CLARICE LISTIK

EFEITOS DA ESTIMULAÇÃO CEREBRAL PROFUNDA NOS LIMIARES SENSITIVOS E DE DOR EM PACIENTES DISTÔNICOS

Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Mestre em Ciências

Programa de Neurologia
Orientador: Prof. Dr. Daniel Ciampi Araujo de Andrade

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CLARICE LISTIK

EFFECTS OF DEEP BRAIN STIMULATION ON SENSORY AND PAIN THRESHOLDS IN DYSTONIC PATIENTS

Dissertation presented to the Faculdade de Medicina da Universidade de São Paulo to obtain the title of Master in Sciences.

Department of Neurology

Advisor: Prof. Dr. Daniel Ciampi Araujo de Andrade

Sao Paulo

2020

DEDICATION

To my parents, Marcia and Sergio, for the unparalleled support, company, and daily inspiration. To my brother Eduardo for his enthusiasm, dedication, help and scientific encouragement.

To patients with dystonia, from whom I learned that anything is possible, and whose determination and efforts know no boundaries, despite the difficulties faced.

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EPIGRAPH

“Learning never exhausts the mind.”

Leonardo da Vinci (1452-1519)

ADOPTED NORMALIZATION

This dissertation is in accordance with the following norms, currently adopted at the time of this publication:

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The journals titles' abbreviations are in accordance with the List of Journals Indexed in Index Medicus.

SUMMARY

LIST OF FIGURES

LIST OF TABLES

LIST OF INITIALS

Initial	Definition
BFM	Burke-Fahn-Marsden dystonia scale
BPI	Brief Pain Inventory
C-TS	Conditioned test stimulus
CAPPesq	*Comissão de Ética para Análise de Projetos de Pesquisa*
CD	Cervical dystonia
CDT	Cold detection threshold
CONEP	*Conselho Nacional de Ética em Pesquisa*
CPM	Conditioned pain modulation
CPT	Cold pain thresholds
CT	Computed tomography
DBS	Deep brain stimulation
DLPT	dorsolateral pontomesencephalic tegmentum
DN4	*Douleur Neuropathique-4*
DNIC	Diffuse noxious inhibitory control
ECP	*Estimulação Cerebral Profunda*
EP	Experimental pain
FAB	Frontal Assessment Battery
GABA	Gamma-aminobutyric acid
GPe	Globus pallidus externus
GPi	Globus pallidus internus

HADS	Hospital Anxiety and Depression Scale
HC-FMUSP	*Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo*
HPT	Heat pain thresholds
HV	Healthy volunteers
LTP	Long-term potentiation
MCD	*Modulação condicionada de dor*
McGill	Short-form McGill pain questionnaire
MDT	Mechanical detection thresholds
MH	Mechanical hyperalgesia
MPT	Mechanical pain thresholds
MRI	Magnetic resonance imaging
NMS	Non-motor symptoms
NPSI	Neuropathic Pain Symptom Inventory
OCD	Obsessive-compulsive disorder
PAG	Periaqueductal gray
PAS	Paired associative stimulation
PD	Parkinson’s disease
PET	Positron emission tomography
PKAN	Pantothenate kinase-associated neurodegeneration
QoL	Quality of life
QST	Quantitative sensory testing
RVM	Rostral ventromedial medulla
S.D.	Standard deviation

SF-12	12-Item Short-Form Health Survey quality of life questionnaire
SF-36	36-Item Short-Form Health Survey quality of life questionnaire
SNc	*Substantia nigra pars compacta*
SNr	*Substantia nigra pars reticulata*
SPSS	Statistical Package for the Social Sciences software
SuC	Pain rating to experimental pain cold stimulus
SuH	Pain rating to experimental pain heat stimulus
TMS	Transcranial magnetic stimulation
TS	Test stimulus
TSQ	*Teste de sensibilidade quantitativa*
U-TS	Unconditioned test stimulus
VAS	Visual analog scale
VDT	Vibration detection threshold
VS	*Voluntários saudáveis*
WDT	Warm detection threshold

RESUMO

Listik, C. *Efeitos da estimulação cerebral profunda nos limiares sensitivos e de dor em pacientes distônicos* [dissertação]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2020.

Introdução: Diferente dos sintomas motores, os efeitos da Estimulação Cerebral Profunda (ECP) sobre os sintomas não motores das distonias ainda é desconhecido. O objetivo desde estudo foi analisar os efeitos da ECP sobre os limiares sensitivos e de dor experimental em um estudo duplo cego ligado/desligado, *cross-over* e comparar estes resultados com os de voluntários saudáveis (VS). Método: Dezesseis pacientes com distonia idiopática (39,9 $\pm$ 13 anos, n = 14 generalizados, n = 2 segmentares) com ECP no globo pálido interno realizaram uma bateria de teste de sensibilidade quantitativa (TSQ) e uma avaliação do sistema modulatório descendente de dor (modulação condicionada de dor, MCD). Resultados de regiões corporais com mais e menos distonia foram comparados nas condições de estimulação ligada e desligada. Os resultados do TSQ e do MCD dos pacientes foram comparados aos de VS com idade e sexo semelhantes. Resultados: A resposta de modulação descendente de dor (MCD) dos pacientes distônicos (0,66 $\pm$ 1,99) foi anormalmente elevada quando comparada à dos VS (-0,43 $\pm$ 0,29, p = 0,0001). Os parâmetros do TSQ dos VS diferiram dos pacientes distônicos, nos quais o limiar de detecção do frio e a dor reportada no supralimiar de estimulação ao frio foram 54,8% e 95,7% maiores nos pacientes distônicos, respectivamente. A MCD durante a ECP ligada correlacionou-se a um escore de incapacidade de Burke-Fahn-Marsden (BFM) maior (r = 0,598; p = 0,014). Enquanto os limiares sensitivos e de dor não foram diferentes com a ECP ligada/desligada, a modulação de dor dos pacientes distônicos foi marcadamente menor e parece ser mais pronunciada pela ECP. Conclusão: A ECP não parece promover mudanças nos limiares sensitivos e de dor na distonia. Pacientes distônicos têm limiares sensitivos e modulação descendente de dor diferente dos VS, o que está em linha com a teoria de perda da discriminação espacial na distonia.

Palavras-chave: Distonia, estimulação cerebral profunda, dor, limiares sensitivos, sintomas não-motores

ABSTRACT

Listik, C. *Effects of deep brain stimulation on sensory and pain thresholds in dystonic patients* [dissertation]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2020.

Introduction: Unlike motor symptoms, the effects of deep brain stimulation (DBS) on non-motor symptoms associated with dystonia remain unknown. The objective of this study was to assess the effects of DBS on evoked experimental pain and sensory thresholds in a cross-over, double-blind on/off study, and compare these results with those of healthy volunteers (HV). Methods: Sixteen patients with idiopathic dystonia (39.9 $\pm$ 13 years old, n = 14 generalized, n=2 segmental) with DBS of the *globus pallidus internus* underwent a battery of quantitative sensory testing (QST) and assessment using a pain top-down modulation system (conditioned pain modulation, CPM). Results for the more and less dystonic body regions were compared in the on and off stimulation conditions. The patients’ QST and CPM results were compared to age- and sex-matched HV. Results: Descending pain modulation CPM response in dystonic patients (0.66 $\pm$ 1.99) was abnormally high compared to HV (-0.43 $\pm$ 0.29, p=0.0001). HV’s QST parameters differed from those of dystonic patients, in which the cold detection threshold and the pain rating to suprathreshold cold stimulation were 54.8% and 95.7% higher in dystonic patients, respectively. On-DBS abnormal CPM correlated with higher Burke-Fahn-Marsden (BFM) disability score (r = 0.598; p = 0.014). While sensory and pain thresholds were not affected by DBS on/off condition, pain modulation was remarkably low in dystonic patients and seemed to be more pronounced by DBS. Conclusion: DBS does not seem to promote changes in sensory and pain thresholds in dystonia. Dystonic patients had different sensory thresholds and top-down modulation of pain when compared to HV which is in line with the lack of spatial discrimination in dystonia.

Descriptors: Dystonia, deep brain stimulation, pain, sensory thresholds, non-motor symptoms.

1 INTRODUCTION

Dystonia is a heterogeneous and complex group of movement disorders that can be of acquired, inherited, or idiopathic etiology.[1] In the last few decades, dystonia research has expanded in many areas such as genetics, pathophysiology, and treatment, both pharmacological and surgical.

The treatment of dystonia is aimed at providing symptomatic relief for the motor symptoms, improving pain, and avoiding musculoskeletal complications such as joint contractures.[2] Medical treatment is usually limited to the side effects and has small symptomatic relief.[3] Botulinum toxin is a good option for focal dystonia; however, in generalized and segmental dystonia it may have a limited effect due to its dose limits. Part of this therapeutic challenge is due to the fact that dystonia is a heterogeneous disease with different phenotypes, instigating different clinical and treatment responses.[2]

Deep Brain Stimulation (DBS) is a surgical option, already established in the treatment of many dystonias. DBS targeting the *globus pallidus internus* (GPi) is the first-line treatment for refractory dystonia[3-5] and provides significant improvement in motor symptoms (43–65%)[2, 6] in a proportion of patients.

Similar to other movement disorders, dystonia is mainly diagnosed, classified, and treated according to its motor symptoms. In fact, the main focus, until now, has been on the motor symptoms themselves and their treatment. Few studies have approached the other clinical aspects in dystonia, such as its non-motor symptoms (NMS), comprised of cognitive, mood, sleep, autonomic and pain complaints.[7] They are, perhaps, less apparent but may also affect the patients' quality of life (QoL)[8] substantially, impacting their personal, social, academic, and work-life.

Some of the established dystonia's treatment, such as DBS, have shown to improve pain [9].Chronic pain is one of the most disabling and frequent complaints in dystonia.[7, 8] In fact, it is thought that pain amelioration is a

considerable drive of post-operative improvements in QoL in dystonia.[4, 5, 10-13] It is considered that pain relief after DBS could be due to increased nociceptive thresholds after DBS implantation, such as described in Parkinson's Disease (PD), or instead, by boosting top-down pain modulatory (i.e., inhibitory) systems.[14, 15] However, there are virtually no studies assessing the mechanisms behind DBS effects on pain and sensory thresholds in dystonic patients.

1.1 Justification

In synthesis, the NMS are vital in dystonia and severely impact the patients' QoL. Pain is one of the most prevalent and crucial NMS. However, few studies have investigated pain and sensory thresholds in dystonic patients. We chose to better understand the effects of one of the most significant treatment options in refractory dystonia, the DBS, in both pain and sensory thresholds, in an attempt to further elucidate the mechanisms of pain and sensory alterations in dystonia.

2 OBJECTIVES

2.1 Main Objective

- Evaluate if the GPi-DBS status (i.e., on or off) changes the sensory thresholds in dystonic patients.

