance after a lesion of STN were observed in rats (Baunez and Robbins, 1997; Temel et al., 2005).

Also the imaging studies in humans show that the effects of STN-DBS are task-specific and depend on particular networks involved in those specific tasks (e.g. Kalbe al., 2009, Mallet et al. 2009, Coulthard et al. 2012). According to a cortico-subthalamic coherence study STN appears to be implicated in motor and behavioural complications in PD, specifically engaging different anatomical and functional territories (Rodriguez-Oroz et al., 2011). Therefore, the

selection of tasks modulated by STN may be determined by the selective involvement of these specific cortical neuronal populations that are interconnected with STN.
In any case, the exact role of STN and BG in cognitive functions remains an important and interesting challenge for future research.

The role of STN in emotions and behaviour

Cognitive processes are closely related to emotions. According to multicomponential view on emotions the emotional reactions were determined by the subjective cognitive evaluation of events, based on the meaning of these event for the individual's wellbeing and the pursuit of their goals (Péron et al., 2013).This function appeared to be not selective for any single category of emotions (e.g. fear) or subprocess involved in different emotions (e.g. autonomic responses), but rather a more general capacity, implying a kind of "meta-role" (Péron et al.,2013). STN acted as a coordinator of neural patterns and was involved in a whole range of emotional processes. STN DBS may change the integration of limbic informations by disrupting emotional processes within STN, or by hampering the normal function of a limbic circuit (Haegelen et al. 2010). STN may play some role in the evaluation of behavioural significance due to changes of environment (Sauleau et al., 2009). The authors found out that warning cues evoked a complex temporal sequence of activities in STN area that differed according to behavioural relevance of cues and dopaminergic state. These data appeared to represent neural processes at the basal ganglia end of circuits between basal ganglia and frontal cortex concerned with attentional processes leading to behavioural resources. STN does not necessarily has to be a place where these processes related to behavioural relevance arise, but it is at least an important node in a circuit elaborating such responses. This hypothesis is in line with our opinion, that many various functions are represented in STN.
STN may also participate in inhibition of certain behavioural processes (Ballanger et al., 2009b). It has been proposed that STN may act as a "gate-control" for selection of behavioural action (Baunez and Lardeux, 2011).

The modulatory role of STN – the viewpoint

STN has been considered as a relay station in the indirect pathway functionally positioned between external and internal globus pallidus (Alexander et al., 1990). A new concept of the hyperdirect pathways that bypass the circuitries and connect several cortical areas and STN directly emerged. To what extent and how STN integrates information received via the hyperdirect and indirect pathways has been unknown so far. The small size of the nucleus indicates that an integration of information processed by the two pathways may occur in STN. The spatial overlap of various functions inside STN described above may be a substrate for this integration or combination of the motor, cognitive, and emotional components of behaviour (Mallet 2007). The simple fact that STN has a very direct link with cortex means that at least some information is processed within STN earlier than the one that is elaborated within the BG circuitry. STN is in the position where it can modulate the function of the output part of the well-known "classical" BG circuitries. It has been shown in animal models, that within the prefrontal cortex-BG circuits, STN participates in the shaping of the inhibitory influence of the direct striato-nigral pathway on the output part of the circuitry (Maurice et al., 1999). Regarding the cognitive activities, we suggest two ways of STN participation. Firstly, STN is a relay nucleus that participates in processing of cognitive and behavioural activities within the cortico-BG- thalamocortical loop. In addition to this known function we suggest that STN may (under direct cortical control conveyed by the hyperdirect pathway) exert a modulatory control over the output part of the cortico - BG - thalamo - cortical loop.

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Legend - Figure 1. Schematic view on position of STN in integration of information from basal ganglia and hyperdirect pathway

A. Situation in healthy individual; B. Parkinson´s disease (PD); C: Parkinson´s disease with DBS STN

Symbols. Solid lines and boxes: Oversimplified scheme of the basal ganglia-thalamocortical (BG) circuitry. Black lines: excitatory pathways; grey lines: inhibitory pathways, Dotted lines: cognitive loop;

(a): the hyperdirect pathway, bolt: the DBS stimulation.

Explanation. The cognitive loop remains relatively spared by the dysfunction of the motor BG circuitry in PD (A and B), the cognitive loop is down-regulated by the DBS STN (C) despite the (relative) normalization of the motor part of the circuitry

3.5 Quality of life after DBS in patients with advanced Parkinson's disease

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Commentary:

In the following paper we analysed long-term quality of life after DBS in patients with advanced Parkinson's disease (PD). DBS does not halt neurodegenerative process and is also a non-curative treatment and one of its main goals should be the improvement of patients' quality of life (QoL). This paper was a first report in Czech neurological literature on influence of DBS STN on QoL. DBS brings along usually quite speedy improvement of major parkinsonian motors symptomatology. However, aim of this treatment, taking into consideration its relatively high financial and personal costs,should be a long-term positive effect on lives of PD patients. We included 26 patients who were observed for 3 years in this study.

We employed disease-specific quality of life questionnaire (PDQ-39). Disease specific questionnaires are designed specifically to capture the influence of respective signs of disease on QoL. PDQ-39 contains 39 items centered on limitations on various acitivities brought along by PD within preceding 30 days. Questions relate to eight key areas of health and daily activities, including both motor and non-motor symptoms. It is scored on a scale of zero to 100, with lower scores indicating better health and high scores more severe symptoms.

We found improvement of 46 % in overall score of PDQ-39 3 years after surgery. The UPDRS III (Unified Parkinson's Disease Rating Scale – subset III - reflecting purely the motor functions) was better by 31 % after 3 years.

Regarding PDQ-39 subscores most changes were present in motor subscores, but important positive statistically significant changes were also in the areas of communication, social support and stigma of disease which belong to non-motor symptomatology.

Overall, our data confirmed a long-term positive influence of DBS on QoL in PD patients. Non-motor aspects of QoL were improved alongside with motor symptomatology.

Kvalita života po hluboké mozkové stimulaci u pacientů s pokročilou Parkinsonovou nemocí

Autoři: M. Baláž, M. Bočková, M. Bareš, I. Rektorová, V. Dírerová, I. Rektor

Autoři - působiště: Centrum pro abnormní pohyby a parkinsonizmus I. neurologická klinika LF MU a FN u sv. Anny v Brně

Článek: Cesk Slov Neurol N 2011; 74/107(5): 564-568

Souhrn

Cíl:

Cílem práce je popsat vliv hluboké mozkové stimulace subthalamického jádra na jednotlivé aspekty kvality života u pacientů s Parkinsonovou nemocí.

Soubor a metodika:

Práce sleduje kvalitu života ve skupině 26 pacientů s Parkinsonovou nemocí před operací, po 12 a 36 měsících od provedení hluboké mozkové stimulace. Kvalita života byla hodnocena pomocí dotazníku PDQ-39.

Výsledky:

Kvalita životů pacientů se zlepšila o 46 % po třech letech od operace ($p < 0,001$). UPDRS III skóre se zlepšilo o 38 % po jednom roce a o 31 % po třech letech ($p < 0,001$).

Závěry

V našem souboru jsme zjistili statisticky signifikantní zlepšení skóre PDQ-39 po 12 i 36 měsících od operace u všech pacientů. Nejvýrazněji se zlepšení odrazilo v motorických příznacích, které jsou DBS STN nejvíce ovlivněny. Lze pozorovat i efekt na sociální důsledky Parkinsonovy nemoci (stigma, sociální podpora, komunikace). Hluboká mozková stimulace má dlouhodobý efekt na kvalitu života.

Klíčová slova

hluboká mozková stimulace – kvalita života – Parkinsonova nemoc

Úvod

Parkinsonova nemoc je neurodegenerativní onemocnění s motorickými, senzitivními, autonomními i neuropsychiatrickými příznaky. Základem terapie je dopaminergní medikace, která má efekt především na motorické příznaky.

Vlivem dopaminergní terapie a progrese onemocnění se u velké části pacientů objevují pozdní hybné komplikace, například motorické fluktuace a dyskinezy [1]. U části pacientů je vhodnou terapií motorických příznaků v pozdním stadiu PN hluboká mozková stimulace (Deep Brain Stimulation, DBS). Nejčastějším cílem implantace hlubokých elektrod u PN je subthalamické jádro (STN) [2].

DBS STN zlepšuje skóre v Jednotné škále pro hodnocení PN (Unified Parkinson's Disease Rating Scale, UPDRS) ve stavu bez medikace – OFF – po roce od operace přibližně o 60 %. Výrazný efekt DBS na jednotlivé podškály (UPDRS II a UPDRS III) trvá i více než pět let od implantace systému (zlepšení o cca 43–57 %) [2].

DBS STN však není prevencí dalšího rozvoje onemocnění a obvykle neovlivňuje symptomy PN, které nereagují na podávání L-DOPA (zárazy v chůzi, nemotorické příznaky). Vzhledem k tomu, že PN je chronicky progredující neurodegenerativní onemocnění, je důležitým předpokladem DBS STN, aby přínos této procedury dlouhodobě převažoval nad nežádoucími účinky, a efekt operace se má projevit především zlepšením kvality života pacientů.

Kvalita života pacienta s PN je ovlivňována motorickými i nemotorickými příznaky a dalšími faktory, jako je například délka trvání nemoci a věk pacientů [3]. Není snadné určit, zda mají na kvalitu života významnější efekt symptomy motorické nebo nemotorické. Zajímavým pozorováním je, že mohutnost efektu L-DOPA na motorické symptomy před operací je prediktorem efektu DBS STN nejen na hybnost (reflektovanou především škálou UPDRS), ale i kvalitu života [4]. Na druhou stranu je některými autory považován dopad nemotorických (například neuropsychiatrických) příznaků za rozhodující faktor ovlivňující kvalitu života [3,5–8].

V současnosti se ke sledování kvality života u PN užívají dva hlavní typy dotazníků – generické a specifické [9,10]. Generické dotazníky (například EuroQOL Five Dimensions – EQ5D, Sickness Impact Profile – SIP, Questions on Life Satisfaction – QLS) pokrývají velké množství aspektů kvality života a dají se použít u rozličných nemocí. To poté umožňuje srovnání kvality života mezi jednotlivými onemocněními.

Dotazníky specifické jsou sestaveny podle příznaků jednotlivých nemocí a dovolují hodnocení dopadu konkrétních příznaků onemocnění na stav pacienta (například Parkinson's Disease Quality of Life Questionnaire – PDQL, Parkinson's Disease Quality of Life Scale – PDQUALIF). Nejčastěji používaným specifickým dotazníkem u PN je Dotazník kvality života u Parkinsonovy nemoci – Parkinson's Disease Questionnaire (PDQ-39). Kvalita života pacientů po DBS STN byla sledována několika autory [9,11–13] a ti udávají celkové zlepšení od 14 do 62 %. Podle Volkmanna et al [9] mají nemotorické symptomy PN (změny nálady, bolesti, poruchy spánku) stejný nebo dokonce časem i větší efekt na kvalitu života než příznaky motorické. Zatím nelze jednoznačně určit, které jednotlivé faktory se nejvíce podílejí na zlepšení kvality života.

V naší práci jsme se zaměřili na hodnocení dlouhodobého vlivu hluboké mozkové stimulace pomocí dotazníku PDQ-39 a sledování změn jednotlivých částí dotazníku před operací a po 12 a 36 měsících od DBS STN.

Soubor a metodika

Soubor

Do studie bylo zařazeno 26 pacientů po DBS STN. Všichni byli pacienty indikovanými k DBS STN v Centru pro abnormní pohyby a parkinsonizmus ve FN u sv. Anny v Brně v letech 2003 až 2006, kteří v čase hodnocení studie dosáhli dobu 36 měsíců od operace. Do studie nebyli zahrnuti pouze dva pacienti, kteří zemřeli v kratší době než tři roky po DBS STN (oba z příčin nesouvisejících s DBS STN – náhodné utonutí šest měsíců po operaci, plicní embolie po 34 měsících od operace).

Soubor zahrnuje celkem 11 žen a 15 mužů s pokročilou PN. Průměrný věk v době operace byl 59,3 ± 7,4 let. Trvání PN v čase operace dosáhlo 10,3 ± 3,2 let. Průměrné trvání léčby přípravky L-DOPA 8,4 ± 2,9 let, stadium PN dle Hoehnové a Yahra dosáhlo v době operace ve stavu OFF průměrně 3,02 ± 0,5.

Hluboká mozková stimulace

Pacienti byli indikováni k provedení DBS STN podle standardních kritérií již opakovaně popsaných v domácí [8,14,15] i zahraniční literatuře [16]. Hlavními indikacemi k provedení DBS STN byly pozdní motorické komplikace Parkinsonovy nemoci (především ON-OFF fluktuace a dyskineze) neovlivnitelné úpravami medikace.

Při DBS neurochirurg do STN stereotakticky zavedl stimulační elektrodu. Během zavádění elektrod byl proveden perioperační elektrofyziologický monitoring a perioperační mikrostimulace. S odstupem 3–7 dnů od zavedení elektrod byl do podkoží v subklavikulární oblasti implantován stimulátor. Podrobný popis průběhu operace je také dostupný v literatuře [2,17].

Efekt hluboké mozkové stimulace v našem souboru pacientů považujeme za velmi dobrý, je reflektován změnou skóre jednotlivých položek UPDRS (tab. 1).

Tab. 1. Charakteristika souboru pacientů.

