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Pallidal stimulation in dystonia affects cortical but not spinal inhibitory mechanisms

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ABSTRACT

Background: Deep brain stimulation (DBS) of the globus pallidus interna is an effective tool for the treatment of dystonia with possible distant effects reaching beyond the basal ganglia network.
Aim: We analyzed the cortical silent period (CoSP) to test inhibitory circuits at the cortical level, and the cutaneous silent period (CuSP) and the H-reflex to test inhibitory circuits at the spinal level.
Methods: The upper limb muscles of 16 patients (9F, aged 54 ± (SD)16 years) with generalized (N = 9) and cervical (N = 7) dystonia treated with DBS bilaterally were examined by the CoSP, CuSP and H-reflex in two states with random order: (i) in DBS ON and (ii) in DBS OFF condition two hours later, and compared with healthy controls.
Results: While the CuSP and H-Reflex did not differ between groups and remained unaffected by DBS, the CoSP was influenced significantly in dystonia. The CoSP onset latency was shortened ($p < 0.05$ corrected) and the CoSP duration prolonged ($p < 0.01$ corrected) in ON versus OFF condition. This effect was especially larger in generalized or phasic type of dystonia. Compared to healthy controls, the CoSP latency and duration became shorter in patients during the OFF condition only.
Conclusion: The pallidal DBS did not affect the spinal inhibitory circuitry in dystonia. However, the abnormally low cortical inhibition was normalized after DBS possibly offering more efficient suppression of aberrant dystonic movements.

1. Introduction

Dystonia is a syndrome marked by involuntary muscle contractions causing twisting movements and abnormal postures in a relatively unchanging pattern [1,2], which can be positively influenced by deep brain stimulation (DBS) of the globus pallidus interna (GPi) [3–5]. However, pathophysiological mechanisms of DBS on dystonia are poorly understood.

Dystonic syndromes are heterogeneous in terms of causes, body distribution and age at the onset of dystonia [2,6,7]. Several abnormalities appear to underlie the pathophysiology of dystonia [8,9]. Firstly, the loss of inhibitory function at spinal, brainstem and cortical levels, which is probably responsible for the excess of movement and overflow phenomena in dystonia [9–11]. Secondly, abnormalities in dystonia are related to disturbed sensorimotor integration at different levels of the central nervous system (CNS) such as the spinal cord, brainstem, basal ganglia and cortex [8,12–14]. For yet unclear reasons, sensory stimuli are misdetected and misinterpreted leading to various functional changes resulting in an aberrant motor pattern [15] especially when complex movements are executed [16]. And thirdly, there is the disruption of homeostatic plasticity, with a prevailing facilitation of synaptic potentiation [17,18] supporting dystonia as a disorder with easy formation of aberrant neuroanatomical connections and with limited inhibition to unwanted co-activated movements.

As previously suggested dystonia is a widely distributed disorder involving the entire sensori-motor network. Therefore, GPi DBS effects in dystonia are probably not limited to the stimulated area and they could also propagate far beyond the basal ganglia. Indeed, some effects of DBS were observed subcortically and cortically by transcranial magnetic stimulation (TMS) and functional imaging, but these results were mostly derived from subthalamic DBS in patients with movement disorders other than dystonia [19–24]. The low number of electrophysiological studies brought rather variable results showing detectable [25] or absent GPi DBS effects on cortical inhibition and reporting some DBS-related increase in the motor threshold [26]. However, there is a lack of evidence on the impact on the cortical and spinal cord circuitry in chronically treated dystonia patients with GPi DBS.

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In our study, we searched for distant effects of GPi DBS manifested in the central or peripheral nervous system using the clinical electrophysiology approach. Expecting impaired inhibition, we tested the cortical silent period to detect GPi DBS-related effects on inhibition at the cortical level. To detect possible GPi DBS effects on inhibitory circuits at the spinal cord, we used the cutaneous silent period and the H-reflex.

The cortical silent period (CoSP) can be elicited by transcranial magnetic stimulation (TMS) of the motor cortex. It is defined as a post-excitatory interruption of ongoing electromyographic activity following the motor evoked potential in a voluntarily contracted target muscle [27]. The CoSP has two phases, first–spinal and the second–cortical, which is thought to be affected by the $GABA_B$ receptor-mediated inhibition [28]. The CoSP has been used in research of various neurological disorders with motor involvement and effects of treatment [29–33].

The cutaneous silent period (CuSP) is the robust cutaneomuscular reflex manifested by a short pause in the electromyographic activity during a voluntary isometric contraction in response to a painful stimulus applied to a cutaneous nerve. It is considered as a spinal inhibitory reflex [34–37] and is mediated predominantly by small-diameter sensory fibers entering the spinal dorsal horn to suppress the activity in spinal motor nuclei in neighboring myotomes [35,36,38,39]. The CuSP is altered not only in diseases affecting the centromedullar part of the spinal cord [40–42] but also in neurodegenerative movement disorders such as Parkinson's disease and multiple system atrophy [43,44].