2.2 Specific Objectives

- Compare the clinical profile of patients with and without chronic pain
- Evaluate QST responses in dystonic patients in both DBS conditions (on-DBS and off-DBS);
- Compare sensory thresholds between different body regions through QST;
- Evaluate CPM responses in dystonic patients in both DBS conditions (on-DBS and off-DBS);
- Compare CPM and QST parameters with those of HV;
- Correlate mood, QoL, dystonia severity, results of pain scales and sensory thresholds of dystonic patients;

3 REVIEW OF THE LITERATURE

3.1 History of dystonia

The term Dystonia comes from the modern Latin *dys*- and the Greek *tonos*[16] and means “altered muscle tone”.[17] It was introduced by Hermann Oppenheim as “*dystonia musculorum deformans*”,[18] proposing an organic cause for the disease.[17]

Different from other neurological diseases, such as epilepsy that has its meaning since the antiquity, dystonia references are difficult to be found in historical documents. [18] Some possible representations in the visual arts and literature predate the first more robust medical descriptions by several centuries. [18]

Dystonia has occupied for several years a shadowed territory between Neurology and Psychiatry, constantly shifting between organic and functional explanations for the disorder.[19] The general thought during the late XVIII, XIX and early XX centuries may be represented by the “*méthode clinico-anatomique*” established by Jean-Martin Charcot. It separated the organic disorders, in which there were known structural alterations in the nervous system, from the functional disorders, like the “*névroses*” and hysteria.[18] Sigmund Freud’s theories made this separation clearer with hysteria and the “*névroses*” terms used only in the context of psychiatric disorders that were understood as non-organic, psychogenic or, as currently termed, functional. The dystonias were classified as such for many years.[18, 19]

In 1888, Charcot described a patient with possible cervical dystonia that began after a significant financial loss, establishing the link between cervical dystonia and functional etiology.[18] Edouard Brissaud established the term “*torticollis mental*” highlighting the psychogenic nature of the disorder using as an argument the fact that the abnormal cervical dystonia’s posture improved with a

light touch to the cephalic region.[20] His students Henry Meige and Louis Feindel described this clinical phenomenon as "*geste antagoniste*" or sensory trick.[18]

In 1929, in the "*Réunion Neurologique Internationale Annuale,"* there was a consensus that the dystonias were, indeed, not a disease of the central nervous system, even with Meige's opposing argument that considered focal cranial dystonias a disorder of the basal ganglia.[18]

Opposing arguments to the established psychogenic/functional thought came in the middle of the XX century[18, 19] and included: the hereditary cause of some dystonias;[21] the clinical improvement of patients that were submitted to lesional procedures like thalamotomy and pallidotomy;[22] the limited efficacy of psychotherapy;[23] and the animal models of dystonia after basal ganglia lesion.[24] Years after, the discovery of the first *locus* (9q32-34)[25] for isolated dystonia and, posteriorly, of its gene [26] (DYT1 or, in current terminology, DYT-*TOR1A*[27]) helped to confirm this theory. The DYT system was designed to indicate the genomic regions linked to specific hereditary dystonias, that a causing gene was not yet identified and was numbered as they appeared in the medical literature. [28] However, the system was so consecrated that it was still used for many years, even after the discovery of the specific genes.[28]

In June 1975, the International Symposium on Dystonia occurred in New York and was coordinated by Stanley Fahn and Roswell Eldridge. David Marsden described types of focal dystonias initiated in the adult life like blepharospasm and writer's cramp, also called "*forms frustes.*"[17] Marsden stated that the identical patterns of the involuntary movements were due to an organic disorder of the basal ganglia, like what occurred in the generalized hereditary dystonias. He proved that there was an abnormal activation of agonists and antagonists muscles using a neurophysiological approach.[29]

For some time after these findings, there was a paradigm shift in the concept that the majority of the dystonias were organic in nature and that the psychogenic/functional ones were rare.[30, 31] With the advent of atypical cases,[32] it was observed that functional dystonias existed and were, in fact, the second

most frequent functional movement disorder with unique phenomenological characteristics.[31]

Another important date was 1984, in which a more profound definition of dystonia was evoked by the *ad hoc* Committee of the Dystonia Medical Research Foundation's Scientific Advisory Board as "a syndrome consisting of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures"[33] that was not modified until 2013.[16]

3.2 The evolution of the surgical procedures for dystonia

There are many surgical treatments for dystonia, and, usually, due to their invasive nature, they are considered for patients that failed the pharmacological therapies and the botulinum toxin application.[34]

The surgical treatment for dystonias primarily aims the symptomatic patient relief. The invasive treatments like the myotomias for torticollis and other procedures that target the musculoskeletal system were used for many years.[35] Other peripherical surgeries, such as selective peripheral denervation, might cause many side effects like hypoesthesia, weakness, and muscle atrophy.[34]

Afterward, the ablative stereotactic procedures usually using the GPi as the main target became popular.[35] Initially, they proved to have a good and lasting therapeutic effect,[22] which, as mentioned before, helped to understand that the dystonias may be organic. The first target for dystonia was the uni- or bilateral thalamus, known as sequential thalamotomy. However, this target showed to be partially effective in some patients, with the need for bilateral lesions to help with motor symptoms and could be associated with undesirable side effects such as dysarthria and paresthesia. [36]

The symptomatic relief of the levodopa-induced dyskinesias and dystonias in patients with more advanced Parkinson's disease that underwent pallidotomy showed that this procedure might be effective for the dystonias.[37] Therefore, pallidotomies and their variants (e.g., pallidoansotomy)[38] were frequently used,

also with some limitations. The main problem was that sometimes bilateral procedures were needed for adequate symptomatic relief, usually in the generalized dystonias. Indeed, the main disadvantages of the ablative procedures were their irreversibility and their side effects (e.g., dysarthria), usually because of the need for bilateral procedures.

With the use of neurostimulation, a new opportunity began because it can replicate the effect of lesional procedures with a more personalized approach, but with better side effects and with the advantage of the reversibility of the procedure. It is still under debate how DBS acts like a “reversible lesion,” though there is some evidence towards the high-frequency acting by inhibiting neurons.[39] However, DBS seems to act on synapses’ plasticity and modulate oscillatory activity.[39] DBS, mainly with GPi as a target, proved to be efficacious and became an established part of dystonia’s treatment, particularly of the generalized forms.[4, 5, 35]

DBS is a type of invasive neurostimulation with the implantation of electrodes in the brain’s parenchyma. They are connected to an implantable pulse generator (IPG), and are used to generate electrical pulses to specific brain targets. The electric stimulation is reversible and programmable, letting the frequency, pulse width, voltage, and current to be adjustable. Specific contacts to be stimulated in each electrode can be selected as well.[40] DBS may modulate dysfunctional brain circuits, acting both locally and remotely. Its main disadvantages are cost, need to frequent adjustments, hardware-related complications, and the need for battery replacement.

The development and advance of imaging methods helped with the improvement of target precision. With magnetic resonance imaging (MRI) of the brain, it is possible to visualize the desired target. The fusion of pre-surgical MRI with computed tomography (CT) and the stereotactic atlas also helps with the DBS target’s accuracy.[41]

3.3 Epidemiology

The dystonias are a heterogeneous group of disorders, and more specific information about their prevalence are difficult to establish because of the lack of available data. The epidemiological studies already published use different methodological approaches with diverse and divergent .[42] Epidemiological studies in this field are generally hampered due to the difficulty in identifying cases through investigation or treatment registries; the fact that the diagnosis of the disease is clinical; and the heterogeneity of the disorder.

In fact, the dystonias are not rare, being, probably, the third most common movement disorder, behind essential tremor and PD. Furthermore, being more prevalent than more famous neurological disorders like motor neuron disease and myasthenia gravis.[43]

In the literature, it is noted that dystonia has a higher predominance in women.[44] In a systematic review, the estimated prevalence of “primary dystonia” (using the previous classification), of focal and segmental dystonias, and more specifically of cervical dystonia was respectively 16.4, 15.4, and 5.0 for each 100,000 people.[42] Another study using medical records estimated a prevalence of 0.61%.[45]

3.4 Pathophysiology

The pathophysiology of dystonia is not yet completely understood. Because of the great etiology heterogeneity of the disease, it is possible that different forms of dystonia have distinct neuroanatomical origins, despite having a common substrate[46] Some neurophysiological alterations have been identified, such as reduction of cortical inhibition, impaired synaptic plasticity, and sensory processing dysfunction.[47, 48]

The abnormal inhibition mechanisms in several levels of the central nervous system may explain some clinical characteristics, for instance, the

overflow,[49] which is an unintentional muscle contraction that accompanies but is anatomically distinct from the primary dystonic movement and that usually occurs at the peak of the dystonic movements.[1, 50] In the past century, with the help of neurophysiology, a loss of inhibition was identified in patients with upper limb dystonia.[51, 52] Also, abnormalities in the blink reflex in patients with blepharospasms were discovered.[53] They could explain the co-contraction of antagonists that defines dystonia.[47] With these studies, it was concluded that the inhibition dysfunction could be related to a dysfunction of the cortico-striatum-thalamo-cortical circuitry.[47] This explains the difficulty to select the appropriate movement and to inhibit the inappropriate one.[47]

In the cortical level, studies using transcranial magnetic stimulation (TMS) demonstrate a reduction of inhibition through a loss in short and long intracortical inhibition, as well as a shortening of the silent period.[47] There is also evidence of a loss of surround inhibition,[47, 49, 50] which is a neurophysiological mechanism to focus the neuronal activity and select the neuronal responses.[54] It is better known in the sensory systems, in which the most central signals are facilitated, and the most eccentric ones inhibited, increasing the contrast between them.[54] In the motor system, the surround inhibition may help to select the execution of desired movements through GABAergic (i.e., that uses GABA - Gamma-aminobutyric acid) transmission.[54] Besides, an abnormal facilitation spreading occurs in dystonia.[47, 50]

An abnormal or increased neuronal plasticity leads to dysfunctional connections. It was demonstrated in the dystonias using TMS with paired associative stimulation (PAS) technique,[49] which uses slow-rate repetitive low-frequency stimulation of the median nerve combined with TMS of the contralateral motor cortex[55]. This technique revealed abnormal plasticity similar to long-term potentiation (LTP),[56] which is a type of synaptic plasticity that enables chemical synapses to change their strength. A study with cervical dystonia showed that the more intense the neuroplasticity, the worse the clinical and functional impairment, and the better the DBS response. Therefore, the evaluation with PAS may be a predictor of post-surgical result.[57]

Moreover, a model for focal action-specific hand dystonia, such as writer's cramp and some musician's dystonia, has two hypotheses: the first would be environmental like peripheral dysfunction or repetitive training, and the second one would be subtle alterations in the plasticity of sensory-motor circuits.[49] Nevertheless, the environmental factors would only lead to dystonia if there was a latent plasticity disorder underneath[49]

Several evidences point to a sensory abnormality contribution to the pathophysiology of dystonia. Sensory symptoms are frequent in focal dystonia, and the so-called sensory tricks can modify the dystonic movements.[58] The sensory tricks or "*geste antagoniste*" lead to partial or total improvement of the dystonic postures and/or movements. Several physiology studies now attempt to explain these tricks, and it is believed that they lessen the unbalance of cortical facilitation/inhibition.[59]

Abnormal somatosensory cortical maps organizations may lead to an alteration of the body parts' cortical representation in the somatosensory cortex,[8] and abnormalities in the motor-sensory integration and in the sensory processing may be involved as well.[60]

Imaging methods in patients with acquired or non-acquired dystonias show structural abnormalities, for instance, an increase in the density of grey matter in the primary sensory cortex and in the volume of the basal ganglia.[56] They also demonstrate functional alterations like abnormal activity in the sensorimotor cortex, supplementary motor area, and premotor cortex during motor tasks.[56] Studies with positron emission tomography (PET) show an increase in the rest glucose metabolism in the lentiform nucleus and in the premotor cortex, as well as an altered D2 dopamine receptor interaction in the putamen. The binding is diminished in focal dystonia and DYT-*TOR1A* and increased in dopa-responsive dystonia.[56]

3.4.1 Circuits pathophysiology

The basal ganglia have an essential role in the pathophysiology of dystonia; however, more recent findings show involvement of other regions, including the cerebellum.[46] Therefore, dystonia may be defined as a circuit disorder that involves both the basal ganglia-thalamo-cortical circuit, as well as the cerebellum-thalamo-cortical one [46]

The classical model, as represented in Figure 1, is that dystonia occurs due to a dysfunction of the basal ganglia through an unbalance of the direct and indirect excitatory pathways.[61] The striatum and the subthalamic nucleus (STN) receive topographically organized information from the cortex. The GPi and the *substantia nigra pars reticulata* (SNr) are the final pathways to the thalamus, through inhibitory projections to the thalamo-cortical projections.