	Před DBS (medikace off)	12 měsíců po DBS (medikace off/stimulace on)	Hodnota p (rozdíl 12 měsíců po vs. před DBS)	36 měsíců po DBS(medikace off/stimulace on)	Hodnota p (rozdíl 36 měsíců po vs. před DBS)
UPDRS II	21,8 ± 4,3	18,2 ± 3,9	0,0032	19,3 ± 4,1	0,0407
UPDRS III	41,6 ± 9,2	25,79 ± 5,0	<0.0001	28, 8 ± 5,2	<0.0001
LED (mg)	1042 ± 305	580 ± 240	<0.0001	630 ± 280	<0.0001
Amplituda stimulace (V)	Bez stimulace	2,8 V ± 0,4V	-	3,4 V ± 0,5V	<0.0001 mezi 12 a36 měs.
PDQ-39 (celkové skóre)	75,16 ± 13,2	40,2 ± 16,3	0,000123	49,3 ± 16,5	0,01

Hodnocení kvality života

U pacientů bylo v rámci standardního předoperačního vyšetření provedeno šetření kvality života pomocí dotazníku PDQ-39. PDQ-39 je dotazník vyplňovaný přímo pacientem, obsahuje 39 dotazů na jednotlivé potíže a omezení způsobená Parkinsonovou nemocí pociťovaná v průběhu posledního měsíce [18].

Tento dotazník pacienti vyplnili i 12 a 36 měsíců po DBS STN.

Před operací pacienti vyplnili dotazník kvality života ve stavu ON (během účinku dopaminergní medikace), zatímco po DBS STN ve stavu ON a se zapojenou stimulací (ON/ON).

Ve výsledcích referujeme i změnu v položkách UPDRS II (aktivity denního života), UPDRS III a IV. Škála UPDRS byla hodnocena před operací u pacientů během tzv. definovaného OFF stavu (12 hod bez dopaminergní medikace). V období po operaci bylo hodnocení UPDRS provedeno se zapojenou stimulací, bez medikace (ON stimulace/OFF medikace). Dále jsou v tabulkách uvedeny i průměrné parametry stimulace a dávka dopaminergní medikace, kterou pacienti užívali v konkrétním čase.
Statistické hodnocení

Ke statistické analýze byly použity ANOVA a Tukeyův test (ke srovnání rozdílů mezi jednotlivými podškálami).

Výsledky

Změny v parametrech UPDRS, amplitudě stimulace a dávce levodopa ekvivalentu (LED) jsou shrnuty v tab. 1. Zlepšení hybnosti, které bylo jasně patrné po roce, bylo zachováno i po dalších dvou letech. Délka trvání dyskinez poklesla v průměru o 68,5 %.

Tak jak bylo možné předpokládat, LED byla významně snížena po DBS STN a toto snížení medikace bylo stále významné i po 36 měsících. U dvou pacientů bylo možno po dobu více než 12 měsíců zcela přerušit podávání dopaminergní léčby a po 36 měsících byly u čtyř pacientů podávány pouze agonisté dopaminových receptorů.

Při analýze naší skupiny pacientů jsme nepozorovali vliv věku nebo délky trvání nemoci na míru zlepšení kvality života.

Po 36 měsících byla průměrná amplituda stimulace 3,4 ± 0,5 V. Frekvence nastavení byla u všech pacientů 130 Hz. Šířka pulzu dosáhla 90 μs, s výjimkou dvou pacientů, kde byla nastavena na 60 μs.

Kvalita života se ve škále PDQ-39 významně zlepšila po 12 a 36 měsících ve srovnání se stavem před operací (graf 1). Mírné zvýšení celkového skóre mezi 12 a 36 měsíci nebylo statisticky významné (p = 0,19). Hvězdička (*) označuje statisticky signifikantní změnu.

Graf 1. Grafické zobrazení celkového skóre kvality života (PDQ-39 – osa Y) před operací DBS, po 12 a 36 měsících (na ose X). Vertikální sloupce zobrazují 0,95 interval konfidence.

Zajímavé výsledky přineslo hodnocení jednotlivých podškál PDQ-39. DBS mělo významný vliv na většinu podškál, a to na motorické příznaky (mobilita) i sociální důsledky PN (stigma, sociální podpora, komunikace). V oblastech, jako aktivity denního života, emoce, kognice, tělesný dyskomfort se však kvalita života pacientů signifikantně po 36 měsících nezlepšila (emoce sice zlepšeny po 12 měsících, ale zlepšení po 36 měsících od implantace již nebylo patrné). Tab. 2 shrnuje výsledky podškál a příslušné hodnoty p.

Tab. 2. Podškály PDQ-39.

Podškála PDQ – 39	Před DBS	12 měsíců po DBS	P	36 měsíců po DBS	p
Mobilita	64,1	32,8	<0,0001	44,4	0,0034
Aktivity denního života	35,9	26,7	0,1116	30,8	0,2746
Emoce	40,2	25,8	0,0171	31,9	0,1512

Stigma	50,8	27,8	0,0007	25,8	0,0002
Sociální podpora	30	16,4	0,0141	17,5	0,0340
Kognice	33	21,8	0,0564	40,8	0,1526
Komunikace	39,7	21	0,0027	26,6	0,0359
Tělesný dyskomfort	25,3	17,3	0,1120	18,9	0,1968

Diskuze

Zlepšení kvality života po DBS STN se v různých pracích pohybuje v poměrně širokém rozpětí 14 až 62 % [19,20]. Někteří autoři pozorovali pouze zlepšení motorických, jiní i nemotorických příznaků PN (neuropsychiatrické příznaky).

V našem souboru jsme zjistili statisticky signifikantní zlepšení skóre PDQ-39 po roce i po 36 měsících od operace u všech pacientů. Jak se dá předpokládat, nejvýrazněji se zlepšení odrazilo v motorických příznacích, které jsou prostřednictvím DBS STN nejvíce ovlivněny. Z tohoto pohledu se naše výsledky přibližují závěrům jiných otevřených studií [12,20–22]. Za zajímavé považujeme však i statisticky signifikantní zlepšení v podškálách stigma, komunikace a sociální podpora, které odrážejí sociální důsledky Parkinsonovy nemoci.

Mírné zhoršení kvality života po 36 mě- sících ve srovnání se stavem po roce od DBS je pravděpodobně výsledkem progrese PN a akcentace příznaků, které jsou jen málo ovlivnitelné pomocí DBS, resp. dopaminergní terapie. Nejvýraznější zhoršení, pokud jde o nárůst bodového hodnocení mezi 12 a 36 měsíci, bylo v podškále kognice a emocí. Tento výsledek je v souladu s publikovanými studiemi [24,25]. U části pacientů po DBS STN bylo pozorováno zhoršení kognitivních (především verbální fluence, verbální paměti, asociativní učení, vizuospaciální paměť) a také některých neuropsychiatrických funkcí [6]. Za příčiny tohoto jevu se považují preoperační faktory (předchozí psychiatrické nemoci), vlivy operace (trvání procedury, trajektorie elektrod, chirurgické komplikace), působení stimulace (umístění elektrod,

stimulační parametry), psychosociální změny po DBS STN a změny související s PN (neurodegenerativní proces, nedopaminergní symptomy). Porucha kognitivních funkcí v anamnéze je jednou z hlavních kontraindikací hluboké mozkové stimulace. Je vhodné potenciální kandidáty informovat o možném mírném poklesu některých kognitivních schopností po DBS STN [26].

Limitací naší studie může být to, že se jedná o retrospektivní zpracování dat z databáze pacientů. Pacienti indikovaní k DBS jsou však poměrně malá skupina (podle literárních údajů je k DBS indikovaných zatím pouze do 4,5 % s PN [23]) a v jejich případě dochází již k jisté preselekci (věk, stupeň pokročilosti PN, menší výskyt jiných onemocnění, dobrý neuropsychologický a kognitivní stav, nepřítomnost dalších kontraindikací k operačnímu výkonu), a proto srovnání se skupinou jiných pacientů shodující se pouze ve věku a trvání onemocnění nemusí mít dostatečnou výpovědní hodnotu.

Předmětem dalšího studia mohou být externí faktory, které zlepšení kvality podmiňují. Při analýze naší skupiny pacientů jsme nepozorovali vliv věku nebo délky trvání nemoci na míru zlepšení kvality života. Zajímavou otázkou je studium korelace zlepšení mezi kvalitou života a motorickými příznaky (vyjádřenými ve škále UPDRS III). Podle práce autorů Lezcano et al [13] se korelace zlepšení motoriky a kvality života, jež je přítomna po 12 měsících, snižuje po dvou letech. Uvedení autoři předpokládají, že po iniciálním zlepšení motoriky, které se projeví na úpravě kvality života po 12 měsících, mají na kvalitu života po dvou letech větší vliv jiné než motorické příznaky PN (např. komunikace). V našem souboru bylo možno (i vzhledem k nutnosti mírného zvýšení amplitudy stimulace a medikace (LED) mezi 12 a 36 měsíci) pozorovat mírnou progresi onemocnění, která se odrazila i v mírném nárůstu skóre PDQ-39 po 36 měsících ve srovnání se stavem po jednom roce. Tato progrese byla v oblasti motorických příznaků kompenzována úpravami stimulačních parametrů a medikace jen částečně (mírné zhoršení motorického skóre ve stavu OFF v UPDRS, nárůst skóre aktivit denního života a motoriky ve škále PDQ-39).

Hodnocení a sledování kvality života u pacientů indikovaných k DBS STN považujeme za velmi významné, přestože hodnocení kvality života je subjektivní a u PN není zcela jasné, které dotazníky jsou pro tento účel nejvhodnější. Při terapeutické metodě, jež není kurativní a má

nezanedbatelné náklady personální a finanční, je nutné indikovat pacienty, kteří mají z této léčby co největší benefit. I proto je kvalita života parametr, který by měl být neurology i neurochirurgy pozorně sledován i při zavádění nových terapeutických metod u PN. Přikláníme se k názoru, že je vhodné upravit kritéria k indikacím DBS STN tak, aby zahrnovala i aspekty související s kvalitou života [20] tak, aby byla metoda nabídnuta pacientům, u kterých můžeme očekávat zlepšení právě v aspektech/doménách nejlépe ovlivnitelných působením stimulace (motorika, aktivity denního života).

MUDr. Marek Baláž, Ph.D.
Centrum pro abnormní pohyby a parkinsonizmus
I. neurologická klinika LF MU a FN u sv. Anny v Brně
Pekařská 53
656 91 Brno
e-mail: marek.balaz@fnusa.cz

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3.6 One year after deep brain stimulation of patients with Parkinson's disease: neuropsychological results

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Commentary:

The following paper summarizes initial neuropsychological outcomes by our group on results of neuropsychological test in patients with advanced Parkinson's disease who underwent DBS STN. Neuropsychological testing and assessment of function is an important prerequisite for DBS STN indication. It was proven that DBS (see e.g. Krack et al 2003) can worsen the cognitive and psychiatric status of the patient in case of pre-existent affective disorder (depression) or cognitive dysfunction (mild cognitive impairment or dementia).

Postoperative evaluation of neuropsychological function is an important step in care of patient with DBS.

In this paper a wide array of well established neuropsychological tests was used both for initial analysis and for final evaluation after one year in group of 19 patients with advanced PD indicated for DBS STN surgery. These included *Wechsler Adult Intelligence Scale Revised, Mattis Dementia Rating Scale, Wechsler Memory Scale, Rey-Osterrieth Complex Figure, Stroop Test, Tower of London, Lexical Fluency, Category Fluency, Beck Depression Inventory and Montgomery-Asberg Depression Rating Scale.*

Patients were strictly evaluated during so called ON state (with good control of motor parkinsonian symptoms) to eliminate negative effect of PD symptoms such as slowness of movements on neuropsychological testing. In all patients sufficient improvement of motor function occurred after DBS STN. There were no siginificant surgical complications present.

We found minor, but statistically significant worsening of attention, executive function and verbal fluency one year after DBS. Our result are in congruence with data published by international groups of authors (e.g. Voon et al, 2006).

As a co-author I participated in preparing the general idea for article, collected data related to DBS procedure, an took major part in preparation of this article.

Jeden rok po hluboké mozkové stimulaci pacientů s Parkinsonovou nemocí: neuropsychologické výsledky

S. Telecká, M. Baláž, I. Rektorová, Z. Fanfrdlová, I. Rektor

Centrum pro abnormní pohyby a parkinsonismus, I.neurologická klinika LF MU a FN u sv. Anny, Brno

Sabina Telecká, I. neurologická klinika FN u sv. Anny v Brně, Pekařská 53, 656 91 Brno, sabina.telecka@fnusa.cz

Podpořeno Výzkumným záměrem MŠM 002162240

Souhrn:

Cíl studie: Zhodnotit stav kognitivních schopností rok po hluboké mozkové stimulaci subtalamického jádra u pacientů s Parkinsonovou nemocí.

Soubor a metodika: 19 pacientů bez příznaků demence podstoupilo neuropsychologické vyšetření před a rok po DBS operaci v motorickém stavu "ON". Pro datovou analýzu byl použit Wilcoxonův párový test.

Výsledky: U všech pacientů bylo zaznamenáno dlouhodobé zlepšení motorického výkonu a motorických komplikací při stimulaci "ON". Analýza ukázala pokles výkonu v případě Stroopova testu, části "Slova-Barvy", verbální fluence sémantické i lexikální, Doplňování obrázků a testu slovního učení „Seznam slov – oddálené vybavení".