The H-reflex is the pure mono-synaptic spinal reflex mediated via sensory afferent and motor efferent fibers of the peripheral nerves and roots with muscle contraction after electrical stimulation of peripheral sensory fibers [45]. As the stimulus increases the H-reflex decreases, a phenomenon, which is under strong regulatory influence from the spinal cord. The usefulness of the H-reflex was well documented on the inhibitory effects of neuro-modulatory treatment with intrathecal baclofen in patients with spastic syndromes [46].

The aim of the study was to detect GPi DBS-related effects on inhibitory mechanisms. We studied the CoSP, CuSP and H-reflex in both conditions with the implanted neurostimulator bilaterally switched ON and OFF for a limited period of two hours and neglecting persistent after-effects of neurostimulation. As the GPi DBS is accompanied with clinical improvement of dystonia we hypothesized that switching neurostimulator ON will normalize impaired inhibition especially at the cortical level.

2. Material and methods

We included 16 patients (9 women, mean age 54 ± (SD)16 years, right hand domination) with dystonia of various distribution (7 cervical, 9 generalized) and origin (14 idiopathic, 1 DYT-1, 1 post-anoxic) with disease duration 14 ± 5 years (Table 1). All patients were treated with bilateral GPi DBS, were on stabile oral medication at least 8 weeks prior enrollment and were examined 23–96 months after implantation. Nine right-handed volunteers (2 women, mean age 48 ± 18 years) without history of neuropsychiatric disorders served as healthy controls. All subjects gave their informed consent to participate and the study was approved by the local ethics committee in compliance with the Declaration of Helsinki.

The study was designed as an open-label with two un-blinded sessions each lasting about one hour separated by a two hour break. The session with patients was carried out either (i) in the GPi DBS ON or (ii) in the GPi DBS OFF state in random order. The clinical scores and electrophysiology testing were assessed in each session. Healthy controls were tested only during one session. Neurophysiological studies were performed using routine electrodiagnostic equipment (EMG Medelec Synergy, version 15.0.).

2.1. GPi DBS specification

All patients were implanted bilaterally with a quadripolar electrode (8 patients with model 3358, generator RC, Medtronic, MN; 3 patients with model 7428, generator Kinetra, Medtronic, MN; 5 patients with

Table 1
Clinical data of the patients group.

#	Age	Sex	Etiology	Body distribution	Tonic/phasic	Dystonia duration (years)	GPi DBS duration (years)	BFMDS PREOP	BFMDS GPi DBS ON	BFMDS GPi DBS OFF	Medication (dose per day)
1	71	M	Idiopathic	Generalized	Tonic	10	4	15	12	12	Mirtazapine 15 mg
2	61	M	Idiopathic	Generalized	Phasic	12	5	39	21.5	30	Biperidene 16 mg
5	64	F	Idiopathic	Generalized	Tonic	10	4	21	15	19.5	Bromazepam 2,25 mg, tramadol 200 mg, venlafaxin 150 mg
7	56	F	Idiopathic	Generalized	Tonic	10	4	33	14	14	Trazodone 150 mg, venlafaxin 150 mg, alprazolam 0,25 mg
8	20	M	DYT1	Generalized	Phasic	10	7	28.5	11	17	–
10	44	F	Idiopathic	Generalized	Tonic	17	8	29	29	29	Clonazepam 1 mg, citalopram 40 mg, biperidene 3 mg, hydromorphone 32 mg
11	53	F	Idiopathic	Generalized	Tonic	27	4	50	18.5	27	Escitalopram 10 mg
15	28	M	Post-anoxic	Generalized	Phasic	16	2	51	51	51	Clonazepam 3,5 mg, biperidene 3 mg, baclofen 20 mg, venlafaxin 225 mg, valproate 600 mg
16	75	M	Idiopathic	Generalized	Tonic	12	4	8	1	1	–
								TWSTRS PREOP	TWSTRS GPi DBS ON	TWSTRS GPi DBS OFF	
3	58	M	Idiopathic	Cervical	Tonic	10	6	29	15	25	Alprazolam 1 mg
4	60	F	Idiopathic	Cervical	Tonic	15	9	24	15	22	Biperidene 2 mg, clonazepam 0,75 mg, sertraline 100 mg
6	78	F	Idiopathic	Cervical	Tonic	12	4	25	24	24	Escitalopram 10 mg, biperidene 2 mg, gabapentin 300 mg, clonazepam 0,5 mg
9	53	F	Idiopathic	Cervical	Tonic	17	5	20	16	17	Baclofen 20 mg, venlafaxin 150 mg, amisulpride 50 mg
12	46	F	Idiopathic	Cervical	Tonic	22	5	24	18	19	Agomelatonine 50 mg, citalopram 30 mg, alprazolam 0,5 mg, quetiapine 50 mg
13	58	F	Idiopathic	Cervical	Tonic	9	2	26	21	22	Clonazepam 1 mg, primidone 325 mg, citalopram 20 mg
14	44	M	Idiopathic	Cervical	Tonic	12	6	24	6	21	–