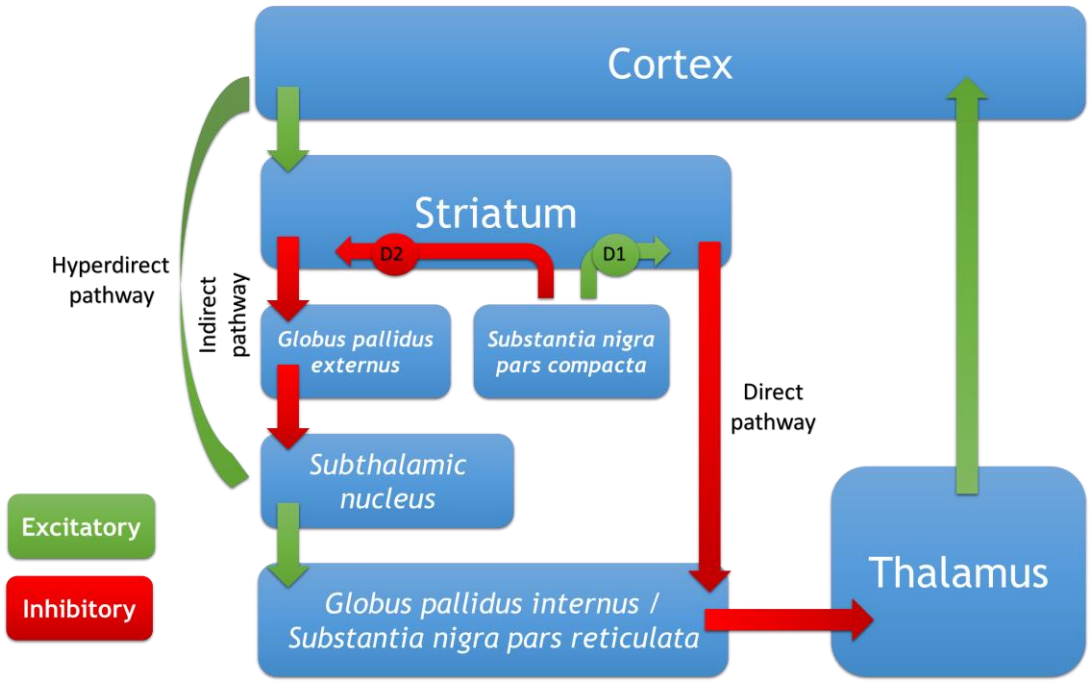

Figure 1. Current proposed model for the basal ganglia connections. The cortical input to the basal ganglia occurs through cortico-striatum and cortico-subthalamic projections. The projections from the basal ganglia to the cortex (output) originate from the *globus pallidus internus* and the *substantia nigra pars reticulata*, passing through the ventral thalamic nuclei. The direct pathway is monosynaptic and inhibitory, while the indirect excitatory pathway is polysynaptic. The hyperdirect pathway is also illustrated. D1, D2 are dopaminergic receptors.

The connections between the striatum and the structures of the final pathway to the thalamus are organized in two main pathways: the direct one has an inhibitory GABAergic synapsis; the indirect is a polysynaptic pathway that includes the STN and the *globus pallidus externus* (GPe) has an excitatory effect on the structures of the final step to the thalamus.

The balance between the direct and the indirect pathway is regulated by dopamine in the striatum through the *substantia nigra pars compacta* (SNc) neurons. Dopamine acting through D1 dopamine receptors increases the activity of the direct pathway, while in the D2 receptors increases the response of the indirect pathway signaling.

In dystonia, there is an increase in the activity of the indirect pathway and abnormal discharges of GPi neurons. Contrary to PD, the direct pathway in dystonias also seems to have increased activity. These altered patterns, including alterations in the synchrony of the discharges, may influence more the clinical manifestations than the increase in the thalamo-cortical activity in this disease.[61]

Additionally, the hyperdirect pathway is thought to link the cortex and the STN.[62] Recently, another hyperdirect pathway was suggested — the cortico-pallidal; therefore, the circuit between the cortex and the basal ganglia is comprised of different parallel pathways, that are distinct both anatomically and functionally.[63]

The striatum, which is comprised of the putamen and the *caudate nucleus*, can be divided into two compartments: the matrix and the striosomes (i.e., patches) that are structured into a mosaic pattern.[64, 65] The matrix forms both the direct and indirect pathways. The striosomes are responsible for the modulation of the nigrostriatal dopaminergic pathway exhibiting an additional motor control. Therefore, the regulation of movement by the basal ganglia depends on the equilibrium of activity in these three mechanisms.

In dystonia, the basal ganglia circuits have a lower depolarization rate, showing altered firing patterns, besides other physiological alterations. It is thought that the increase of the striatal activity may occur because of a loss of

neurons with striatal projections, either from the striosomes or the matrix, leading to an unbalance of the direct and indirect pathways.[66] Nevertheless, more studies are needed to confirm this information. Besides, there is new evidence of the involvement of the cerebellum-thalamo-cortical circuit in dystonia. Both neuroimaging and animal studies have been showing promising data that indicates abnormalities in this circuit, revealing that dystonia is a network disorder that also includes the cerebellum.[66, 67]

More recently, there has been a growing interest in the role of the cerebellum in the pathophysiology of dystonia.[68] The basal ganglia's and the cerebellum's outputs converge in the cortical motor areas, but there is also evidence of a reciprocal connection between them. There is a pathway between the dentate nucleus and the striatum, as well as another one between the STN and the cerebellar cortex.[68]

3.5 Clinical diagnosis

The most recent definition of dystonia was established in 2013, according to Albanese et al. (2013, p. 866)[1] as follows:

> "Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation".

Therefore, dystonia's diagnosis is a clinical one, based on the phenomenology of the movements presented by the patient.

The current classification (Table 1), also from 2013, separates the dystonic syndromes in two axes: clinical characteristics and etiology.[1]

Table 1. Dystonia's Classification. The most recent dystonia's classification by Albanese et al.[1]

Axis I. Clinical characteristics		
Clinical characteristics of dystonia	Age at onset	1. Infancy (birth to 2 years) 2. Childhood (3 to 12 years) 3. Adolescence (13 to 20 years) 4. Early adulthood (21 to 40 years) 5. Late adulthood (> 40 years)
	Body distribution	1. Focal 2. Segmental 3. Multifocal 4. Generalized (with or without leg involvement) 5. Hemidystonia
Clinical characteristics of dystonia	Temporal pattern	Disease course 1. Static 2. Progressive Variability 1. Persistent 2. Action-specific 3. Diurnal 4. Paroxysmal
	Associated features	Isolated dystonia or combined with another movement disorder 1. Isolated dystonia 2. Combined dystonia The occurrence of other neurological or systemic manifestations

Table 1. **Dystonia's Classification** (continuation).

Axis II. Etiology		
Etiology	Nervous system pathology	Evidence of degeneration
		Evidence of structural (often static) lesions
		No evidence of degeneration or structural lesion
	Inherited or acquired	Inherited
		Autosomal dominant
		Autosomal recessive
		X-linked recessive
		Mitochondrial
		Acquired
		Perinatal brain injury
		Infection
		Toxic
		Drug
		Vascular
		Neoplastic
		Brain injury
		Psychogenic
		Idiopathic
		Sporadic
		Familial

The dystonias can be classified as isolated (i.e., forms that have only dystonia and/or dystonic tremor), or combined (formerly known as dystonia-plus) that have other movement disorders associated (e.g., myoclonus or parkinsonism). The term primary dystonia is no longer used because of its dual meaning: it was both used to describe "genetic or idiopathic cases where dystonia is isolated, and there is no consistent pathologic change" and to "define syndromes in which dystonia is the sole phenotypic manifestation (with or without dystonic tremor)."[1] That is why the new classification changed this nomenclature. The international panel assessed on Albanese et al. (2013) also believed that the former term "secondary dystonias" lacked clarity.

Regarding the etiology, the dystonias may have acquired causes like infections, perinatal brain injury, neoplastic and others; inherited through autosomal dominant, autosomal recessive, X linked, and mitochondrial genes; and idiopathic causes. The monogenic forms have been designated, as mentioned before, for many years as DYT and a sequential number (e. g. DYT1, DYT6, and DYT16). Nowadays, a new classification system has been proposed and uses the gene implicated in the dystonia (e.g., DYT-*TOR1A*, DYT-*THAP1*, and DYT-*PRKRA*, respectively).[27]

3.6 Non-motor symptoms

The non-motor characteristics of dystonias are not clearly defined, and have been less studied, even though it is known that the NMS may substantially impact the patients' QoL.[7] The NMS include psychiatric symptoms like anxiety and depression, cognitive, autonomic, sensory, pain, and sleep alterations.[7]

When psychiatric symptoms are concerned, patients with dystonia have higher rates of depression and anxiety with a prevalence, according to a 2011 report, between 25–50%.[7] It is still unknown if the psychiatric manifestations are a primary characteristic of dystonia or whether they are secondary to the motor manifestations. Nevertheless, one study with patients with cervical dystonia showed that half of the patients had psychiatric symptoms before the dystonia manifested.[69]

Most of the knowledge of the psychiatric manifestations in dystonia comes from studies in cervical dystonia.[70] One of them showed that 40% of the patients had an anxiety diagnosis, 37.5% had major depression, with 42.5% fulling the criteria before the beginning of the cervical dystonia.[71] Even though this study has a recall bias, it is possible that dystonia's pathophysiology plays a role in these patient's mood disorders. Some studies have found that a cortical-limbic-striatal dysfunction is involved in depression and other related disorders.[8]

Other psychiatric disorders that have been documented in dystonia are panic attacks, obsessive-compulsive disorder, abuse, or dependence of both licit and illicit drugs.[7, 69, 72]