Závěr: Zjistili jsme mírný, avšak statisticky signifikantní pokles výkonu u testů měřících pozornost, exekutivní schopnosti a verbální paměť (volné vybavení); zatímco nálada (deprese) nebyla DBS nijak ovlivněna.

Klíčová slova: hluboká mozková stimulace, subtalamické jádro, kognitivní schopnosti, exekutivní, deprese

Zkratky:

DBS – hluboká mozková stimulace

PN – Parkinsonova nemoc

STN – subtalamické jádro

Key words: deep brain stimulation, sutthalamic nucleus, cognitive functions, executive, depression.

Úvod

Hluboká mozková stimulace (deep brain stimulation, DBS) je indikována nejčastěji k terapii pozdních hybných komplikací Parkinsonovy nemoci (PN), které neodpovídají na úpravy farmakoterapie. Nejčastějším anatomickým cílem DBS u pokročilé PN je subtalamické jádro (STN). Jde o bezpečný a účinný postup, který u pacientů výrazně zlepšuje hybné symptomy PN, pozdní hybné komplikace a zvyšuje kvalitu života [1,2,3].

Výtečný symptomatický efekt na třes, rigiditu a hypokinézu, spolu s možností snížení dopaminergní terapie v pooperačním období, přispěl k rozšíření této metody. DBS STN snižuje motorické fluktuace, čas trvání levodopou (L-DOPA) indukovaných dyskinezí a umožní snížit antiparkinsonskou terapii L-DOPA ekvivalentu ve srovnání s předoperačním stavem [4].

Díky výraznému efektu na motorické skóre (v UPDRS III – Unified Parkinson Disease Rating Scale III – jednotná škála k hodnocení tíže hybných symptomů PN – výrazné pooperační zlepšení), snížení motorických fluktuací (trvání dyskinezí a off stavů) a zlepšení kvality života pacientů (PDQ-39 – Parkinson Disease Quality of Life - snížení skóre) v dlouhodobém sledování, je DBS mimořádně efektivním terapeutickým postupem u pacientů s pozdními hybnými komplikacemi PN [1].

Antiparkinsonskou medikaci je možno posléze redukovat, což vede k signifikantnímu snížení nežádoucích účinků (viz webové stránky NINDS – DBS, www.ninds.nih.gov/disorders/deep_brain_stimulation/deep_brain_stimulation.htm).

DBS má jako každý funkční neurochirurgický výkon rizika spojená s chirurgickou intervencí (krvácení, infekce), působením stimulace (ovlivnění okolních anatomických struktur) a další rizika přináší umístění cizího materiálu (infekce, rejekce, lokální iritace kůže) [5].

Z hlediska neuropsychologického literatura nejčastěji hovoří o snížení schopností v oblasti verbální paměti a verbální fluence [např. 6,7].

Výraznějším nežádoucím účinkům je však možno se vyhnout přísným dodržením indikačních a vylučujících kritérií, Tab. 1 [blíže viz 1]. Z psychologického hlediska jde především o to nezařazovat pacienty trpící významnějším kognitivním deficitem nebo psychiatrickými symptomy (halucinace, psychóza, těžší forma deprese).

Neuropsychologické charakteristiky pacientů s PN

Neuropsychologický deficit u PN je charakterizován progresivním „dysexekutivním“ syndromem s paměťovým deficitem a poruchou abstraktního myšlení [např.8], viz též Tab. 2. Kognitivní poruchy mírného stupně jsou časté již v rané fázi onemocnění a mohou progredovat do demence až u 78,2 % pacientů v pozdním stádiu nemoci [9]. Demence významně snižuje kvalitu života pacientů a zkracuje dobu jejich přežití, způsobuje dvojnásobný nárůst mortality [8]. Riziko rozvoje demence u pacientů s PN je 1,7-5,9 x vyšší než u běžné populace stejného věku, vzdělání a pohlaví [10].

Většina pacientů také prožívá deprese, mnohdy kombinované s úzkostí. Psychotické projevy jsou častější především u pacientů s kognitivním deficitem; celkově se však objevují u menší části nemocných zejména jako nežádoucí efekt dopaminergní terapie.

Jeden rok po STN DBS u pacientů s PN - neuropsychologické výsledky z našeho pracoviště

Cíl výzkumu*:*

Zhodnotit kognitivní schopnosti a změny nálady po DBS STN u pacientů s PN.

Soubor a Metodika*:*

19 pacientů bez příznaků demence (průměrný věk 58,8 ± 8,2 roku; vzdělání 12,6 ± 2,1 roku, skóre Mattisovy škály demence 141 ± 3,8) podstoupilo neuropsychologické vyšetření před a po DBS operaci v motorickém stavu "ON" (mediánový interval mezi DBS a neuropsychologickým vyšetřením byl 11 měsíců). Pro datovou analýzu byl použit Wilcoxonův párový test.

Testová baterie*:*

Wechslerova inteligenční škála pro dospělé (Wechsler Adult Intelligence Scale Revised, WAIS-R, WAIS-III; [11])*:* Nejčastěji používaná metoda ke komplexnímu mapování intelektových schopností pacientů. V našem výzkumu jsme použili zkrácenou verzi [12], obsahující subtesty *Doplňování obrázků, Počty, Symboly, Podobnosti*.

Mattisova škála demence (Mattis Dementia Rating Scale, DRS; [13]*):* Často používaná screeningová zkouška. Obsahuje subtesty měřící pozornost (opakování čísel), iniciaci a perseveraci (schopnost začít a dokončit určitou činnost), konstrukci (kopírování vzorů dle předlohy), konceptualizaci (podobnosti) a verbální a nonverbální krátkodobou paměť (opakování vět, rozpoznávání obrazců).

Wechslerova paměťová škála (Wechsler Memory Scale, WMS-III; [14]*)* – část S*eznam slov*: Jeden z tzv. testů verbálního učení - zaměřuje se na verbální učení, organizaci a paměť. Součástí testu je také složka znovupoznání.

Test komplexní figury (Rey-Osterrieth Complex Figure, R-O; [15]*):* Hojně využívaný test, který mapuje vizuo-spaciální konstrukční schopnosti, vizuálně-motorickou kontrolu a pozornost a mnestickou kapacitu – bezprostřední i oddálenou. Lze využít i část „znovupoznání" (recall).

Stroopův test (Stroop Test; [16])*:* Měří schopnost přepínání pozornosti (shifting); je měřítkem flexibility. Je citlivý na detekci mozkových poškození, zejména ve frontální oblasti.

Londýnská věž (Tower of London, TOL; [17]*)*: Test mapuje exekutivní schopnosti, především schopnost strategického plánování a vizuálně-prostorového řešení problému a schopnost dodržení nalezeného schématu.

Lexikální cílená verbální fluence (Lexical Fluency): Úkolem je za jednu minutu vytvořit co nejvíce slov začínajících na dané písmeno (neplatná jsou vlastní jména, číslice a stejná slova s rozdílnou příponou). V anglosaské literatuře jsou používána písmena F,A,S; u nás N,K,P)
Sémantická cílená verbální fluence (Category Fluency): v případě fluence sémantické je úkolem za jednu minutu vyjmenovat co nejvíce slov spadajících do určené kategorie – např. „zvířata“, „potraviny“ či „oblečení“.
Beckova škála deprese (Beck Depression Inventory, BDI; [18]*):* Sebeposuzovací stupnice, která se používá v klinické praxi i ve výzkumu. Položky jsou zaměřeny na afektivní, kognitivní, motivační a fyziologické symptomy deprese. Dotazník měří aktuální stav, ne depresivitu jako rys osobnosti.
Škála MADRS (Montgomery-Asberg Depression Rating Scale; [19]*):* Objektivní škála určená k posuzování míry deprese; je citlivá k zachycení změn v čase, je validizována pro diagnostiku deprese u PN.

Výsledky*:*

U všech pacientů bylo zaznamenáno dlouhodobé zlepšení motorického výkonu a motorických komplikací při stimulaci “ON”.
Medián stimulačních parametrů byl 2,6 V± 0,4 V, 130 Hz a 90 usec. U všech 19 pacientů bylo zapojení stimulace monopolární (s aktivní katodou v oblasti STN).
Významné zlepšení motorického skóre (UPDRS III) bylo zjištěno u všech stimulovaných pacientů. UPDRS III při medikaci OFF/ stimulaci ON pokleslo o 68,5 % a při medikaci ON/ stimulaci ON o 70 % ve srovnání se stavem před operací. Medián stimulačních parametrů byl 2,6 V, 130 Hz a 90 usec.
Tabulka 3 ukazuje porovnání souborů výsledků neuropsychologických testů před a po operaci. Hodnota **p** je pravděpodobností shody obou souborů; při nízké hodnotě **p**□ 0,05 tedy hypotézu o shodě souborů zamítáme.
Analýza ukázala statisticky signifikantní změny u následujících testů (vždy se jednalo o pokles výkonu ve srovnání se situací před operací): Stroopův test, část “Slova-Barvy” (p = 0,004), Verbální fluence: sémantická (p = 0,018) a lexikální (p = 0,022), Doplňování obrázků (subtest WAIS-R; p = 0,016); Seznam slov – oddálené vybavení (subtest WMS-III; p = 0,019). Pokles ve

výkonu u sledovaných schopností byl spíše mírný, v celkovém klinickém dojmu se výrazněji neprojevuje.

V období 1 roku po DBS se u pacientů neprojevují žádné psychiatrické symptomy jako jsou bludy, halucinace, porucha kontroly impulzů (patologické hráčství, neadekvátní sexuální chování, patologické nakupování, žravost), či kompulzívní nadužívání dopaminergní medikace (dopamine dysregulation syndrom). Rovněž se neobjevil statisticky signifikantní rozdíl v míře deprese.

Diskuse*:*

U sledovaných pacientů jsme zjistili mírný, ale signifikantní pokles v oblasti pozornosti, exekutivních schopností a verbální paměti. Nepozorovali jsme žádné změny nálady.

Pokud jde o kognitivní změny po DBS STN, výsledky jednotlivých studií se liší a nejsou konzistentní.

Nejčastěji v literatuře nacházíme informace o mírných parciálních změnách kognitivních schopností, zejména u verbální fluence, verbální paměti a pozornosti [např.6,20,21]. York et al. [7] hovoří o mírném frontostriatálním kognitivním deficitu (verbální fluence, pozornost, rychlost zpracování informací a verbální paměť). Naše výsledky jsou v souladu s výsledky těchto studií.

Podstatné je, že uváděné selektivní kognitivní změny nemívají dle literatury výraznější vliv na kvalitu života pacientů [2,22]. Nejedná se o signifikantní změny v globálním kognitivním výkonu [2, 23]. Pokud se objeví demence, je to obvykle přičítáno přirozenému vývoji PN, nikoli vlivu DBS [např.20, 3]. V naší práci jsme se však na hodnocení kvality života nezaměřovali, nemůžeme se tudíž k dopadu mírného zhoršení výkonu v některých kognitivních testech na kvalitu života našich konkrétních pacientů vyjádřit.

Witt et al. [2] zjistili pokles výkonu ve Stroopově testu a verbální fluenci, zatímco verbální paměť, pracovní paměť a pozornost podle nich zůstaly beze změn. V některých studiích nebyl pozorován žádný pokles kognitivních schopností [např.24]. Existuje dokonce i práce, která referuje o zlepšení některých kognitivních schopností po DBS STN: např. v případě některých aspektů exekutivních schopností - pracovní paměti, řešení problémů, rychlost zpracování informace, mentální flexibility [25].

Patofyziologie selektivních kognitivních změn pozorovatelných u pacientů po STN DBS není doposud plně objasněna. Změny by mohly souviset s implantací elektrod a zejména s jejich přesným umístěním, s vlastní stimulací a použitými stimulačními parametry, nebo i se změnou dopaminergní medikace (jejím snížením) po STN DBS [2,26,27] .

Recentní randomizovaná studie porovnávající kognitivní efekty STN DBS a DBS vnitřního pallida u pacientů s PN [28] prokázala po 7 měsících sledování srovnatelný pozitivní efekt na hybné symptomy PN, avšak zhoršení v testu verbální fluence v porovnání s výkonem před DBS pouze v případě stimulace STN, a to zejm. v „off" stavu (po vypnutí stimulace). Autoři uzavírají, že zhoršení kognitivního výkonu v testu verbální fluence u pacientů s STN DBS souvisí pravděpodobně spíš s chirurgickým výkonem (implantací elektrod) než s vlastní stimulací.

Hypotézy o kauzálních mechanismech těchto změn vycházejí zejména ze studií na zvířecích modelech PN nebo z výsledků studií s použitím funkčních zobrazovacích metod (PET) u pacientů s PN. Např. Campbell et al. [27] zjistili pomocí vyšetření $H_2{}^{15}O$ PET, že pacienti s kognitivním deficitem navozeným DBS měli stimulací navozené zvýšení regionálního průtoku krve v oblasti dorsolaterálního prefrontálního kortexu a předního cingula a naopak pacienti se zlepšením kognitivních funkcí v důsledku stimulace měli snížený průtok krve ve stejných oblastech mozku. Co je ale podkladem těchto změn na buněčné úrovni, není jasné. Autoři např. uvádějí hypotézu, že vnucená frekvence vybíjení STN na jedné straně zlepšuje motorické funkce pacientů s PN, na druhé straně může interferovat s fázickou aktivitou dopaminergních neuronů mající vztah ke kognitivním funkcím.

Pokud se týká psychiatrických potíží, Voon et al. [29] popisují přechodné a terapeuticky ovlivnitelné neuropsychiatrické symptomy (přechodná zmatenost, pooperační hypománie, transientní apatie, zrakové halucinace); a dále epizody pooperační deprese – které mají tendenci se v průběhu dalších let postupně zmírňovat. V našem souboru jsme nezjistili žádnou výraznější změnu depresivní symptomatologie, v korelaci s jinými autory [např.7].

Závěr*:*

Zjistili jsme mírný, avšak statisticky signifikantní pokles výkonu u testů měřících pozornost, exekutivní schopnosti a verbální paměť (volné vybavení); zatímco nálada (deprese) nebyla DBS

nijak ovlivněna. Naše výsledky jsou srovnatelné s výsledky dalších studií publikovaných v literatuře.

Potenciální kandidáti DBS by měli být informováni o možnosti mírného poklesu některých kognitivních schopností, při současné šanci výrazné úpravy motorických obtíží.

Budoucí studie by měly být zaměřeny na detailnější studium patofyziologických mechanismů kognitivních a behaviorálních změn u pacientů po DBS a na hledání rizikových faktorů predikujících individuální změny navozené DBS.

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- Věk nad 70 let
- Předoperační neuropsychiatrické dysfunkce (nediagnostikovaná demence, deprese, behaviorální poruchy
- Komplikace operačního výkonu DBS (infekce, hemoragie, léze)
- Nadměrně prodlužovaná perioperační elektrofyziologie s větším množstvím trajektorií mikroelektrod
- Nadměrná nebo nedostatečná dopaminergní stimulace (v závislosti na pooperačních změnách dopaminergní terapie)

Tabulka 1: Pacienti s vyšším rizikem kognitivního postižení po DBS STN – možné rizikové faktory [1]

- Exekutivní schopnosti + pozornost

  Dysexekutivní syndrom: potíže při vytváření a flexibilitě pracovních plánů a strategií, přepínání pozornosti („set shifting“), distribuci pozornosti, cílené verbální fluenci

Paměťové schopnosti

Snížená pracovní paměť, snížená výbavnost informací (s přetrvávajícím benefitem nápovědy), potíže při asociativním učení

Vizuo-spaciální schopnosti (alterovaná exekutivní složka)

Může být postižena řeč

Tabulka 2: Neuropsychologický deficit u PN

Neuropsychologický test	***N***	***Před DBS průměr***	***Sm. odch.***	***Po DBS průměr***	***Sm. odch.***	***Wilcoxonův test, p (2-tail)***
WAIS-R	12	108,5	11,5	101,3	7,9	0,136
WAIS-R – Počty	13	10,8	2,2	9,6	1,9	0,917
WAIS-R – Podobnosti	13	11,2	2,1	11,0	2,1	0,861
WAIS-R – Doplňování obrázků	13	13,0	2,7	11,4	2,4	**0,016**

WAIS-R – Číselné symboly	12	8,4	1,6	7,7	1,4	0,784
Mattis DRS	13	140,6	4,5	135,2	9,7	0,701
R-O bezprostřední	17	59,1	11,8	56,3	13,2	0,356
R-O oddálená	17	56,2	10,4	54,2	12,9	0,670
R-O znovupoznání	9	50,3	8,1	50,7	12,6	0,594
Stroop – Slova	18	54,5	11,8	51,0	7,4	0,965
Stroop – Barvy	18	39,7	6,6	42,2	12,0	0,214
Stroop – Slova-Barvy	18	41,1	9,2	37,8	10,7	**0,004**
Londýnská věž	11	45,0	14,0	39,3	11,9	0,722
Lexikální fluence	19	35,7	10,9	28,1	13,4	**0,022**
Sémantická fluence	19	20,8	6,3	15,8	6,0	**0,018**
Seznam slov – bezprostřední	19	10,0	3,6	8,7	3,8	0,507
Seznam slov – oddálený	19	11,2	3,0	12,4	3,6	**0,019**
Seznam slov – znovupoznání	14	10,9	2,9	10,7	2,4	0,331
MADRS	18	6,0	3,2	6,3	4,4	0,571
BDI	17	8,1	4,3	9,7	7,3	0,522

Tabulka 3 – Srovnání souborů výsledků testů před a po operaci

3.7 Involvement of subthalamic nucleus in cognitive functions – a concept

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Commentary:

The involvement of subthalamic nucleus (STN) in a broad spectrum of various non-motor functions – attention, executive functions, verbal learning and memory, verbal abstract reasoning, conflict resolution, and emotions – has been reported. In following review we describe a variety of changes that appeared in recent respective literature. We also define a concept of STN functioning within the structures involved in cognitive functions. The STN has an anatomically central position within basal ganglia (BG)-thalamocortical motor, associative and limbic circuits. Recent studies have demonstrated that specific oscillations in the STN are involved in cognitive and behavioral information processing. STN might interfere with non-motor functions as an indirect modulator rather than a regulator. Mechanisms modulating the motor and non-motor functions might differ. STN has been implicated in control of non-motor behaviors via the tuning of specific circuits depending on the task. STN might modulate selected non-motor functions via contextual modulation of certain cortical areas. Based on intracerebral recordings, we proposed that the non-motor activities in BG are organized in some way other than the well-known organization of the cortico-BG-thalamocortical circuits. These findings support the hypothesis of a cortico-STN bypass of the BG-thalamocortical circuitry under some circumstances.

Overall, it is evident that at least in some patients the change in cognitive functions after STN-DBS may have clinical importance. The exact mechanisms of possible cognitive after-effects of STN-DBS are not known.

Involvement of the subthalamic nucleus in cognitive functions – a concept

Marek Baláž, Martina Bočková, Irena Rektorová, Ivan Rektor

Central European Institute of Technology – CEITEC, Department of Neurology, St. Anne's University Hospital, Medical School of Masaryk University, Pekařská 53, 656 91 Brno, Czech Republic

Abstract

The involvement of the subthalamic nucleus (STN) in a broad spectrum of various non-motor functions – attention, executive functions, verbal learning and memory, verbal abstract reasoning, conflict resolution, and emotions – has been reported. The STN has an anatomically central position within the basal ganglia(BG)-thalamocortical motor, associative and limbic circuits. The STN might interfere with non-motor functions as an indirect modulator rather than a regulator. Mechanisms modulating the motor and non-motor functions might differ. The STN has been implicated in control of non-motor behaviors via the tuning of specific circuits depending on the task. The STN might modulate selected non-motor functions via contextual modulation of certain cortical areas. Based on intracerebral recordings, we proposed that the non-motor activities in the BG are organized in some way other than the well-known organization of the cortico-BG-thalamocortical circuits. These findings support the hypothesis of a cortico-STN bypass of the BG-thalamocortical circuitry under some circumstances. The exact role of the STN and the BG in non-motor functions remains an important and interesting challenge for future research.

Key words: Subthalamic nucleus; Basal ganglia; Cognitive functions; Deep brain stimulation; Hyperdirect pathway

Introduction

The role of the basal ganglia (BG) in cognition is largely unknown, but it has been suggested that the BG play an integrative role in cognitive processing [1].

Within the BG, the subthalamic nucleus (STN) has received significant attention as a therapeutic target, because its inactivation by high-frequency stimulation has been successfully used to treat Parkinson's disease (PD) [2]. Inactivation of the STN by deep brain stimulation (DBS) is used mainly to improve motor deficits.

The STN, however, appears to be involved in the processing of certain cognitive and executive functions. Experimental and clinical observations have suggested that this structure is involved in modulating motivation and seems to be sensitive to drugs of abuse [3,4]; this is probably why STN-DBS may improve dopamine dysregulation syndrome, impulse control disorders, and punding in PD [5]. It seems that the STN has an anatomically central position within the basal ganglia-thalamocortical associative and limbic circuits and is functionally a potent regulator of these pathways. In our review, we try to establish evidence from published papers that describe the participation of the STN in cognitive functions.

1. STN and cognition, anatomical connections

The STN is a small lens-shaped midbrain nucleus lying on the dorsomedial surface of the internal capsule. The STN is thought to play a prominent role in the pathophysiology of PD [6]. The STN not only plays a key role in motor behavior, but is also a potent regulator in the limbic and associative circuits [7].

As the only glutamatergic structure of the BG, it is a major source of excitation. The STN innervates mainly the globus pallidus interna (GPi) and the substantia nigra, but also the globus pallidus externa GPe), ventral pallidum, pedunculopontine nucleus, and, to a lesser extent, the striatum, nucleus accumbens, and ventral tegmental area.

The major subcortical inputs to the STN arise from the ventral pallidum and the GPe (the indirect pathway), the thalamus, pedunculopontine nucleus, dorsal raphe, ventral tegmental area, and pars compacta of the substantia nigra [8].

Before the 1970s, the literature was conclusive on human corticosubthalamic connections [9]. Direct cortical projections to the STN were described [10], but they were considered to be sparse, and therefore regarded as less important. According to recent views, the STN has not only a crucial position in the indirect pathway of the BG, but it also receives direct cortical projections, especially from the frontal lobe, namely the primary motor cortex, supplementary

motor area, and the dorsal and ventral divisions of the premotor cortex, such as the hyperdirect pathway from the inferior frontal cortex (IFC) [11-14].

In 2004, Strafella indicated that the role of the cerebral cortex in regulating the activity of the STN was not known in humans. Transcranial magnetic stimulation of the motor cortex changes the neuronal activity of the STN [15].

Diffusion Weighted Imaging (DWI) tractography demonstrated a three-way white matter network between the preSMA, the IFC, and the STN region in the right hemisphere in tasks related to reversing initiated motor responses, as revealed by the stop-signal paradigm [16].

The anatomic source of control over the putative cognitive function of the STN is less well described, but it is clear that the STN is involved not only in motor but also in associative and limbic cortico-BG-thalamocortical loops.

The direct connections to the STN from the prefrontal cortex and the relation of the STN to structures such as the nucleus accumbens and the ventral pallidum (both well known for their involvement in motivational processes) may explain why the STN contributes to functions well beyond motor activities.

2. STN and cognition, clinical relevance

From a clinical point of view, STN-DBS modulates not only motor but also cognitive and affective functions [7]. In some patients, STN-DBS has been followed by cognitive impairment and other neuropsychiatric disturbances such as depression, (hypo)mania, personality changes, hypersexuality, apathy, and aggression. About half of STN-DBS patients did not experience behavioral changes [7,17-20]. According to some authors, DBS causes only minor changes, related perhaps more to the effect of surgery than the stimulation itself [21]. A randomized multicenter study showed that STN-DBS did not reduce overall cognition or affectivity, although there was a selective decrease in frontal cognitive functions and a decrease in patient anxiety after the treatment [22]. According to a meta-analysis, cognitive problems were faced by up to 41% of patients after STN-DBS [23].

While the impact of the STN on non-motor functions appears to be accepted by most authors, its clinical significance is still controversial [24]. This review article underlined certain methodological differences in papers related to neuropsychological and cognitive disorders

connected with this procedure [24]. The vast literature on cognitive short-term as well as long-term outcomes after bilateral DBS surgery of the STN varies widely. Mild to moderate decreases in verbal learning, abstract reasoning, and selective frontal functions (and verbal fluency in particular) have been reported as the most common cognitive after-effect of the procedure, while development of dementia has been generally related to the PD progression itself [17, 21, 22, 24-32].

In a retrospective study by our group [32], we found a mild but clinically significant decline in the results of neuropsychological tests measuring attention, executive functions, and verbal memory (free recall) in PD patients one year after DBS STN surgery.

Overall, it is evident that at least in some patients the change in cognitive functions after STN-DBS may have clinical importance. The exact mechanisms of possible cognitive after-effects of STN-DBS are not known. Temel et al. claimed that the STN not only plays a key role in motor behavior, but also serves as a potent regulator in the limbic and associative circuits [7]. The precise location of the active electrode contact and the spatial extent of the effects of stimulation as well as the frequency, voltage, and amplitude of STN stimulation, or patient variables such as degree of dopaminergic denervation, could be involved [33,34].

3. STN animal studies and cognition

An integrative function of the STN in both motor and cognitive operations [35-37] has been suggested. Experiments in animals have shown involvement of the STN in attentional and motivational functions [3,4,36, 38-41]. The cognitive side-effects of high-frequency STN stimulation were shown in animal studies as well as in clinical practice. A transient decrease in attention and accuracy of task performance was described in rats [42].

4. STN and cognitive local field potentials

Recent functional neurosurgery has provided the opportunity to record directly from the human BG, most commonly in patients with PD undergoing DBS electrode implantation. Single unit recordings and local field potentials can be recorded intraoperatively via microelectrodes; local field potentials can also be measured from the DBS macroelectrodes, which are

externalized a few days after operation [43]. In PD patients, abnormal prominent and synchronized neuronal oscillations at frequencies 8-35 Hz were repeatedly described. This abnormal activity is suppressed by treatments that improve parkinsonism, and it seems to be intimately related to voluntary movement and linked to both bradykinesia and rigidity [44-51]. Changes in beta oscillatory activity were detected in the STN not only during movement performance, but also during movement observation; therefore, the STN is probably engaged in the human mirror system [52,53]. Beta frequency modulation patterns are regulated by the dopamine levels in the system [54] and also by the DBS stimulation [55]. Disturbances in gamma (60-80 Hz) and higher frequency range (300 Hz) oscillations and their coupling between beta activity are an important pathophysiological mechanism in PD [56,57]. Recent studies have demonstrated that specific oscillations in the STN are involved in cognitive and behavioral information processing: action representation is mediated through 13-35 Hz oscillations, decision making processes through 5-12 Hz oscillations, limbic and emotional information through 8-12 Hz oscillations [58]. Evoked local field potentials related to executive functions and attention were found in the STN during performance of both visual and auditory cognitive paradigms [13,59,60]. These papers by our group indicate a specific, task-related involvement of the STN in cognitive activities. Cognitive processing in the STN may be processed via the hyperdirect pathway. These recordings were performed either directly from the motor part of the STN or from its immediate vicinity. Therefore we have suggested that neuronal pools involved in cognitive activities may be located close to, or even overlap with, the neurons active in motor functions [61]. Our results have revealed an important involvement of the STN in cognitive functions and emotion control and could explain the occurrence of post-DBS behavioral disturbances.