Regarding the cognitive complains and impairment, patients do not seem to have significant deficits in intellectual ability, memory, attention, language, or executive function when compared to HV.[8, 70] Attention deficit and subtle cognitive abnormalities were implied in a set of studies, although many of them are compromised due to the heterogeneity of the sample or the pharmacological treatment.[8] However, dystonic patients may have an impairment in visuospatial function, worse semantic verbal fluency, and greater susceptibility to interference[70]

Patients with some acquired types of dystonia like tardive dyskinesia due to schizophrenia or patients with pantothenate kinase-associated neurodegeneration (PKAN — formerly known as Hallervorden-Spatz disease), frequently have cognitive impairment. Nevertheless, it is difficult to find more concrete evidence due to methodological issues like small and heterogeneous samples, or the absence of a control group.[70]

Few studies evaluated autonomic dysfunction. Some autonomic symptoms, including obstipation, urinary retention, xerostomia may be caused by the treatment with, for instance, anticholinergic drugs. Some patients with cervical dystonia submitted to botulinum toxin type A may have subclinical abnormalities in the cardiovascular autonomic regulation and the cardiopulmonary baroreflex sensitivity.[73]

Dystonia significantly impacts the QoL of patients, primarily concerning physical function, social function, and leisure activities.[74] Dystonia may also bring difficulties regarding employability, income, and family life.[75, 76]

The NMS pattern may vary in the different types of genetic dystonias; however, due to a small sample and variability of evaluation, more studies are needed to characterize their differences properly[70]

3.6.1 Sensory symptoms and pain in dystonia

Chronic pain is prevalent in the population. Breivik et al. (2006) reported that 19% of European adults have a chronic pain condition that would importantly impact their QoL in many areas related to personal and work life.[77] Pain in dystonia may be disabling and bring QoL worsening.[76, 78] There are no specific criteria for the classification of pain in dystonia,[79] probably due to the scarceness of studies focusing on pain in this disorder.[72] Many dystonic patients complain of possible myofascial or musculoskeletal pain.

Several authors describe a pain localized in the cervical region with irradiation and a feeling of a “pulling” in cervical dystonia.[80] Nevertheless, there is evidence that demonstrates that pain in dystonia is not only of muscular origin.[79] Besides that, the dystonia severity may not correspond to the intensity or the presence of pain.[80, 81] Therefore, it is possible that pain in dystonia could have peripheral, as well as central components. One component may be the changes in the thalamo-cortico-basal ganglia loops integrating different responses to the pain, be that emotional, motor, and cognitive aspects.[9]

Even though many patients report pain, the usual clinical sensory exam and neurophysiological tests are usually normal.[58] Nevertheless, some studies have shown abnormalities in graphesthesia in patients with focal dystonia.[82] Dystonic patients may also have an abnormal perception of the vibration-induced illusion of movement,[83] suggesting dysfunction of the central processing of the sensory inputs.[58]

Other abnormalities described in the somatosensory system of dystonic patients, like the abnormal representation of body parts, may also be involved in pain mechanisms.[84] It is also important to mention that dystonia’s co-morbidities, like depression and sleep alterations, may influence pain.[7, 85]

Several studies have demonstrated that there is an involvement of the sensory systems in dystonia, including an abnormal processing and altered spatial and temporal discrimination[8] of tactile stimuli.[60, 84] Also, some studies

show that some of the dystonia's treatment like botulinum toxin[86] and DBS[87] does not change this abnormal temporal discrimination.

One method to investigate somatosensory integrity is through the quantitative sensory test (QST)[88] that evaluates different sensory qualities like cold, warm, pain, pressure, and vibration. A previous study by Paracka et al. (2017), investigated patients with focal, segmental, and generalized dystonia (without DBS).[88] It showed that QST might detect subtle sensory abnormalities in dystonia, even without apparent sensory deficits. Some of its findings were that the cold detection threshold (CDT) was lower, and the dynamic mechanical allodynia increased when compared to matched controls. Small sensory alterations were found in the hands of patients with cervical dystonia, showing that, even in regions without dystonia, there can be subtle alterations in sensory thresholds.

Another interesting information is that there was not a relation between the QST abnormalities and the dystonia's severity. Only an additional study used QST in patients with writer's cramp.[89] It found higher CDT, warm detection threshold (WDT), and mechanical pain thresholds (MPT) when compared to HV. The CDT and WDT were also higher when the affected limb was compared to the unaffected one.

One of the possible explanations of the pain in dystonia is the existence of a lower pain threshold.[7] One study found that the pressure pain threshold was two times lower in dystonic patients than in HV.[90] It also showed a lower pain threshold in unaffected muscles, adding to the hypothesis of a possible abnormal pain processing in these patients.

3.7 Pharmacological therapy and its limitations

Many different medications have been tested for dystonia. The anticholinergics are one important class of drugs highly prescribed for dystonic patients. [91] Some examples are biperiden and trihexyphenidyl. Their adverse

effects are sedation, hallucination, and cognitive alterations that can be avoided with slow titration. The benzodiazepines like clonazepam, diazepam, and lorazepam are also commonly used. Baclofen, a GABAergic agonist, may also play a role in inherited dystonia and spastic dystonias. Its intrathecal formulation may be useful, especially in the spastics dystonias .[91]

Even though most of the patients will not have a good response to levodopa, this drug should always be tested, especially in children and young adults, as a set of dystonia is dopa-responsive. Most of them are associated with DYT-PARK-*TH* (formerly known as DYT5) and reveal an impressive improvement with 50–1000 mg/day of levodopa.[91] Dopamine antagonists should not be used due to the risk of tardive dyskinesia and/or a possible worsening of dystonia.

Clozapine, an atypical antipsychotic, may be used in refractory cases, especially in the tardive dyskinesias; however, there are some side effects such as sedation, orthostatic hypotension, and agranulocytosis, which demands routine medical evaluation and screening.[91] Tetrabenazine, a monoamine uptake inhibitor, may be helpful in tardive dyskinesias.[91]

Botulinum toxin is the first-line treatment in most types of dystonia,[92, 93] and, more importantly, in the focal and segmental ones. It acts inhibiting the release of acetylcholine in the presynaptic neuron, leading to temporary chemical denervation and temporary muscular weakness.[94]

Most of its adverse effects depend on the localization, technique, and amount of the toxin's application. It may cause dysphagia, weakness, eyelid ptosis, xerostomia, and other autonomic effects.[94] Immunological resistance to the toxin may also occur, in which antibodies generated against the toxin lead to a secondary failure to treatment. In this case, a first and positive response is observed and the following applications can present shorter duration of the toxin's effect, or even a decrease of its effect.[94]

Besides the motor response to botulinum toxin, current evidence suggests that it alters nociceptive processing both locally, on the sensory afferent terminals, and more centrally, as it has been shown that the neurotoxin

undergoes transport to the dorsal root ganglia and the spinal dorsal horn terminal.[95] Moreover, botulinum toxin is currently approved for some pain syndromes, including chronic migraine.[96]

Patients often use other treatments like acupuncture, relaxation techniques, homeopathy, and others, but the literature lack well-designed studies to report how relevant they may be for optimal treatment.[91]

A non-pharmacological treatment of importance is physiotherapy.[97] A study compared the combined treatment with botulinum toxin and physiotherapy to a therapy with only botulinum toxin, and only the group with both interventions had significant improvements in pain and disability scores.[98] Nevertheless, most studies that focused on physiotherapy have small samples and are open-label.[99]

3.8 Selection of candidates for surgical treatment

In general, most dystonic patients are selected for surgical treatment when the pharmacological treatment has revealed inadequate response.[91, 100] As previously mentioned, the pharmacological treatment for generalized dystonias is frequently unsatisfactory or associated with side effects.[91, 101] For the focal or segmental dystonias, the pharmacological treatment is always the first choice, generally correlated with beneficial results; nevertheless, some patients may become refractory to this line of treatment.[91]

Many factors are considered when there is an indication for DBS in dystonia. Most of them are patient's characteristics like age, comorbidities, neuropsychological and neuropsychiatric factors, as well as the duration of the disease, type of dystonia, past medical, and surgical treatments.[102] It is crucial to consider the most troubling symptoms for the patient and whether DBS may improve them.

Regarding the age for the surgical treatment and the duration of the disease in the inherited/idiopathic generalized dystonias, most of the current data come from retrospective studies. It is ideal to undergo the procedure before the

fixed deformities (i.e., sustained abnormal posture regardless of other factors, and that may cause structural deformity) appear.[102] Some papers suggest that a shorter disease time and age are predictors to a better outcome, but additional data are still needed to confirm this information.[102] For the segmental or focal, including cervical dystonias, patients tend to be referred for surgical treatment a little older. DBS seems to be safe for patients until 78-years-old; nevertheless, with longer disease duration, there are more substantial risks of deformities, namely cervical myelopathies (e.g., in the cervical dystonias). Therefore, DBS must be considered before these complications occur.[102], In the inclusion and exclusion criteria for DBS in dystonia, age is not a contraindication but should be considered. Data regarding children younger than seven years old is scarce.[102]

Screening for psychiatric comorbidities like depression and suicidal ideation is recommended.[102] If the psychiatric symptoms are important and not stabilized, this may prevent the surgical indication, until a more stable period. The evaluation of risk and benefit also needs to be made with patients with cognitive impairment and other comorbidities.

DBS must be considered for dystonic patients with functional limitations caused by motor symptoms or pain. There is no evidence to delay treatment if it is indicated. A specific recommendation does not exist on how severe dystonia should be before indicating this surgical procedure. Additionally, no specific cut-off in the dystonia scale exists for the same matter.[102] The patient and the medical team must discuss the limitations and disabilities that the patient has, his/hers QoL, as well as, the patient's expectations before DBS indication.[102]

DBS should be considered in the inherited or idiopathic generalized dystonias that do not have reasonable symptomatic control with medication and in which disabilities impact the patient's QoL. In inherited or idiopathic segmental and focal dystonias and other acquired forms like tardive dyskinesia or cerebral palsy, it should be considered when refractory to pharmacological treatments.

Therefore, the patient's selection is always individualized and should bear in mind the patient's expectations, social background, and support network. This individualized evaluation of risks and benefits is essential.

The general recommendations[2, 101-103] for patient selection are:

1. A diagnosis of inherited or idiopathic generalized or segmental dystonia after a failure with medications like benzodiazepines, anticholinergics, levodopa, and botulinum toxin. In the case of acquired dystonia, individualize the decision;
2. There is no particular age limit as explained above;
3. Evaluate the patient's comorbidities and life expectancy. Patients with uncontrolled comorbidities should be excluded;
4. Patients with significant structural lesions in imaging studies like severe microangiopathy or brain atrophy should probably be excluded;
5. Do a cognitive and neuropsychological screening: patients with severe cognitive deficits and/or dementia should be excluded;
6. Do a psychiatric screening, and patients should be controlled before the surgery.