Discussion

The involvement of the STN in a broad spectrum of various non-motor functions – attention, executive functions, verbal learning and memory, verbal abstract reasoning, conflict resolution, and emotions – has been reported. [2-4,7,8] Neuropsychiatric disturbances after DBS indicate that the STN is involved in cognitive impairment as well as in depression or mania,

personality changes, apathy, aggression, impulse control disorder, and hypersexuality [5, 17, 18, 20-24,27-31].

The STN is involved in a variety of functions, motor and non-motor, despite the fact that it is a very small structure. It is hard to imagine that the limited number of STN neurons could process all these functions separately. Functional imaging shows that stimulating the STN, even though it is quite small, induces modifications of the pattern of brain activation involving large scale cerebral networks [62]. A model was proposed in which three functional modalities, emotional, cognitive, and motor, are not processed in a segregated manner but can be subtly combined within the small volume of the STN. This nucleus would thus serve as a nexus that integrates the motor, cognitive, and emotional components of behavior [63]. We have shown that there is a spatial overlap of sites regulating various functions in the STN as the local fields of the cognitive related potentials were recorded through the electrode contact located in the site with the best motor effect [13,59,60]. Similarly, in the pallidum and striatum, based on direct depth electrode recordings in patients with epilepsy, we also observed a spatial overlap of several cognitive and motor control functions [1]. It appears that various non-motor and motor functions that are processed or influenced by the STN have a common denominator that is as yet undefined.

The involvement of the STN in motor function regulations is unequivocal. DBS has an immediate and robust clinical effect on PD. It might be explained by the functional position of the STN within the BG-thalamocortical circuitry. The involvement of the STN in non-motor functions is far less robust and usually temporary. The STN might interfere with non-motor functions as an indirect modulator rather than a regulator. Mechanisms modulating the motor and non-motor functions might differ. Similarly, we suggested in earlier works that the mechanism for processing the motor and cognitive functions in the striatum and pallidum are different. Based on intracerebral recordings, we proposed that the cognitive activities in the BG are organized in some way other than the well-known organization of the cortico-BG-thalamocortical circuits. [1,64]. Actually, the separated BG-thalamocortical circuitries are only one of several hypothetical options defining the functional linkage between the BG and the cortex. Other hypotheses [65,66] have also been proposed. In the STN, the “hyperdirect” connections with the cortex that bypass the circuitries might underlie the processing of at least some of the non-motor functions. Several findings support this idea. At variance with the

striatum/pallidum, the standard oddball cognitive (P3) potentials are not generated in the STN [59,60]. Similarly, epileptic spikes were recorded in the STN but not in the other BG [67,68]. Repetitive transcranial magnetic stimulation (rTMS) of the IFC, which is a source of the hyperdirect pathway to the STN, but not of the dorsolateral prefrontal (DLPF) cortex, which is implicated in the cortico-thalamocortical circuitry, modifies certain cognitive potentials recorded in the STN [59]. These findings support the hypothesis of a cortico-STN bypass of the BG-thalamocortical circuitry under some circumstances.

The involvement of the STN in the increased cognitive loads but not by more simple cognitive tasks [59,60,61]. The results of imaging studies also show that the effects of STN-DBS are task specific and depend on the particular networks engaged by specific tasks. DBS probably tunes specific circuits depending on the task [62]. In contrast to the other BG except the striatum, the STN is targeted by important “hyperdirect” pathways directly from the prefrontal, inferofrontal, and pericentral cortices. This may indicate that the STN plays an important and specific role in processing certain functions, mostly those concentrated in the frontal lobe. Possibly, the selection of tasks modulated within the STN is determined by the selective involvement of cortical neuronal populations that are interconnected with the STN. Our group’s earlier data [13] demonstrated that event-related potentials evoked by an executive function task and recorded in the STN are modulated by rTMS of the inferofrontal but not of the DLPF cortex.

We suggested that the BG, specifically the striatum (from which we obtained the bulk of our recordings), participate in the cognitive processing of external information [1,64]. The BG may play an integrative role in cognitive information processing, in motor as well as in non-motor tasks. We suggested the following mechanism: the BG form a non-specific system that progressively converges data concerning various functions from various parts of the cortex. The converged data are processed in the BG and positively or negatively modulate the relevant cortical areas. The BG is the site at which information from various function systems (sensory, attention, memory, etc.) may be processed in a mutual context. This contextual modulation may be important for the functioning of the individual cortical areas.

The STN has been implicated in inhibitory control of non-motor behaviors via the tuning of specific circuits depending on the task [62]. The STN might modulate selected non-motor functions in a similar way, via contextual modulation of certain cortical areas. In any case, the

exact role of the STN and the BG in non-motor functions remains an important and interesting challenge for future research. modulation of certain non-motor activities is selective, i.e. the local electrical activity recorded in the STN is generated or modulated by the tasks with increased cognitive loads but not by more simple cognitive tasks [59,60,61]. The results of imaging studies also show that the effects of STN-DBS are task specific and depend on the particular networks engaged by specific tasks. DBS probably tunes specific circuits depending on the task [62]. In contrast to the other BG except the striatum, the STN is targeted by important "hyperdirect" pathways directly from the prefrontal, inferofrontal, and pericentral cortices. This may indicate that the STN plays an important and specific role in processing certain functions, mostly those concentrated in the frontal lobe. Possibly, the selection of tasks modulated within the STN is determined by the selective involvement of cortical neuronal populations that are interconnected with the STN. Our group's earlier data [13] demonstrated that event-related potentials evoked by an executive function task and recorded in the STN are modulated by rTMS of the inferofrontal but not of the DLPF cortex.

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3.8 Involvement of subthalamic nucleus and globus pallidus internus in attention

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Commentary:

The following paper was aimed at describing the recordings of electrical activitiy from deep brain structures – namely subthalamic nucelus (STN) and globus pallidum internum (Gpi).

We included seven patients with advanced Parkinson's disease (PD) and one patient with generalised dystonia. Patients were examined in the interoperative period between deep brain electrode implantation and implantation of a neurostimulator. Relatively low number of patients is caused by specificity of used methods and paradigms.

ERPs and ERD/S in the alpha and beta frequency range were analysed. As a test paradigm a visual three-stimulus protocol was used (frequent stimulus, target stimulus, and distractor). The frequent (non-target, standard) stimuli, which were 70 % of all the stimuli, were small blue circles. These were not to be followed by a reaction. The target stimuli, which were 15 % of all the stimuli, were larger blue circles. The subjects were asked to press an electrically connected button at the time of the target detection. The distractors (rare non-target stimuli), which were present 15 % of the time, were black and white checkerboards; no response was required.

Time frequency analysis was used to determine the event-related de/synchronizations (ERD/S) in the alpha and beta frequency ranges. A decrease in band power indicates induced event-related desynchronization (ERD), an increase in band power indicates event-related synchronization (ERS). The ERD of the alpha and beta rhythms is interpreted as a correlate of an activated cortical area with increased excitability. The ERS in the alpha and lower beta bands can be interpreted as a correlate of a deactivated cortical area, i.e. cortical idling or active inhibition (Pfurtscheller 2001).

The non-target and distractor-related waveforms manifested similar shapes. A specific positive ERP peak around 200 ms and a low alpha frequency ERS were detected from the STN as a response to the distractor stimuli in six of the patients with PD Parkinson's disease and also in the primary dystonia patient's GPi. This positivity probably reflects an attentional orienting response to the distractor stimuli.

We therefore presented data showing the activity of STN during attentional orientation which expands our previous results demonstrating participation of STN in cognitive processing. Direct intracerebral recordings remain invaluable source for getting time specific information on functioning of deep brains structures.

As a co-author I participated in manuscript preparation and revision, I participated in patient preparation for recording from deep brain electrodes.

Involvement of the subthalamic nucleus and globus pallidus internus in attention.

M. Bočková*, J. Chládek**, P. Jurák**, J. Halámek**, M. Baláž*, I. Rektor*

* First Department of Neurology, Masaryk University, St. Anne's Hospital, Brno, Czech Republic

** Institute of Scientific Instruments of the Academy of Sciences of the Czech Republic, v.v.i., Brno, Czech Republic

Address correspondence to:

Dr. Martina Bočková

First Department of Neurology, Medical Faculty of Masaryk University
St. Anne's Teaching Hospital
Pekarska 53
656 91 Brno
Czech Republic
phone: + 420 543 182 623
fax: +420 543 182 624
e-mail: martina.bockova@fnusa.cz

key words: basal ganglia, ERP, ERD/S, attention, DBS

Abstract:

Background: We studied the appearance of cognitive event-related potentials (ERPs) and event-related de/synchronizations (ERD/S) in the subthalamic nucleus (STN) and globus

pallidus internus (GPi). We particularly focused on the rare non-target (distractor) stimuli processing.

Methods: ERPs and ERD/S in the alpha and beta frequency range were analysed in seven Parkinson's disease patients and one primary dystonia patient with implanted deep brain stimulation (DBS) electrodes. A visual three-stimulus protocol was used (frequent stimulus, target stimulus, and distractor).

Results: The non-target and distractor-related waveforms manifested similar shapes. A specific positive ERP peak around 200 ms and a low alpha frequency ERS were detected from the STN as a response to the distractor stimuli in six of the patients with Parkinson's disease and also in the primary dystonia patient's GPi. This positivity probably reflects an attentional orienting response to the distractor stimuli.

Conclusion: The STN and GPi are probably involved in attentional cerebral networks.

Introduction:

Deep brain stimulation (DBS) has become a routine functional neurosurgery operation. It is an effective long-term treatment for motor symptoms in advanced Parkinson's disease (PD) (Krack et al. 2003). The most frequently used DBS target is the subthalamic nucleus (STN). The STN plays a major role in motor control and receives projections from the pallidum and from the motor cortical areas (Nambu et al. 2002, Hamani et al. 2004, Aron et al. 2007). In addition, the STN receives projections accounting for involvement in emotional and cognitive activities from the anterior cingulate, and inferior frontal cortex, as well as the medial and dorsolateral prefrontal cortices (Aron et al. 2007, Benarroch 2008). An integrative function in both motor and cognitive operations (Parent and Hazrati 1995, Baunez 1999b, Graybiel 1997) has been suggested. The STN has a central position within the basal ganglia-thalamocortical motor, associative, and limbic circuits and might serve as a potent regulator of these pathways. STN-DBS may modulate cognitive and affective functions (Temel et al. 2005). That is probably why, for some patients, the beneficial effects of STN- DBS on motor functions may be accompanied by cognitive impairment and other neuropsychiatric disturbances (Saint- Cyr et al. 2000, Herzog et al. 2003, Anderson et al. 2005, Bellanger et al. 2009). While the impact of STN on non-motor functions appears to be accepted by most authors, its clinical significance is still controversial (Voon et al. 2006). Up to 41% of PD patients treated by STN- DBS face cognitive problems (Temel et al. 2006). However, randomized multicentre studies showed that STN-

DBS does not impair overall cognition or affectivity, although there was a selective decrease in frontal cognitive functions after the treatment (Witt et al. 2008). DBS causes only minor changes in most cases, possibly related to the effect of surgery (Okun et al. 2009). However, at least in some patients the change in cognitive functions after STN-DBS may have a clinical importance.

Intracranial recording studies provide direct access to the deep brain nuclei. Although the electrical event- related activities (evoked as well as induced activities) in the cortical structures during cognitive processing have been quite widely studied, identifying the role of the human subcortical structures has been delayed because of their inaccessibility for scalp measurements. Stereo-electro-encephalography (SEEG) recordings in epilepsy surgery patients have enabled the study of electrophysiological phenomena in the basal ganglia. Generators of cognitive event- related potentials were detected in the putamen, pallidum, caudate, and cortex (Rektor et al. 2003, Rektor et al. 2005). Recent functional neurosurgery has provided the opportunity to record directly from the STN and GPi, most commonly in patients with PD and primary dystonia undergoing implantation of DBS electrodes (Brown and Williams 2005). In studies based on direct recordings from the STN, it has been suggested that the STN takes part in executive functions processing (Baláž et al. 2008, 2010). The role of the frontal cortex in executive functions is well known. We wondered whether the STN might also play a role in other cognitive functions that implicate the frontal cortices. Experiments in animals have shown an involvement of the basal ganglia nuclei in attentional and motivational functions (Baunez and Robbins 1997, 1999 a,b, Christakou et al. 2001, Rogers et al. 2001, Baunez et al. 2002, 2005). Bilateral high- frequency stimulation of the subthalamic nucleus in both intact and parkinsonian rats transiently decreased accuracy in performing a visual attentional task, suggesting impaired attention (Baunez et al. 2007). The aim of this work was to study the involvement of the STN in attentional and orienting processes that are linked to the rare distractor stimuli (Squires et al. 1975, Desmedt 1981, Halgren 1995a).