3.9 The effect of *globus pallidus internus*' deep brain stimulation on the motor symptoms

The most frequent DBS target for dystonia is the GPi,[2, 4, 5, 11, 102] but new targets like the STN are being studied with equivalent results.[2, 104, 105]

The *globus pallidus* is formed by two parts: the GPe and the GPi, each with different projections and functions. The GPe is at the center of many feedback loops in the basal ganglia's circuits. It gives way to a GABAergic inhibitory loop that connects with most of the basal ganglia and even with the GPe itself. Its inhibition of the STN and the GPi are its main connections.[106]

As for the GPi, it receives information from the striatum, the GPe, and the STN. It is the main output of the basal ganglia to the thalamus, and then, to the cortex.[106] The postero-ventrolateral GPi has its motor circuits and exerts effects on both striatopallidal pathways: the direct and indirect ones. As mentioned before, both pathways are dysfunctional in dystonia; therefore, the GPi is a good target because it is located where both of these pathways converge.[101]

The most important evidence of GPi-DBS effects in the treatment of inherited or idiopathic generalized or segmental dystonias comes from two studies. The first one is a class 1 multicenter randomized sham-controlled study[4] that showed 39% of improvement in motor severity and 38% in the disability. It evaluated 20 patients three months after GPi-DBS.

The other study is a class 2 French prospective controlled study with 22 then called “primary generalize dystonia” patients with a severity improvement of 51% after a double-blind three-month evaluation.[5] For a long-term effect, the same group showed that the 51% one-year improvement was maintained after three years (58% improvement).[11]

The acquired dystonias have scarcer literature.[2] They usually don’t respond as well to DBS when compared to the above group, except the tardive dystonias.[2, 102, 107, 108] This is specifically the reason why patients should always be evaluated in case-by-case terms.[101, 109]

The lower number of dystonic patients submitted to DBS when compared to PD, and the complexity of the different types of dystonias make the identification of DBS’s predictive factors more difficult.[101] Some studies show that a lower duration of symptoms and a lower age at the surgery are good outcomes predictors,[66, 108] but specialists debate that a greater proportion of life lived with dystonia would also be a predictive of a good surgical result.[110] Others say that a more severe disease would be a good predictor,[110] while additional studies contradictorily establish a less severe disease as such.[107] Some studies argue whether specific genetic dystonias have better DBS outcomes than others, but most studies show that DYT–*TOR1A* has a good DBS response.[2, 107, 108, 110, 111] Some combined genetic dystonias like some myoclonus dystonias (DYT–*SGCE*) have good DBS safety and outcome.[108] On the other hand, fixed skeletal deformities may have a more unsatisfactory outcome.[108]

3.9.1 Deep brain stimulation's complications

DBS is an elective procedure that is usually well tolerated by most patients. It is a safe procedure;[4, 5] however, like all other surgical treatments, it has its risks and is not complication-free.[112] All patients with DBS indication need a pre-surgical screening due to possible hemodynamic complications during the procedure like hypo- or hypertension, brady- or tachycardia. This is why an experienced anesthesiologist is essential.[113]

From the surgical complications, brain hemorrhage is one of the most serious, fortunately though, most of them are small and asymptomatic.[113] The estimated incidence of all intracranial hemorrhages in stereotactic surgeries (i.e., not only DBS) is of 1–5%; however, the severe sequelae rate seems to be considerably lower.[113] Good intra-operative control of blood pressure and competent presurgical planning to avoid blood vessels is crucial.[113]

The DBS hardware is a foreign body, and, as such, infections are another morbidity factor. There is a risk between 4–12% of surgical infection, and prophylactic antibiotic therapy is recommended.[112, 113] Electrode fracture or disconnection may also occur, as well as lead migration. Lead migration may happen at the moment when the electrode is fixated, but with intra-operative fluoroscopy, it can be corrected during the surgical act.[113] Other complications are extension's fracture or erosion and IPG malfunctioning.[112]

Post-surgical delirium and confusion may occur,[114] but are generally transitory. Patients are selected for a surgical indication with a neuropsychological test to exclude dementia.

A long-term side effect in some patients is the appearance of parkinsonism related to the stimulation.[108] It is mainly reported in patients with cervical dystonia, probably because it is more apparent,[11, 115] and may comprise of bradykinesia, [115] and hypokinetic gait, including the freezing of gait.[116, 117]

3.10 Non-motor symptoms' response to GPi-DBS for dystonia

A recent review in this topic highlights that DBS studies, even now, focus mainly on motor outcomes, and recommends a systematic evaluation of the NMS both before and after DBS.[9] Some reports on this topic are contradictory, and more studies are still needed.[8] GPi-DBS may also influence associative and limbic regions with effects on executive function and behavior.[9]

3.10.1 Cognition

The antero-medial GPi connects to the prefrontal cortex through the dorsolateral prefrontal circuit, which is important for executive function and motor planning; and through the lateral orbitofrontal circuit that can lead to apathy, lack of initiative and of interest.[9]

Post-operative cognitive alterations are uncommon. More than half of the studies in a meta-analysis did not demonstrate cognitive abnormalities.[114] Another review, more focused on the dystonias, also did not find greater adverse effects of GPi-DBS concerning cognitive performance.[9] Some studies even found that the patients would have a slight cognitive improvement.[9, 70, 118] The pharmacological management after surgery may influence because the drugs like the anticholinergics may be reduced.[108] Besides that, a motor improvement (e.g., severe posture and contractions) may influence the attentional component.

However, the lack of more robust controlled studies shows that the conclusions about cognitive changes in GPi-DBS still need caution.[9] Some authors recommend the use of Frontal Assessment Battery (FAB) and other scales like the Mini-Mental State Examination for research and clinical practice.[70]

3.10.2 Psychiatric alterations

As mentioned before, GPi-DBS for dystonia is safe and beneficial.[5, 9, 10] Well placed electrodes may help to improve psychiatric symptoms, but harmful effects may occur in poorly placed electrodes or in situations in which STN or GPi stimulation spreads to non-motor circuits or parts of these nuclei.[119] The GPi's ventromedial portion and the GPe are parts of limbic circuitry and may be influenced by the stimulation current.

A general metanalysis with movement disorder's patients found a prevalence of 2–4% of depression, 0.9–1.7% of mania, and 0.3–0.7% of suicidal ideation.[114] Most of the patients with suicidal ideation or completed suicide had STN-DBS (81%), while 12.5% of them had GPi-DBS. The depressive symptoms improved after DBS in most studies,[9] with only 2.7% of them reporting their worsening.[114]

Another review concluded that GPi-DBS for dystonia with stable slight or moderate depression is safe, and the surgical intervention may even be beneficial to the psychiatric symptoms.[9, 70] Nevertheless, because patients with severe depression and inherited or idiopathic generalized dystonia were excluded from the studies, their outcomes are uncertain. For the acquired dystonias, the results are more heterogeneous.[109]

There are some reports of GPi-DBS in dystonic patients that committed suicide: a patient with cervical dystonia without prior psychiatric symptoms and another with generalized dystonia with prior psychiatric symptoms.[120] The cohort's authors suggest psychological and psychiatric evaluations both before and after surgery[120] They hypothesize that patients with prior depression and high expectations regarding the surgery may have a higher suicidal risk; also, they might have a more difficult adaptation to post-surgical clinical changes.

Even though obsessive-compulsive disorder (OCD) seems to be common in dystonia,[8] there is no information regarding the effects of DBS in these symptoms.[70] In a cohort study, the only patient with OCD had improvement after DBS.[109]

Overall, a neuropsychiatric screening is recommended, and one of the scales that is suggested for evaluation is the Hospital Anxiety and Depression Scale (HADS).[70] Patients with severe depression or prior suicidal attempts, as well as those with current ideation, should be evaluated and treated by a psychiatrist before being considered for DBS.[70]

3.10.3 Quality of life

Several studies showed a significant improvement in patient's QoL after GPi-DBS,[12, 13, 70, 101, 108, 121, 122] probably due to the motor improvement, but also to the improvement of the NMS.[9] Most studies use the 36-Item Short-Form Health Survey quality of life questionnaire (SF-36)[70] or its variants.

3.10.4 Pain and sensory abnormalities

The effects of DBS on pain in dystonic patients have scarce literature, and the studies generally apply different scales to evaluate pain.[9, 123] Most articles report patients with cervical dystonia.[124, 125] DBS's pain effect seems to be dissociated from the motor outcome, with patients reporting an improvement of pain even when their motor symptoms are refractory to stimulation.[9, 91] A case series of patients with cervical dystonia and GPi-DBS showed an improvement in pain, without the improvement of the motor symptoms.[123] This finding may suggest that the basal ganglia dysfunctional circuits, a central component, may result in an altered nociception processing, contributing to the generation or maintenance of pain.[126]

A more recent review of NMS' outcomes after GPi-DBS in dystonia showed that it reduced pain related to dystonia both on the short- and long-term.[9] However, most studies briefly mentioned or, in most cases, did not mention at all how the management of oral medication and botulinum toxin was performed.[9]

In comparison, it is established that STN-DBS in PD decreased pain after surgery[127] with an improvement of the discriminative, as well, as the affective components of pain, helping to improve patient's QoL.[127] In the same group of patients, some sensory thresholds (e.g., lower thermal, mechanical detection, higher cold pain thresholds) changed after surgery, but these differences in STN-DBS for PD could not be correlated to either motor or clinical pain improvement after surgery.[15]

Definitely, more studies are needed for the pain and motor outcomes after surgery, as well as reports on other factors that may confound results (e.g., drugs).[9]

3.11 An overview of pain

Pain is one of the most frequent reasons for medical care consultation.[128] It is currently defined according to Merskey and Bogduk (1994)[129] as:

> "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."

It is vital to differentiate pain from nociception, as both terms are frequently used in a confusing manner.[130, 131] Pain, as the definition implies needs subjectivity and consciousness, while nociception continuously protects the body from noxious stimuli from the environment in a subconscious manner. [131]

Chronic pain is characterized as a pain that persists or recurs for more than three months and is present in most of the days.[132]. Its many causes are between the most disabling diseases in the world.[133] Pain has many different dimensions, such summarized Figure 2, that are used to describe and better understand the many components of the experience of pain.

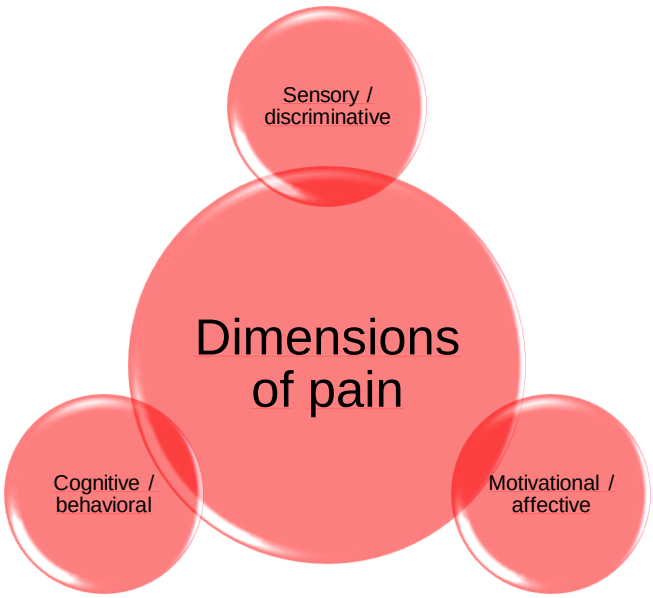

Figure 2. The three dimensions of pain. The sensory/discriminative dimension describes the discrimination of the pain experience (e.g., its intensity, location, duration, and so forth), while the motivational/affective assesses the unpleasantness and the individual urge to scape it. Finally, the cognitive/behavioral dimension describes how the person analyses the pain through his/her cultural background.

3.11.1 Pain modulatory systems

The experience of pain depends not only on the quality and intensity of the peripheral stimulus but also on the status of pain modulatory systems.[134]

Pain may be variably perceived due to different psychological and cultural aspects. However, there are also endogenous pain modulatory systems that can modulate pain.[134] These modulatory descending pathways may both facilitate and inhibit pain.

The most well-known pathway involves the midbrain periaqueductal gray (PAG) matter, the rostral ventromedial medulla (RVM), and the spinal cord.[134] Another important pathway is the dorsolateral pontomesencephalic tegmentum (DLPT), which comprises of cuneiform nucleus in the midbrain and the locus coeruleus, as well as other structures.

3.11.2 Conditioned pain modulation (CPM)

The concept that a painful stimulus is capable of diminishing or, even, masking pain (i.e., pain inhibiting pain) elicited by another far away (i.e., heterotopic, extrasegmental) stimulation is known since Hippocrates.[162] It is thought to happen due to inhibition of the neurons involved in the nociception transmission. This inhibition may happen when there is a peripheral nociceptive stimulation and was found to happen at a stage as early as the spinal cord. It was described and studied in animals as diffuse noxious inhibitory control (DNIC).[162, 163]

Conditioned pain modulation (CPM) is a psychophysical test that helps to assess how a painful conditioning stimulus affects another painful stimulus placed on a different body segment.[163] It is thought to be related to the DNIC described in animals and assesses the descending inhibitory pathways.[162-164] CPM has been shown to predict pain after thoracotomy[165] and cesarean section, [166] as well as to evaluate pain's response after medication.[167]

4 MATERIAL AND METHODS

4.1 Type of study

This study enrolled patients with idiopathic or inherited segmental or generalized dystonia that have already undergone DBS treatment targeting the GPi. Patients were assessed under their usual treatment with a neurological examination and completed pain, mood, cognitive, and QoL questionnaires in a cross-sectional part (Figure 3). Afterward, a double-blind, randomized controlled investigation (Figure 3) was performed to assess the effects of DBS on sensory and pain thresholds using a QST battery and a pain descending modulation analysis by CPM. A researcher with no secondary role in the study switched the DBS between on/off (namely on-DBS or off-DBS, respectively), according to a computer-generated randomization file (www.randomizer.org). After a 30-minute wash-out, QST and CPM were performed again. Thus, patients were always evaluated with the same QST/CPM battery in the off- and on-DBS condition.

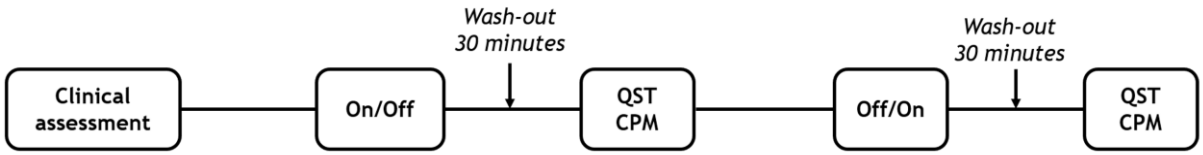

Figure 3. Study design. Patients underwent a clinical assessment using the following validated tools and questionnaires. Afterward, a double-blind, randomized controlled study was performed to assess the effects of deep brain stimulation on sensory and pain thresholds using QST and CPM. An unblinded researcher maintained or changed the DBS status (on-DBS or off-DBS, respectively), as previously randomized. After a 30-minute wash-out, QST and CPM were performed. QST: Quantitative Sensory Test; CPM: Conditioned pain modulation.

4.2 Study settings

Patients' evaluation and data collection was done in the Functional Neurosurgical Outpatient Clinic of the *Instituto de Psiquiatria do Hospital das*

Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). The QST and CPM batteries were performed in the *Laboratório de Análise Quantitativa de Sensibilidade no Serviço de Estimulação Magnética Transcraniana do Instituto de Psiquiatria do HC-FMUSP*.

4.3 Duration of the study

This study began in November 2017 and patients were evaluated until April 2018. Data analysis and manuscript elaboration were finished in June 2019.

4.4 Ethics

The Institutional Ethics Committee approved this study (*Comissão de Ética para Análise de Projetos de Pesquisa, CAPPesq, do HC-FMUSP*, nº 2.236.556, nº 2.487.234 and nº 2.509.998, ATTACHED FILE A, ATTACHED FILE B, and ATTACHED FILE C, respectively); and by the Department of Neurology board. All patients gave written informed consent (ATTACHED FILE D) to participate in the study after understanding the information given in the informed consent paper according to the current Brazilian legislation for research in human beings (*Resolução do Conselho Nacional de Ética em Pesquisa, CONEP 196/96*).

4.5 Patients

Patients included had idiopathic or inherited segmental or generalized dystonia[1] who underwent GPi-DBS for refractory motor symptoms. They were cognitively able to understand and authorize the informed consent paper. Exclusion criteria were patients younger than 18 years old, with other types of dystonia, those having received botulinum toxin injections over at least the preceding three months, who did not consent to participate, who had cognitive

impairment or other neurological diseases and those who could not have their DBS turned off for the blinded evaluation.

4.6 Patients' clinical and functional status assessments

4.6.1 Clinical, neurological and motor evaluation

Disease and medication histories were obtained. Clinical and neurologic examinations were performed by a neurologist specialized in movement disorders. Oral medication was not changed during the evaluation.

Patients were assessed by the motor and disability parts of the Burke-Fahn-Marsden (BFM) scale, with higher scores indicating worse dystonia and worse disability.[168]

We used the Portuguese version of the Edinburgh Handedness Inventory[169] that was kindly provided to us by the first author of the validation paper. In this scale, different activities like writing and drawing are awarded one point if the activity is preferably done by one of the hands and two if it is strongly performed by one of the sides. If the activity is done equally well by both hands, both sides receive a single point. The laterality/handedness coefficient (L_c) is calculated as:

$$L_c = \frac{right\ hand - left\ hand}{right\ hand + left\ hand} \qquad \text{Equation 1}$$

4.6.2 Quality of life and other non-motor symptoms evaluation

The QoL measurement was made through the 12-Item Short-Form Health Survey quality of life questionnaire (SF-12),[170] which is composed of 12 items derived from the SF-36. It addresses eight different QoL's domains, considering the person's perception regarding aspects of his/her health in the last four weeks. The Brazilian version was adapted in a study with a chronic pulmonary obstructive disease population.[170] The use in this study was previously authorized

by Optum® (Eden Prairie, MN, USA), the enterprise that developed and owns the rights of the SF scales. The scale has the following eight domains:

1. Physical functioning: disposition for daily activities that involve mental or physical conditioning;
2. Role limitations because of physical problems: problems with work or other daily activity due to physical health;
3. Bodily pain: painful physical symptoms and their influence at work or other general activities;
4. General health: analysis of their own physical or mental health and their susceptibility to falling ill compared to the general population;
5. Vitality: evaluation regarding the feeling of their vital physical energy like tiredness, vigor, or burn-out;
6. Social functioning: influence of physical and emotional factor in social activities;
7. Role limitations because of emotional problems: difficulties at work or other daily regular activity due to emotional problems;
8. Mental health: state of their feelings regarding vital psychological energy like irritability, happiness, and tranquility.

The mood evaluation was made using the HADS. It is a 14-item scale, half of them related to anxiety and the other half to depression. Each item scores 0–3, with a total sum of 0–21.[171]

The FAB was used as a screening for cognitive impairment. It was chosen because it is of practical use and does not need any drawings, an issue related to our patients' motor symptoms. This scale was previously used in patients with blepharospasm[172] and has been previously recommended for use in the dystonic patient.[70] The FAB consists of 6 items:

1. Similarities: abstract thinking, the evaluation between the link of two words of the same category (e.g., banana and orange);
2. Lexical fluency with the letter ‘S’: helps in the evaluation of cognitive flexibility and the ability to change topics;

3. Motor series or “Luria test”: a sequence of gestures performed to evaluate the ability to organize, maintain and execute successive actions;
4. Conflicting instructions: similar to the Stroop test, the participant needs to inhibit a stimulus and select the appropriate response (i.e., sensitivity to interference);
5. Go/no go (inhibitory control): the participant needs to make a response to a signal (go) and inhibit the response at another sign (no go);
6. Prehension behavior (environmental autonomy): reflex, such as grasping, elicited by a pressure applied to the patient’s hand.

4.6.3 Pain assessment scales

Below are the questionnaires used for pain assessment, like in other studies from the Department of Pain.[15, 173] Patients were asked regarding their pain status and afterwards classified in chronic pain and non-chronic pain groups.

These scales and questionnaires were applied only once, with patients under their usual DBS and pharmacological treatment; thus, before the QST/CPM on/off study:

1. The Short-form McGill pain questionnaire (McGill), in which pain descriptors are categorized into three dimensions of pain: sensory (questions 1–8), affective (questions 9–13), and evaluative (questions 14–15). Also, there is an item for pain intensity by the visual analog scale (VAS, 0–100 mm, in which 0 means no pain and 100 stands for maximal pain imaginable);[174]
2. The Brief Pain Inventory (BPI) short-form, which gives two main scores: pain severity score (mean of questions 3–6, items about pain intensity, each ranging between 0–10), and pain interference score in daily activities (mean of questions 9A to 9G, each ranging from 0–10);[175, 176]

3. The *Douleur Neuropathique-4* (DN4), which assesses a possible neuropathic component of the pain. Scores of ≥ 4 are considered positive. This estimates sensory pain quality (items 1–7) and the last three items (8–10) are based on clinical examination (i.e., hypoesthesia and allodynia);[177, 178]
4. Neuropathic Pain Symptom Inventory (NPSI) also evaluates different clusters of descriptors of neuropathic and varies from 0–10 (total score is the sum of the ten descriptors: 0–100) with two additional items related to the duration and frequency of paroxysmal pain.[179, 180]

4.6.4 Psychophysics assessment

4.6.4.1 Quantitative Sensory Test

Patients underwent a comprehensive QST battery that may analyze both large (A-β) and small (A-δ, C) somatic sensory inputs, as well as experimental pain (EP) measurements through suprathreshold stimuli. The tests performed were similar to previous studies by the Department of Pain.[15, 173] Stimuli were applied to the thenar eminence of the asymptomatic (i.e., no dystonia, or less symptomatic) limb and the most dystonic trapezium (Figure 4) in both conditions.