Methods and materials:

Subjects

Seven Parkinson's disease patients suffering from late L-DOPA-induced motor complications and one primary generalized dystonia patient (suffering predominantly from trunk lateroflexion) with externalized DBS electrodes implanted in the STN or GPi participated in the

study (Table 1, Table 2). We had to exclude three other dystonic patients from the data analysis because their severe abnormal movements produced too many artefacts. All patients were indicated for the DBS surgery by the Commission for Neuromodulation Surgery of the Brno Movement Disorders Centre. All the subjects were informed about the character of this study and gave their informed consent. The study received the approval of the local ethics committee. The measurements were performed during the patient's "on" state in PD, approximately 1 hour after morning dopaminergic medication dose. The medication was stable in all subjects.

Before the operation, all subjects underwent a detailed neuropsychological examination; the examination showed no signs of dementia (Table 3).

Table 1

Table 1 Patient characteristics

Su. No.	Sex	Age (years)	Dg.	Target	Medication	LEDD (mg)	HD	DD (years)
1	M	65	PD	STN	L-DOPA, entacapone, pramipexol, amantadine	1150	Right	13
2	M	55	PD	STN	L-DOPA, entacapone, ropinirole, amantadine	1800	Right	11
3	F	66	PD	STN	L-DOPA, entacapone, ropinirole	1150	Right	6
4	F	69	PD	STN	L-DOPA, entacapone	600	Right	7
5	M	56	PD	STN	L-DOPA, entacapone, rotigotine	1100	Left	7
6	F	68	PD	STN	L-DOPA, entacapone, pramipexol	1450	Right	14
7	F	55	PD	STN	L-DOPA, entacapone, pramipexol	800	Right	12
8	M	50	GD	Gpi	None	0	Right	30

Su. subject, *No.* number, *Dg.* diagnosis, *HD* hand dominance, *DD* disease duration, *LEDD* levodopa equivalent daily dose, *PD* Parkinson's disease, *GD* generalized dystonia, *STN* subthalamic nucleus, *GPi* globus pallidus internus

Table 2

Table 2 DBS clinical effectiveness in PD patients—UPDRS III scores

Subject no.	(1) UPDRS III—preoperative	(2) UPDRS III—postoperative
1	61	20
2	54	40
3	24	6
4	28	11
5	44	NA
6	64	NA
7	39	14

(1) Off medication preoperative, (2) on stimulation/off medication 12 months after operation

Table 3

Table 3 Neuropsychological examination (preoperative)

su	WAIS	Mattis	roI	roL	roR	stI	stW	stC	stWC	TL	MADRS	BDI
1	91	144	51	60	39	54	20	33	34	29	2	3
2	106	144	60	44	47	53	45	44	45	32	10	18
3	90	136	51	51	60	49	38	40	37	NA	17	10
4	116	144	51	51	54	66	48	59	70	32	6	12
5	97	144	51	50	43	60	47	42	31	33	7	9
6	120	140	54	55	55	64	49	55	67	30	6	7
7	100	140	64	64	64	57	36	38	47	31	14	17
8	95	130	NA	NA	NA	NA	NA	NA	NA	28	0	NA

su subject number, *WAIS* Wechsler Adult Intelligence Scale—IQ score, *Mattis* Mattis Dementia Rating Scale—raw score, *roI* Rey-Osterrieth Complex Figure Test, immediate reproduction—*T* score, *roL* Rey-Osterrieth Complex Figure Test, later reproduction—*T* score, *roR* Rey-Osterrieth Complex Figure Test, recognition—*T* score, *stI* Stroop Test-interference—*T* score, *stW* Stroop Test words—*T* score, *stC* Stroop Test colours—*T* score, *stWC* Stroop Test words/colours—*T* score, *TL* Tower of London Test—raw score, *MADRS* Montgomery-Asberg Depression Rating Scale—raw score, *BDI* Beck depression inventory—raw score; *NA* not available

Surgical procedure

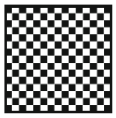
The stereotaxic frame used during the surgical procedure (electrode implantation) was the Leibinger open frame with the Praezis Plus software and the Talairach diagram. The STN coordinates used were in respect to the AC-PC (anterior commissure–posterior commissure) line: 12.0 mm laterally, 5.0 mm below, and 3.0 mm behind the midpoint of the AC-PC line. The GPi coordinates were: 20.0 mm laterally, 4.0 mm below, and 3.0 mm in front of the midpoint of the AC-PC line. The stimulation electrodes (Medtronic, Inc.) were implanted bilaterally into the targeted structure by stereotaxic MRI-guided technique under local anaesthesia (general anaesthesia in the GPi case because of generalized dystonia). The definitive electrode placement was confirmed by four microelectrode recordings. The motor part of the STN was identified by recording the specific patterns of neuronal activity and background activity, and by following motor responsiveness to intraoperative stimulation. Once the final target coordinates were determined, a permanent quadripolar DBS electrode (model 3389, with 1.5 mm contact length and 0.5 mm intercontact distance) was implanted**.** The electrode position was verified by the intraoperative use of fluoroscopy comparing the position of the microrecording electrodes trajectories with the definitive quadripolar macroelectrode trajectory and also by a post- operative CT scan. In the immediate post-implantation period, the electrodes remained externalized. A special externalized cable enabled the intracranial EEG recording. The internalization and the stimulator implantation were performed within a week after the positioning of the DBS electrodes.

Experimental protocol and recordings

The EEG signal was recorded in the post-operative period during which the electrodes were externalized. For cognitive testing, a visual three-stimulus protocol was used (Conroy and Polich 2007, Polich 2007) (see Table 2). The frequent (non-target, standard) stimuli, which were 70% of all the stimuli, were small blue circles. These were not to be followed by a reaction. The target stimuli, which were 15% of all the stimuli, were larger blue circles. The subjects were asked to press an electrically connected button at the time of the target detection. The distractors (rare non-target stimuli), which were presented 15% of the time, were black and white checkerboards; no response was required.

Table 4

Table 4 Experimental paradigm

Category	Description	Image	Dimension	Duration (ms)	Response	Trials	Proportion (%)
Target P3b	Large blue circle		Diameter = 3.5 cm	200	Press a button	30	15
Non-target	Small blue circle		Diameter = 3.0 cm	200	No response	140	70
DistractorP3a	Large black and white checkerboard		Side = 14.0 cm	200	No response	30	15

The interstimulus interval was 4 seconds. The duration of the stimulus exposure was 200 ms. The visual stimuli were presented in a random order on a monitor 1.5 m in front of patients. Subjects received clear instructions and practiced the task briefly before the recordings. Subjects reclined comfortably in the monitoring bed, in a quiet room with a constant temperature. They were instructed to remain calm, to keep their eyes fixed on the monitor, and to avoid unnecessary movements. Subjects received clear instructions and practiced the task briefly before the recordings.

The EEG system TruScan 32 channel (Deymed Diagnostic, Alien Technic) was used for the recording. The recordings were monopolar, with a linked earlobe reference. The sampling rate was 1024 Hz. Standard anti-aliasing filters were used.

Data analysis

The EEG signal was processed and analysed off-line using ScopeWin and ScopeMat software. The data were first segmented according to the visual stimuli trigger onset (vertical line marks in the EEG trace indicating the time of visual stimuli presentation to the subjects). The segments of 4 s length were visually inspected, and segments containing artificial signals or mistaken responses were removed. After trend elimination in each segment, data were filtered with 0.2-40 Hz bandwidths and averaged to obtain evoked responses: event- related potentials (ERPs). The baseline interval was determined 600-100 ms before stimuli presentation. The mean values from the baseline intervals were subtracted within each trial. The unipolar reference (Figure 1) analysis was followed by a bipolar montage (Figure 2) evaluation to exclude the volume conduction from surface neocortical discharges or transsynaptic propagation along cortical- subcortical pathways and confirm the local generation of the potentials (Wennberg and Lozano 2003). Contacts in the STN are placed very close together. Any EEG signal on the common reference is eliminated by a bipolar montage. Even a small bipolar montage activity corresponding with the common reference activity can display the origin of detected activity in the STN.

Time Frequency Analysis (TFA, Figure 3) (Akay 2000) was used to determine the event-related de/synchronizations (ERD/S) in the alpha and beta frequency ranges. A decrease in band power indicates induced event-related desynchronization (ERD), an increase in band power indicates event-related synchronization (ERS) (Pfurtscheller and Aranibar 1977). The ERD of the alpha and beta rhythms is interpreted as a correlate of an activated cortical area with increased excitability. The ERS in the alpha and lower beta bands can be interpreted as a correlate of a deactivated cortical area, i.e. cortical idling or active inhibition (Pfurtscheller 2001). TFA produces a matrix in which each row represents the over trials averaged signal power envelopes in a 2 Hz frequency band width (x-axis represents time; y-axis represents frequency). The frequency step between two lines was 1 Hz. In the baseline-normalized TFA matrix, ERS is represented by positive values (yellow, red) and ERD by negative values (green, blue).

Statistical analysis

Two types of statistical significances were tested:

- The statistical significance of the differences between the mean amplitude observed during the baseline region and the mean value computed as a mean from the neighbourhood of each point (150ms length) after stimuli was expressed as a probability value (p) using a non-parametric Wilcoxon Rank Sum (Signed Rank) test for paired samples. The amplitude changes were considered as significant when $p < 0.05$; see Figure 1 significance to baseline.
- The differences between stimuli were analyzed by the post hoc Scheffe test for multiple comparisons. The level of significance was set at $p<0.01$; see Figure 1 inter-stimuli significance.

Results

We evaluated the signal recorded from four contacts placed in the STN and GPi bilaterally in each subject. The ERP shape was individual; latencies and amplitudes varied according to the stimulus type and among the subjects, and did not fully correspond to the P300 potentials commonly observed from scalp recordings. In six subjects (in subjects 4 and 7 only on the right side) we found a late positivity in the latency range 400-600 ms related to the target stimuli in the STN as well in the Gpi. The majority of the subjects were right-handed and the motor task was performed using the right hand. For this reason, we think that the potentials are not potentials associated with movement (they were present bilaterally or only in the right STN), but that they are related to the cognitive activity processed by target stimuli response performance. The non-target and distractor-related waveforms manifested similar shapes. The amplitude of the distractor ERPs was slightly higher. The most prominent difference between the ERPs was in the appearance of an early positive peak around 200 ms evoked by the distractor that was not displayed after the target and non-target stimuli. This positivity probably reflects the attentional orienting response to the distractor stimuli. This potential was detected in all subjects except subject 3. In subject 7, the EEG signal in the domain of frequent stimuli appeared to be contaminated by artefacts (probably tremor- related) on the left side, however, even in this subject the distractor evoked 200 ms potential could be recorded.