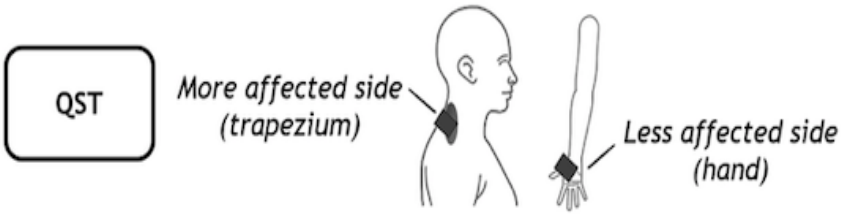

Figure 4. Quantitative sensory test. The QST battery was applied in the thenar eminence of the asymptomatic (i.e., no dystonia or less symptomatic) limb (i.e., hand) and in the most affected (most dystonic) trapezium. QST: Quantitative Sensory Test.

Mechanical detection thresholds (MDT) and MPT were measured using von Frey hairs (NC 17775; Bioseb, France,

Figure **5**).[15, 173] A mechanical suprathreshold stimulus was measured through VAS and established as mechanical hyperalgesia (MH). Vibration detection threshold (VDT) was measured using a graduated tuning fork (Rydel-Seiffer tuning fork; Martin, Tuttlingen, Germany).[181]

Figure 5. The von Frey hairs. They were used for the measurement of the mechanical variables.

Thermal thresholds were assessed using a TSA-2001 device (Medoc, Ramat Yshai, Israel) with a 20 × 35 mm thermode (Figure 6).

A

B

Figure 6. Devices used to establish thermal thresholds. (A) The VSA-3000/TSA-2001 device that establishes the thermal thresholds. (B) The 20 × 35 mm thermode used to establish the thermal thresholds.

For thermal detection thresholds (WDT and CDT), the forced-choice method (Figure 7)[15, 173] was used to avoid bias due to higher motor reaction time related to the more affected dystonic body region.[15].

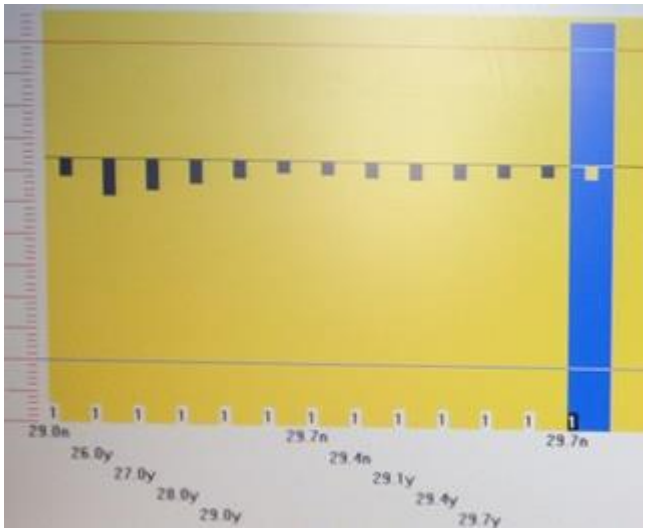

Figure 7. Forced-choice method to establish thermal thresholds. The image shows an example of the forced-choice method to establish the cold detection threshold.

The temperature was increased or decreased at a rate of 1 °C/s[182] (from 32 to 35 °C if the variable was the WDT or to 29 °C if it was the CDT). After each trial, patients had to answer yes/no depending on whether the stimulus was perceived. A “yes” would lead the software to decrease the temperature difference to 1 °C, and then to 0.3 °C subsequently, whereas a “no” would lead to increases in temperature. The final warm/cold detection threshold was established after three consecutive “yes” responses. No dummy stimulus was performed in this run.

Heat (HPT) and cold pain thresholds (CPT) were established through a method of limits (1 °C/s starting from 32 °C). Interstimuli intervals were 15–20 s for heat pain thresholds, and 20–30 s for cold pain thresholds. Temperatures were maintained between 0 °C and 50 °C to avoid lesions. All thermal thresholds were expressed as absolute temperature values. Experimental pain was studied by pain rating to experimental pain heat (SuH) and cold (SuC) stimuli.[15, 173] Stimuli above (46°C and 48°C) and below (5 °C and 10 °C) heat and cold pain thresholds, respectively, were delivered for 2 s and VAS scores were recorded.

4.6.4.2 Conditioned pain modulation

CPM was done with a painful thermal test stimulus (set at 5 °C above HPT for 5s) applied to the left anterior thigh. This was performed both before (unconditioned test stimulus), and after (conditioned test stimulus) the delivery of a painful conditioning stimulus at the contralateral upper limb immersion in 4 °C water until pain reached a VAS of at least 60/100 mm (i.e., cold pressor test).[164, 173, 183, 184] CPM is based on the modulatory effect that a painful conditioning stimulus (i.e., the upper limb immersion in cold water) has on a painful test stimulus applied in a different body segment (i.e.., heterotopic). Thus, it is calculated as the change in pain intensity, measured by VAS, by the subtraction of the conditioned test stimulus and the unconditioned test stimulus. Therefore, normal individuals have negative CPM values, as a normal response is to have a lower pain intensity after the painful conditioning stimulus is delivered (Figure 8).

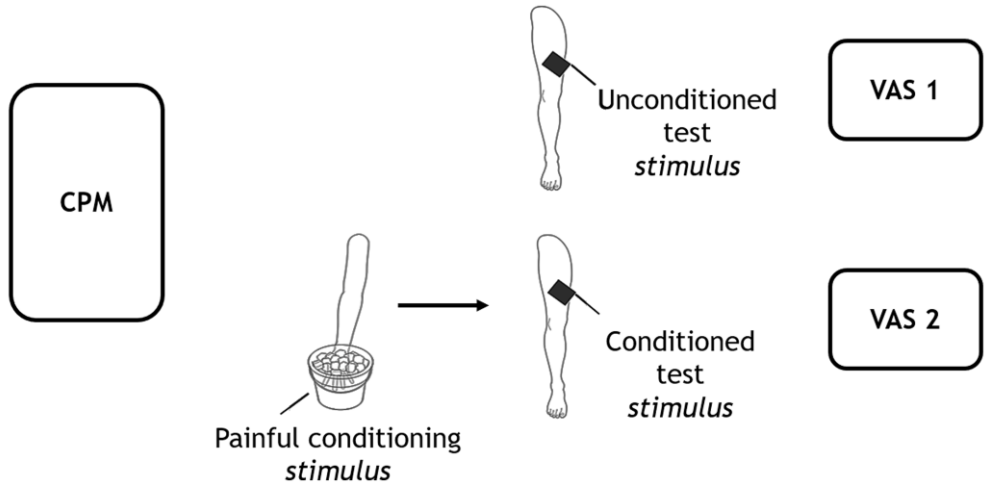

Figure 8. Conditioned pain modulation. The CPM battery was done with a thermal test stimulus applied to the left anterior thigh. The unconditioned test stimulus was the pain intensity measured by the Visual Analog Scale (VAS, 0—100 mm) to a stimulus set at 5 °C above the heat pain threshold (HPT) applied for 5 s (VAS 1). The conditioned test stimulus was the pain intensity (VAS 2) to the same stimulus described above, while the patients submerged their right hand in a 4 °C water bath with ice blocks and cold water (painful conditioning stimulus). CPM effect is calculated as follows: VAS 2–VAS 1, as the expected response in healthy volunteers is VAS 1 > VAS 2, it is usually a negative number. CPM: Conditioned pain modulation.

4.7 Statistical Analysis

Data were expressed as mean ± standard deviation (s.d.) (min–max). We compared the QoL, BFM, FAB, and HADS scales between patients with and without chronic pain using the Mann-Whitney test for independent samples.

Non-normal data were evaluated using the Wilcoxon non-parametric test. The Bonferroni correction ($p < 0.025$) was used to adjust multiple comparisons. Correlation analyses were performed by the analysis of Spearman's rank correlation coefficient.

An index, i, was created to establish the difference between QST results between body sites (hand *vs.* trapezium) for each QST parameter variable. It was calculated in the following way:

$$i = \frac{trapezium_{QST,p} - hand_{QST,p}}{hand_{QST,p}} \qquad \text{Equation 2}$$

in which either trapezium or hand QST, p represents the referred QST variable applied in the index calculation. These calculations aimed to assess potential differences concerning the extent to which the more and less dystonic body regions were affected.

The following comparisons were made:

1. Over the less affected body region (hand) – off- *vs.* on-DBS for each QST parameter;
2. Over the more affected body region (trapezium) – off- *vs.* on-DBS for each QST parameter;
3. Data from each QST index – off- *vs.* on-DBS for each QST parameter;
4. In the off-DBS condition – hand *vs.* trapezium for each QST parameter;
5. In the on-DBS condition – hand *vs.* trapezium for each QST parameter;
6. CPM effect (off- *vs.* on-DBS condition);

7. QST parameters were compared to reference values obtained from age- and sex-matched HV from our pain center laboratory's normative database;
8. CPM effect in dystonic patients compared to reference values obtained from our pain center laboratory's normative database;[164]

Findings in QST/CPM analyses were correlated with motor (BFM), pain intensity (BPI), mood (HADS), and QoL (SF-12) scores.

All statistical calculations were performed using the Statistical Package for the Social Sciences software (SPSS, version 20.0.0; SPSS Inc., Chicago, IL, USA), and statistical significance was set at $p < 0.05$.

5 RESULTS

5.1 Sample description

Sixteen patients (39.9 ± 13.8, 18–61 years) were included. Fourteen had generalized dystonia and two segmental dystonia (Table 2). Our sample had four women and 12 men. Dystonia onset was at 17.8 ± 14.9 (4–54) years, but patients reported a dystonia diagnosis after 5 ± 6 (1–21) years of dystonia onset (2 patients could not estimate how long it took to have their dystonia diagnosed).

Table 2. Demographic data description of our sample regarding gender, age, and formal education.

Variable		Values
Gender	Male	12 (75%)
	Female	4 (25%)
Age at evaluation (years)		39.9 ± 13.8 (18–61)
Age of dystonia's onset (years)		17.8 ± 14.9 (4–54)
Formal education (years)		10.8 ± 3.6 (2–16)

Most were reported being right-handed except two patients. Our patient's mean L_c was 55.0 ± 53.7 (-100–100).

A family history of dystonia was present in 25.0% of the patients, and 43.8% had consanguinity. Seven patients underwent genetic analyses: DYT-*TOR1A* (n = 2); DYT-*THAP1* (n = 3); and DYT-*PRKRA* (n = 2). Age at dystonia onset was 17.8 ± 14.9 (4–54). Only three patients had a family history of dystonia (two in siblings and one maternal aunt).

All patients had previously tried botulinum toxin, but six (37.5%) of them did not report a clinical improvement. Only seven patients were currently using botulinum toxin for their treatment, and all were evaluated at least three months after their last injection.

DBS parameters used were a mean frequency of 145.6 ± 31.4 Hz (60–180) on both sides, a pulse width of 128.7 ± 96.2 μs (60–450) on both sides and an amplitude of 2.7 ± 0.8 mA (1.5–4.3) on the right lead and 3.3 ± 1.4 mA (1.8–7.8). Patients contact stimulation were as described in Table 3. Unfortunately, we were unable to perform volume of tissue activated imaging in this group of patients due to the fact that many patient's CT's and MRI's data were not available.

Table 3. The pattern of DBS's stimulation. Each electrode has four contacts beginning as follows: most ventral, ventral, dorsal and most dorsal, respectively.