Figure 1

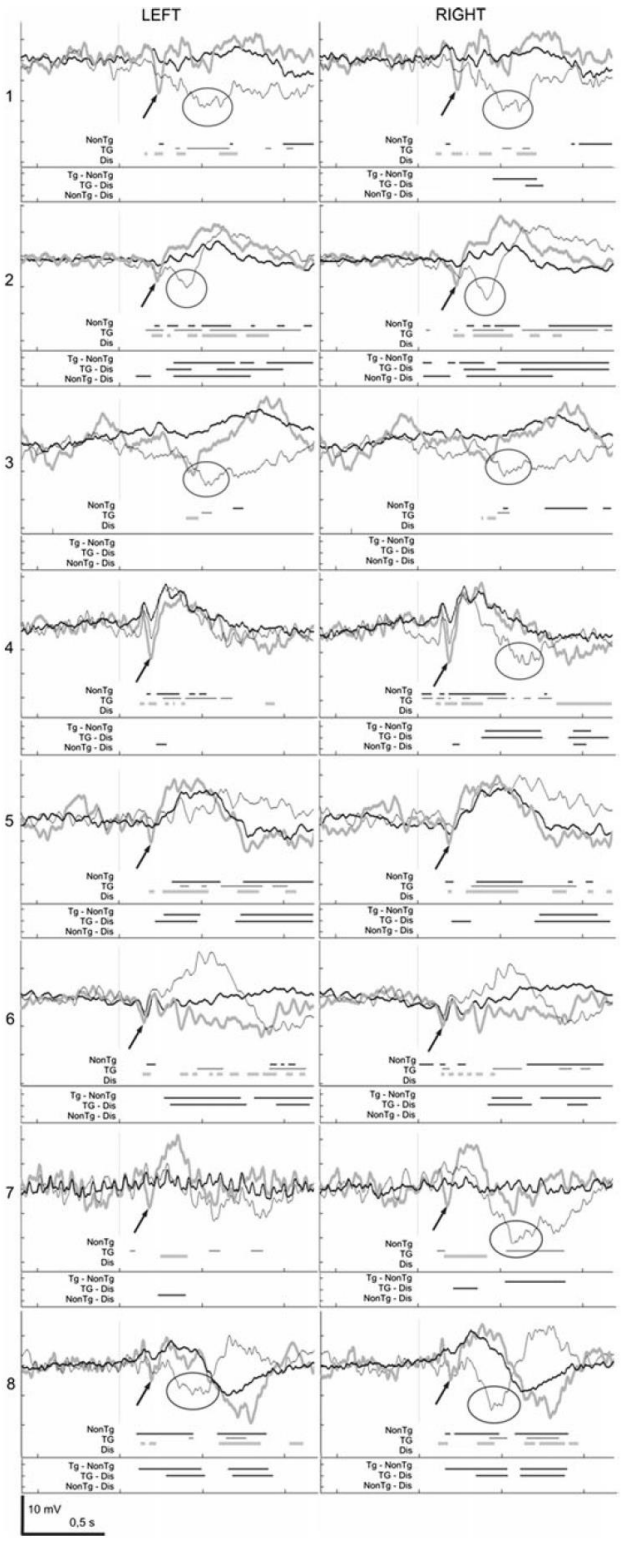
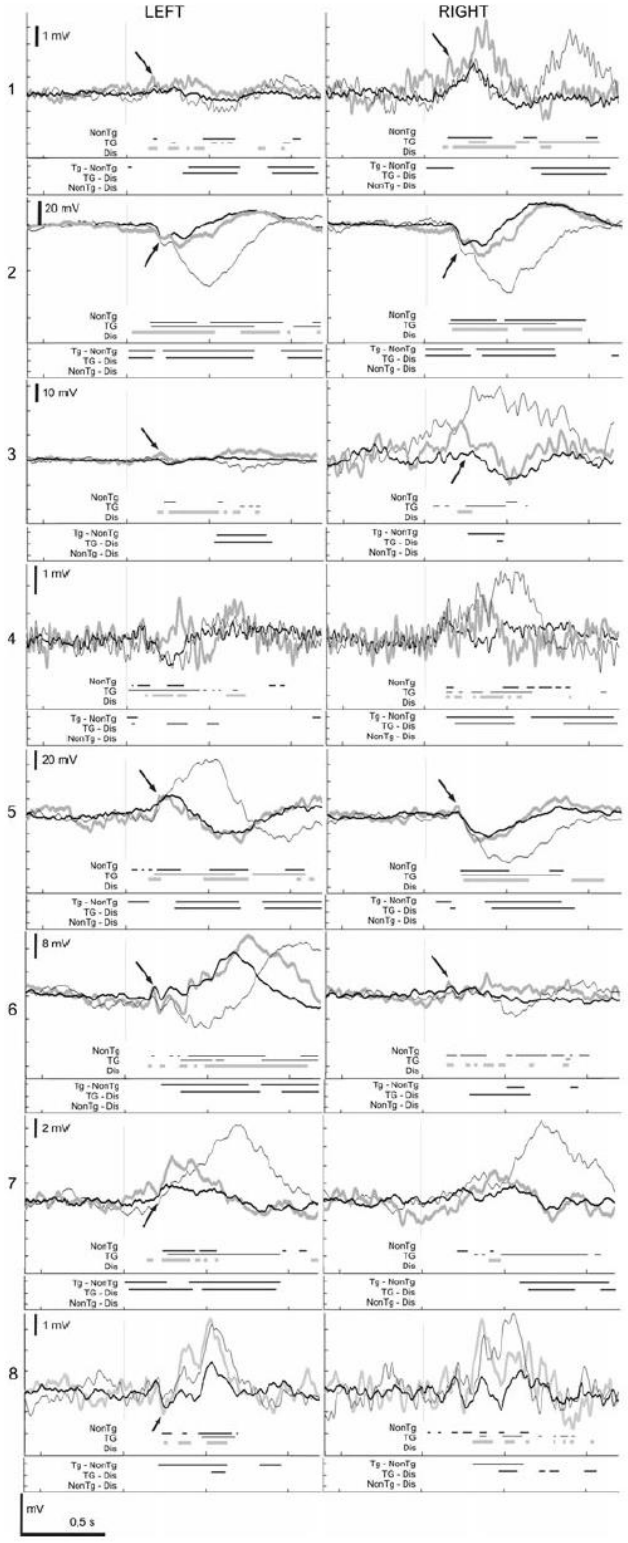


Fig. 1 ERPs recorded in the STN and Gpi. Of the four DBS electrode contacts, the most reactive contact (i.e., the contact with the highest amplitude event-related potential) from the four contacts of the DBS electrodes is shown for each subject. In the majority, the most reactive contact corresponds to the contact located within the STN (or Gpi) as defined by the intraoperative microrecording and the postoperative CT scan. It is usually also the contact with the best clinical effect on motor symptoms during DBS stimulation. Subject no. *1–7* Parkinson's disease STN, subject no. *8* generalized dystonia Gpi. *Thick grey line*—distractor, *medium black line*—non-target, *thin line*—target. The distractor-related early positive peaks with latency around 200 ms are marked by *arrows*. The target-related late positive waves with latency around 400–600 ms are marked by *circles*. *Horizontal bars* below curves indicate significance. *Upper horizontal bars* determine significance to baseline: *thick grey bar*—distractor, *medium black bar*—non-target, *thin bar*—target. *Bottom horizontal bars* determine inter-stimuli significance—pairs are marked on the left

The bipolar montage analysis was also performed, and the local generation of the potentials was confirmed. Local field sources of the distractor- evoked early positive peak were found in six STN PD patients and in the primary dystonia Gpi (Figure 2).

Figure 2

Fig. 2 The most reactive (with the highest amplitude) bipolar montage (montage between the contacts within the DBS electrode). Next description is the same as in Fig. 1. For most subjects, the distractor activity can be observed and is marked with an *arrow*. This activity corresponds to the marked activity in Fig. 1. This finding confirms the assumption that the detected STN activity is not artificial and that this early positive peak originated in the STN (and Gpi). The volume conduction from surface neocortical discharges or transsynaptic propagation along cortical–subcortical pathways are excluded



The induced oscillatory activities (ERD/S) in the alpha and low beta frequency range were analyzed using the TFA. We observed a constant early increase (ERS) in the low alpha band power in all subjects (except subject 3), which corresponds to the specific distractor-related

early peak in ERPs, more pronounced on the right side. In addition, there was a late higher alpha power decrease (ERD) related to the target stimuli (also except in subject 3), which temporally followed the P3b-like wave in the ERPs.

Figure 3

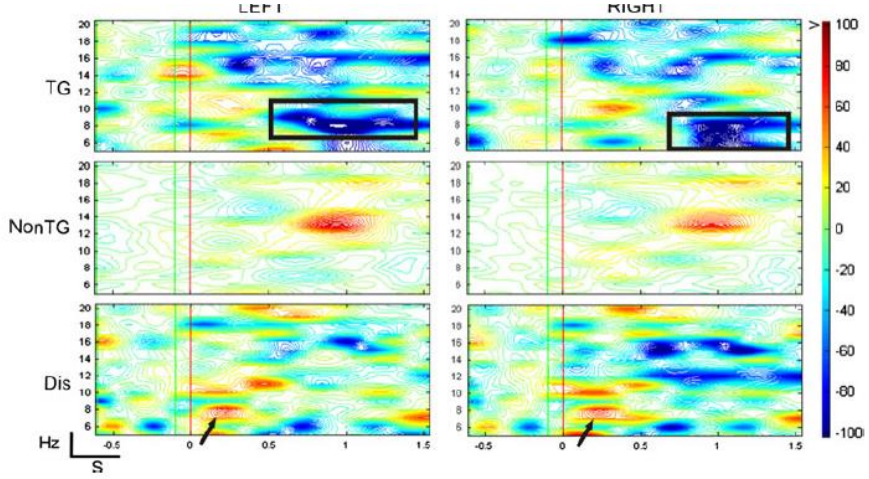


Fig. 3 Time frequency analysis (TFA) in the alpha and low beta frequency range. The *horizontal axis* represents time, *vertical axis* represents frequency. Subject No. 1, contacts in the STN on the left and right side. *Red* indicates ERS—event-related synchronization, increase in band power. *Blue* indicates ERD—event-related desynchronization, decrease in band power. TFA values are normalized to baseline region (*green vertical lines*) 600–100 ms prior stimulus (*red vertical line*). A positive value 100 (ERS) means two times power increase, and a negative value (ERD) −100 means two times power decrease to the mean from the baseline region. ERS values higher then 100 are cut away. The specific distractor-related early ERS is marked by *arrows*, the target-related late ERD by *rectangles*

The different results in subject 3 in comparison to the whole group could have been caused by a worse cognitive performance of the paradigm. The percentage of this patient's correct responses was the lowest (86% subject 3, 98-100% other subjects). The preoperative neuropsychological examination did not show any significant deficits in comparison to the other subjects, only MADRS (Montgomery-Asberg Depression Rating Scale) score was the highest in this subject. We may hypothesise only that depression or a microlesional effect in the STN after the electrode implantation could have caused an attentional deficit during the performance of the experimental paradigm.

Discussion

We studied the electrical phenomena accompanying the cognitive processing recorded in the STN in seven Parkinson's disease patients and in the GPi in one primary dystonia patient.

A three-stimulus visual experimental paradigm was used. This paradigm is similar to the classical oddball task consisting of frequent (non- target) stimuli and rare (target) stimuli that evoke cognitive event- related potential called P300 (or P3). In a three stimulus paradigm a third, non-frequent stimulus appears without any required response (Polich 2007). This distractor stimulus evokes a response called P3a on the scalp (Courchesne et al. 1975, Grunwald et al. 1998, Knight 1984, Knight 1997). This response is task-irrelevant, but insufficiently ignored, and precedes the task-relevant target stimulus evoked potential (called P3b) (Squires et al. 1975, Schröger and Wolff 1998, Kaipio et al. 2000). The distractor-evoked ERP had a frontocentral maximum on the scalp (latency around 375 ms), whereas the target-related ERP had a parietal maximum (latency range 450-475 ms) in a study using the same protocol that was used in this study (Conroy and Polich 2007, Polich 2007). The distractor-related evoked potential is interpreted as an orienting response, an involuntary rapid shift of attention to new (never previously experienced), unexpected (out of context), or unpredictable stimuli. The ERP occurrence indicates that the distractor stimulus has involuntarily captured the attention and is most likely within the focus of attention (Friedman et al. 2001). It was suggested that the distractor-related response represents the cortical component of the early attentional system, while target processing reflects a higher cognitive closure, perhaps including memory processes (Halgren et al. 1995a).

Intracerebral recording in epilepsy surgery patients displayed multiple cortical and subcortical generators of various cognitive ERPs (Rektor et al. 2007). The shape of intracerebral potentials frequently varies, and it is often difficult to identify the equivalents of individual components recorded on the scalp. The generators (steep amplitude gradients or phase reversals indicating a local origin of the potential) of distractor- related ERP were found in several frontal areas, and they were also recorded in more posterior cortical areas, namely the parietal, temporal, and limbic cortices. The latencies in the frontal lobe were shorter than that of P3a recorded on the scalp. The latency of the distractor- evoked ERP in the prefrontal cortex was also shorter than the latency of ERP recorded in the parietal or temporal lobes. A temporal hierarchy within the network for directed attention was suggested, with a key role played by the prefrontal cortex (Halgren et al. 1995a, Halgren et al. 1995b, Baudena et al. 1995). The central role of the prefrontal cortex in directing attention to novel events was also confirmed by other studies (Daffner et al. 2000, Bledowski et al. 2004, Kiehl et al. 2005, Strobel et al. 2008). The prefrontal cortex can have both an excitatory and inhibitory influence on the neural

generators of early ERP components and is involved in early attentional processing stages (Herrmann and Knight 2001).

In our study, as the first step in the analysis, we analysed the ERPs from the STN and Gpi. We observed a late positive potential in the latency range around 500 ms linked to the target stimuli processing. The distractor stimuli were accompanied by a specific short positive peak in the latency range around 200 ms. ERP latency depends on the classification speed, which is proportional to the time required to detect and evaluate the stimulus (Kutas et al. 1997, Magliero et al. 1984, Polich 2007). The latency of this early distractor-specific potential might indicate a fast evaluation and categorisation of the distractor stimuli in the basal ganglia. The nearly simultaneous appearance of the early distractor-specific potentials in the two structures forming consecutive parts of the cortico-basal ganglia-thalamocortical circuitry, i.e. GPi and STN, may be interpreted as a sign of the specific involvement of the basal ganglia in orienting and attentional processes. Local field generation of this early distractor related activity was confirmed using the bipolar montage analysis. The only patient with GPi electrodes also displayed a short latency distractor- evoked potential. Unfortunately, we had to exclude other dystonia Gpi patients because of severe abnormal movement- related artefacts. We decided to present the data from the only analysable subject because the results were interesting in the context of the STN recordings and because technically correct recordings from Gpi in dystonia are rare. We are aware that data obtained from only one subject must be further verified by recordings in more subjects.

Event-related cerebral activity may be evoked or induced. Evoked potentials (ERP) are time and phase locked to the stimuli. Induced changes (ERD/S) are time locked, but not phase locked to the stimuli. As the second step, we were interested in the relationship of the ERP to the ERD/S, especially in the lower and higher alpha frequency range, as it is known that alpha band spectral power co-varies with P300. Other frequency ranges demonstrate similar associations, but slow alpha activity yields the strongest correlation (Intriligator and Polich 1995, Polich 1997). Alpha ERD occurs during cognitive processing; target related P3 potential is clearly related to the desynchronization of late alpha frequency EEG (Boiten et al. 1992, Pfurtscheller and Klimesch 1991, Klimesch 1997, Pfurtscheller and Klimesch 1992, Polich 2007, Sergeant et al. 1987, Yordanova et al. 2001). We have observed ERD in higher alpha frequencies following the late positive response in the ERP (latency 500-1500ms) induced by the target stimuli. This probably represents the performance of the target-related cognitive-

motor response. An early lower alpha frequency band ERS was observed exclusively after the distractor stimuli. There was a temporal overlap of the distractor specific ERS and ERP. As the ERS in the alpha band is considered as a correlate of an active inhibition, this reaction probably represents suppression of an involuntary shift of attention and then inhibition of further cognitive processing of the distractor stimuli. Both early distractor related ERS and ERP may share common mechanism with the N200 response in the scalp recordings. The amplitude of N200 is higher in stop trials than in go trials in go/no and stop-signal tasks (Enriquez-Geppert et al. 2010). The inferior-frontal cortex (IFC) plays an inhibitory role in motor control. It was demonstrated that the IFC may modulate various cognitive functions of the basal ganglia and specifically of the STN via a direct functional projection between the IFC and the STN (a "hyperdirect" pathway) (Aron and Poldrack 2006, Aron et al. 2007, Balaz et al 2010). Apart from the striatum, the subthalamic nucleus (STN) is the only structure in the basal ganglia that receives a direct cortical projection (Albin et al. 1989; Parent and Hazrati). For this reason, we would expect a later latency of the attentional phenomena in the Gpi. An early positive peak was present in the Gpi at around 200 ms after the distractor stimuli. In the Gpi, a slow wave with a latency around 800 ms following the distractors was also observed. The early activation of the STN may lead to response suppression (in our case, inhibition of further cognitive processing of the distractor stimuli and suppression of the motor response). The co-activation of the Gpi (Mink 1996) may lead to subsequent inhibition of the thalamo-cortical motor program (Coxon et al. 2006, Aron et al. 2007).

We evaluated the human event-related EEG signal recorded via intracerebral depth electrodes. The main disadvantage of all intracerebral recordings is that they are performed in structures that could be modified by pathological processes (in this case by Parkinson's disease and generalized dystonia) and that the results could be influenced by medication. The other limitation of this study is the absence of simultaneous scalp recordings (Fz, Cz, Pz), which could not be placed because of the sterile bandaging over the parietally localized electrode extensions as we respected the patients safety and the prevention from infectious complications. On the other hand, as the depth electrodes are submerged directly into the brain tissues and record from their immediate vicinity, the results are obtained directly from cerebral structures. Some of them are almost inaccessible by scalp measurements, so the data measured by the depth recordings provide important information about the function of the subcortical structures. We performed simultaneous scalp recordings (Fz, Cz, Pz- in this case

they could be placed because of other electrode trajectory) using the same experimental paradigm in an epilepsy surgery group of patients with implanted deep brain electrodes. We did not observe the distractor- related early short positive peak on the scalp.

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3.9 Cognitive Event-Related Potentials and Oscillations in the Subthalamic Nucleus

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Commentary:

The review article presented below corroborated our previous papers on STN recordings that were commented on above.

According to our earlier studies based on intracerebral recordings of cognitive event-related potentials (ERPs) in epilepsy surgery candidates, the cognitive activities in the basal ganglia (BG) are organized in some way other than the well-known organization of the cortico-BG-thalamocortical circuits (Rektor et al. 2005) . We report the results of three substudies here. In the first two, the auditory oddball ERPs were recorded from the area of the subthalamic nucleus (STN). Finally, a cognitive event-related desynchronization/ synchronization (ERD/S) study in α- and β-frequency bands was performed. Our results indicate a specific, task-related involvement of STN in the cognitive activities. Cognitive processing in STN is possibly processed via hyperdirect cortico-STN pathway. Certain effects of deep brain stimulation surgery on cognitive performance could be explained by a direct effect on 'cognitive' parts of the STN.

As a co-author I participated in conception of idea for an article, was a first author of two out of three articles reviewed in the following article.

Cognitive Event-Related Potentials and Oscillations in the Subthalamic Nucleus

Ivan Rektor, Marek Baláž, Martina Bočková

First Department of Neurology, Masaryk University, St. Anne's Hospital, Brno , Czech Republic

Prof. Dr. Ivan Rektor, CSc
First Department of Neurology, Masaryk University
St. Anne's Hospital, Pekarska 53

CZ–656 91 Brno (Czech Republic)
Tel. +420 543 182 623, Fax +420 543 182 624, E-Mail irektor @ med.muni.cz

Key Words

Cognitive activities; Subthalamic nucleus; Basal ganglia; P3-like potential; Event-related desynchronization/synchronization

Abstract

Background: The cognitive role of the subthalamic nucleus (STN) remains largely unknown.
Methods/Results: A modified protocol with a dual task elicited local field event-related potentials (ERPs) within the STN. No generators of ERPs were elicited by the standard oddball protocol in the STN (at variance with recordings from the putamen, caudate and pallidum). Repetitive transcranial magnetic stimulation (rTMS) over the right inferior frontal cortex caused a shortening of latencies of ERPs in standard and dual protocols. No changes were observable after the rTMS over the dorsolateral prefrontal cortex and sham stimulation. In the STN, only the tasks with an increased demand on executive functions produced the α -/β -event-related desynchronization/synchronization in visuomotor tasks with single letters writing.
Conclusion: Our results indicate a specific, task-related involvement of the STN in the cognitive activities. Cognitive processing in the STN is possibly processed via hyperdirect cortico-STN pathway. Certain effects of deep brain stimulation surgery on cognitive performance could be explained by a direct effect on 'cognitive' parts of the STN.

According to our earlier studies based on intracerebral recordings of cognitive event-related potentials (ERPs) in epilepsy surgery candidates, the cognitive activities in the basal ganglia (BG) are organized in some way other than the well-known organization of the cortico-BG-thalamocortical circuits [1] . We report the results of three substudies here. In the first two, the auditory oddball ERPs were recorded from the area of the subthalamic nucleus (STN). Finally, a cognitive event-related desynchronization/ synchronization (ERD/S) study in α- and β-frequency bands was performed.

Methods

Recordings were obtained from patients with Parkinson's disease from externalized four-contact deep brain stimulation (DBS) electrodes implanted in the STN. Usually, two of the four contacts of each electrode (0.5-mm intercontact distance and 1.5 mm electrode contact width) were positioned inside the STN according to clinical effect, perioperative microrecording and stimulation. The recording of bioelectrical activity was performed during the interoperative period (before battery implantation). Recordings were performed using the 8-channel Nihon Kohden Neuropack 4200EP/EMG device, and later using the 32-channel EEG system TruScan Alien. The signal was filtered in the range 1–200 Hz, time base 1,200 ms; a biauricular reference electrode was used. The sampling rate was 256 Hz.

In 10 patients, involvement of STN in executive functions was tested by an auditory oddball paradigm [2] . Tones were delivered through earphones, at a 2-Hz frequency: frequent tones were delivered at 1,000 Hz and 70 dB, for 0.1 s; rare (target) tones were delivered at 2,000 Hz and 70 dB, for 0.1 s. The tones were randomly generated at a 5: 1 ratio. The subjects were instructed to recognize the target tones and to silently count them in the standard protocol. A modified paradigm increased demands on executive functions.

The tasks consisted of silently changing a date upon each target presentation. The subjects were given a two-item date which included the day of the week and the ordinal date (e.g. Monday the 19th). The date had to be updated after each target stimulus [2] .

We found a local source, a steep rise in amplitude, in the ERPs (P3-like potential) recorded during the dual task protocol within the STN in 8 of the 14 electrodes. In the remaining 6 electrodes, there were no ERP generators present. The occurrence of generator activity in STN was significant (p ! 0.0001; test of homogeneity of binomial distribution). We did not observe a voltage change in the ERPs recorded during the standard protocol. ERP latencies were significantly longer in the modified protocol in the contacts with the best motor response (Wilcoxon matched pairs test). In the second study, we raised the question whether the STN connections with cortical structures influence its participation in cognitive functions and examined two possible candidates for such a cooperation – the dorsolateral prefrontal cortex (DLPFC) and the inferior frontal cortex (IFC).

The repetitive transcranial magnetic stimulation (rTMS) modifies the cortical excitability. One rTMS session (600 pulses) of 1-Hz stimulation was delivered to each patient over the right IFC (BA 44) or over the right DLPFC (BA 9, 46). The DLPFC has been associated with executive

functions and with higher cognitive functions, while the IFC was shown to be important for the executive functions as well. The direct connection between the IFC and
the STN – the 'hyperdirect' pathway and its putative influence on motor aspects of STN activity has been described earlier. The ERPs were recorded using the same method and technique as described above. rTMS over the right IFC caused a statistically significant shortening of latencies of ERPs in both protocols in all patients. No such changes were observable either after the sham rTMS of IFC or after the active rTMS of the DLPFC area.

There was again a voltage change present in the STN with a modified protocol.

The aim of this work was to examine the involvement of the STN in the neurocognitive networks in four visuomotor cognitive tasks with single letters writing. The α- and β-ERD/S was used as the method of the EEG signal analysis. The ERD of the α - and β - bands is interpreted as a correlate of an activated cortical area, and the ERS correlate of a cortical deactivation.

The EEG signal was recorded from the STN in 5 patients. The used experimental protocol was previously tested in a SEEG study in epilepsy surgery patients and showed a specific activation of the prefrontal and lateral temporal neocortex [3] . The letters of the alphabet, presented in a random order on a monitor, served as the visual stimuli. The duration of the stimulus exposure was 200 ms, of the interstimulus interval 16 s; the mean number of trials
was 50. Subjects performed four visuomotor cognitive tasks: (1) single letter counting, (2) copying, (3) writing another letter (planning, inhibition of automatic responses) and (4) writing another letter inversed (planning, inhibition of automatic responses, mental inversion). Data were first segmented according to the stimulation trigger onset. The individual frequency windows were determined in the α -band (7–14 Hz) and the β -band (16–30 Hz) using time frequency analysis (TFA). The trials were processed by a complex demodulation technique to ascertain the envelope of power in the individual frequency bands and averaged. A decrease in band power indicates induced (nonphase-locked,
noncoherent) ERD, and an increase in band power indicates event-related synchronization ERS. The significance of the differences between the mean power observed during the baseline and that measured inside evaluated interval was expressed as a probability
value (p) using a nonparametric Wilcoxon rank sum (signed rank) test for paired samples.

Results

The α - and β-ERD were expressed during the two more complex tasks with increased demand on the executive functions: task 3 (in 3 of 5 subjects) and task 4 (in
4 of 5 subjects; table 1). No significant changes were detected during the first two tasks.
The results demonstrated specific and selective activation in the STN evoked by complex cognitive tasks.

Table 1. ERD (%) in α- and β-frequency ranges during performance of the four tasks of the experimental protocol

Subject No.	ERD			
	task 1	task 2	task 3	task 4
1	0	0	–40%, IF 12–16 Hz bilaterally	NA
2	0	0	0	–60%, IF 14–20 Hz bilaterally
3	0	0	0	–50%, IF 10–14 Hz bilaterally
4	0	0	–40%, IF 10–14 Hz right side	–30%, IF 14–18 Hz right side
5	0	0	–50%, IF 8–18 Hz bilaterally	–60%, IF 14–18 Hz bilaterally

IF = Individual frequency; 0 = no significant changes.

Discussion

The role of the BG in cognitive processing is largely unknown. An integrative role of the BG, with subsequent modulation of cortical cognitive processing has been suggested [1] . In some cases, direct connections with the cortex that bypass the circuitries might underlie the processing of specific cognitive functions. This might be the case of STN. The standard oddball ERP (P3-like potentials) was recorded in the putamen, caudate and pallidum [1]
but not in the STN. STN seems to be specifically involved in the processing of some cognitive activities, e.g. of the executive functions. A modified protocol with a dual task elicited local-field ERPs within the STN. rTMS 1 Hz over the right IFC caused a significant shortening of latencies of ERPs in both protocols. No such changes were observable either after the sham rTMS or after the active rTMS over the DLPFC. In the STN, only the tasks with an increased demand on executive functions produced the α - and β -ERD/S. ERD/S was tested in visuomotor tasks with single letters writing. Our results indicate a specific, taskrelated involvement of the STN in the cognitive activities. Cognitive processing in the STN is possibly processed via a hyperdirect pathway. These findings are more intriguing if we consider that

our target was either directly in the motor part of the STN or in its immediate vicinity, according to the perioperation microrecording results and the effect of the DBS procedure on the motor performance of the patients. The neuronal pools involved in cognitive activities may be located in close vicinity to, or even overlap with, the neurons active in motor functions. Certain effects of DBS surgery on cognitive performance could be explained by a direct effect on 'cognitive' parts of the STN.

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4 Conclusion

STN occupies an influential position within BG structure. Despite being primarily a motor structure, results of our research indicate that STN takes active part in cognitive and non-motor activities. Its participation in these activities is conditioned by the difficulty of the task, i.e. it participates in more demanding cognitive tasks.

With growing numbers of procedures and centers involved in deep brain stimulation for treatment of movement disorders and other conditions, interest in various aspects of stimulation keeps growing.

It seems that STN cooperates directly with the inferior frontal cortex in its cognitive-related performance. The connection of subthalamic nucleus with the dorsolateral prefrontal cortex seems to be at best indirect. Modulation of STN activity by continuous DBS can influence wide array of non-motor function in addition to its well described and usual effect on motor symptoms of PD.

From its subcortical position it has a potential to influence cortical structures via direct connections with IFC. Our findings are in line with a concept of BG having potential to modulate the cortical cognitive processing.

We have also described improvement of some non-motor aspects by increasing the amplitude of DBS STN.

The proof of participation of subthalamic nucleus in executive functioning underlines the need of meticulous selection of candidates for deep brain stimulation surgery of this target in PD. We plan to develop a new application for evaluation of cognitive status prior to DBS in order to further refine candidate selection process.

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