Number of patients	Right side	Left side
8	0-00	0-00
3	--00	--00
1	0--0	0--0
1	-000	-000
1	0-00	000-
1	00+-	0-+-
1	0+-+	0-00

Abbreviation: "-" cathode; "+" anode; "0" unused contact.

5.2 Patients' motor and non-motor characteristics

Patients were evaluated at 3.7 ± 3.8 years after DBS surgery with no surgery-related complications. They had a total BFM motor score of 48.0 ± 21.1 (20–78) and a disability score of 10.0 ± 5.0 (2–19) (Table 4). Patients with and without chronic pain did not differ when the motor score was analysed. Figure 9 shows the patients' individual BFM's scores.

Table 4. Motor scale. Burke-Fahn-Marsden's dystonia severity and disability scale of all the patients and the comparison between patients with and without chronic pain. Here are data regarding motor scores of all the patients, patients with chronic pain, and without pain. All scores and sub-scores of the mentioned scales were compared between patients with or without chronic pain. No significance was observed at $p < 0.05$. Results are presented as mean ± s.d. (min–max).

BFM	All patients (n = 16)	Chronic pain (n = 9)	Without pain (n = 7)	p
Eyes	0.87 ± 2.41	0.88 ± 2.66	0.85 ± 2.26	1.000
(0–8)	(0–8)	(0–8)	(0–6)	
Mouth	2.18 ± 3.01	2.05 ± 2.96	2.35 ± 3.30	0.681
(0–8)	(0–8)	(0–6)	(0–8)	
Speech and swallowing	5.25 ± 5.56	4.11 ± 5.25	6.71 ± 6.01	0.536
(0–16)	(0–16)	(0–16)	(0–16)	
Neck	4.62 ± 2.02	4.66 ± 2	4.57 ± 2.22	0.918
(0–8)	(0–8)	(2–8)	(0–6)	
Right arm	9.00 ± 4.66	7.55 ± 4.95	10.85 ± 3.80	0.210
(0–16)	(1–16)	(1–12)	(4–16)	
Left arm	7.93 ± 5.39	7.44 ± 6.02	8.57 ± 4.85	0.837
(0–16)	(0–16)	(0–16)	(0–16)	

Table 4. Motor scale. (continuation).

BFM	All patients (n = 16)	Chronic pain (n = 9)	Without pain (n = 7)	p
Trunk (0–16)	8.25 ± 4.94 (0–16)	8.44 ± 5.81 (0–16)	8.00 ± 4.00 (0–12)	0.681
Right leg (0–16)	6.00 ± 6.23 (0–16)	7.11 ± 6.86 (0–16)	4.57 ± 5.50 (0–12)	0.470
Left leg (0–16)	3.87 ± 5.08 (0–16)	4.88 ± 5.92 (0–16)	2.57 ± 3.77 (0–8)	0.536
Total motor score (0–120)	48.00 ± 21.09 (20–78)	47.16 ± 24.72 (20–78)	49.07 ± 17.17 (24.50–68)	1.000
Total disability score (0–29)	10.00 ± 5.03 (2–19)	9.89 ± 5.20 (2–19)	10.14 ± 5.2 (3–16)	0.918

Abbreviation: BFM, Burke-Fahn-Marsden scale.

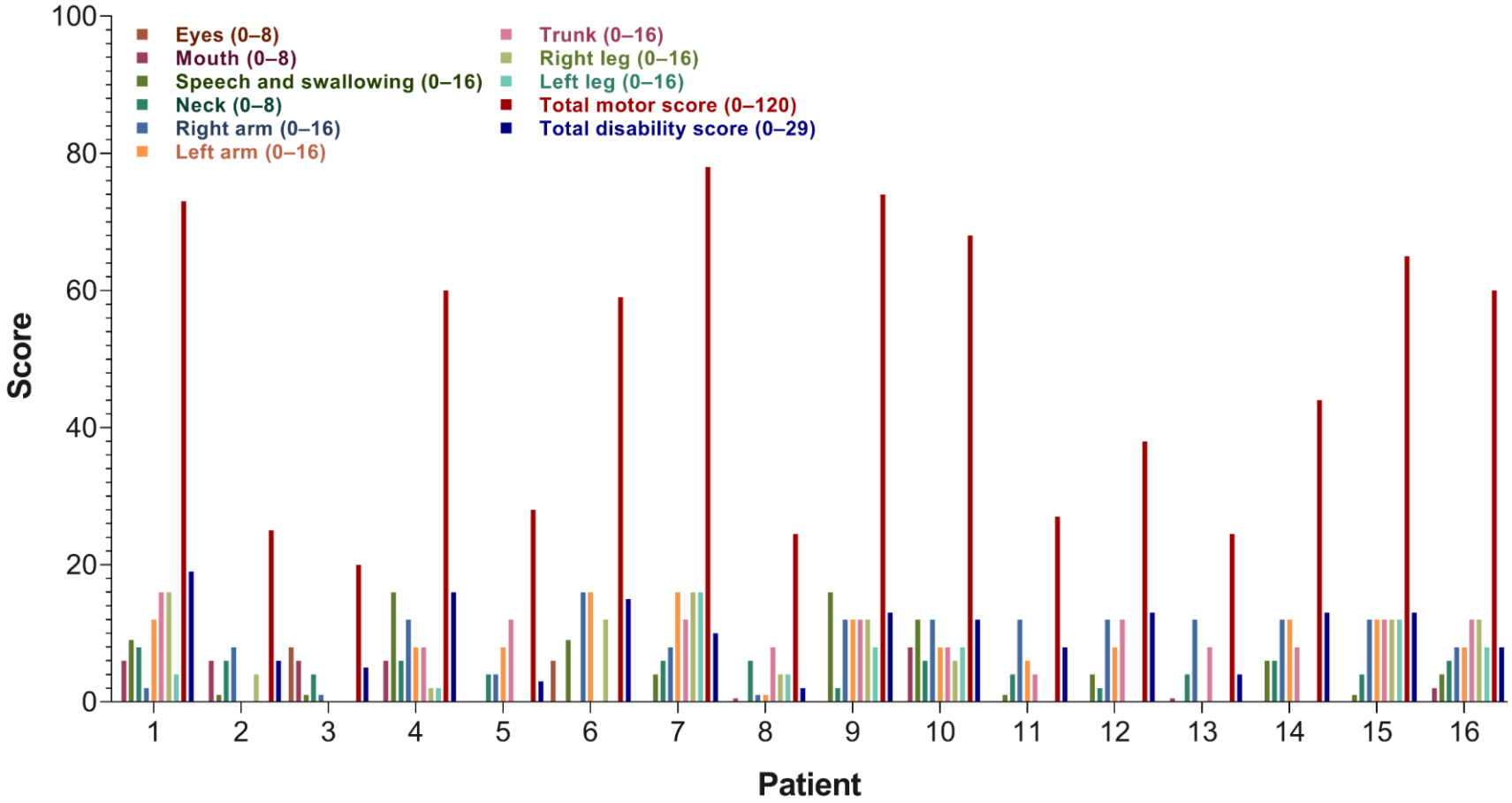

Figure 9. Individual BFM's scores. BFM's total and subscores for each patient in our sample.

Nine patients (56.3%) reported current chronic pain, defined as pain that lasts or recurs for longer than three months.[185] A single patient reported the presence of chronic pain before the development of dystonia. The BPI pain severity index was 3.3 ± 1.9 (0.0–6.2), and its pain interference in daily activities was 2.4 ± 2.7 (0.0–8.7) (Table 5). Two patients had a positive DN4 (both with a score of 4).

Table 5. The pain scales' scores of patients with chronic pain. This table reports the pain scales (DN4, BPI, NPSI, and McGill) results of the patients with chronic pain. Results are presented as mean ± s.d. (min–max).

	Chronic pain (n = 9)	
DN4	Total score (0–10)	1.33 ± 1.32 (0–4)
BPI	Pain severity score (0–10)	3.27 ± 1.93 (0–6.25)
	Interference score (0–10)	2.37 ± 2.71 (0–8.71)
	Worst pain (0–10)	4.78 ± 2.48 (0–8)
	Least pain (0–10)	1.78 ± 1.85 (0–5)
	Pain on average (0–10)	3.67 ± 2.73 (0–7)
	Pain right now (0–10)	2.89 ± 1.96 (0–5)
	General Activity (0–10)	2.56 ± 2.83 (0–8)
	Mood (0–10)	3.67 ± 3.74 (0–10)
	Walking Ability (0–10)	3.33 ± 3.46 (0–10)
	Work (0–10)	2.44 ± 3.67 (0–10)
	Relations with other people (0–10)	2.22 ± 3.70 (0–9)
	Sleep (0–10)	0.89 ± 2.66 (0–8)
	Enjoyment of life (0–10)	1.56 ± 2.35 (0–7)

Table 5. The pain scales' scores of patients with chronic pain. (continuation).

		Chronic pain (n = 9)
NPSI	NPSI total score (0–100)	13.44 ± 9.00 (0–26)
	Burning (superficial) spontaneous pain (0–10)	1.11 ± 1.76 (0–4)
	Squeezing pain (0–10)	0.56 ± 1.66 (0–5)
	Pressure pain (0–10)	3.33 ± 2.95 (0–8)
	Electric shocks (0–10)	0 ± 0 (0–0)
	Stabbing (0–10)	0 ± 0 (0–0)
	Pain provoked or increased by brushing (0–10)	0.44 ± 1.33 (0–4)
	Pain provoked or increased by pressure (0–10)	4.56 ± 4.66 (0–10)
	Pain provoked or increased by contact with something cold (0–10)	1.89 ± 3.01 (0–8)
	Feel pins and needles (0–10)	0.44 ± 1.33 (0–4)
	Tingling (0–10)	0.67 ± 2.00 (0–6)
McGill	Sensory (0–8)	3.44 ± 1.42 (2–6)
	Affective (0–5)	2.67 ± 0.86 (1–4)
	Evaluative (0–2)	1.44 ± 0.52 (1–2)
	Total score (0–15)	7.56 ± 1.33 (6–10)
	Pain's intensity (0–100)	10.00 ± 15.19 (0–50)

Abbreviations: DN4, *Douleur Neuropathique*-4; BPI, Brief Pain Inventory; NPSI, Neuropathic Pain Symptom Inventory; McGill, Short-form McGill Pain Questionnaire.

According to the HADS, four patients (25.0%) had anxiety scores higher than 8.0, and none had major depression (score > 9.0). SF-12's bodily pain (p = 0.023) and mental health (p = 0.042) subscores were significantly worse in patients with chronic pain when compared with pain-free dystonic patients (Table 6). Also, patients with chronic pain had worse total (p = 0.005), depression (p = 0.008) and anxiety (p = 0.023) scores in the HADS (Table 6).

Table 6. The patients' non-motor scales' score. Here are data regarding non-motor scores (HADS, FAB, SF-12) of all the patients, patients with chronic pain, and without pain. All scores and sub-scores of the mentioned scales were compared between patients with or without chronic pain. Significance set at *p < 0.05 and at **p < 0.025 after Bonferroni correction. Results are presented as mean ± s.d. (min–max).

	Scales	All patients (n=16)	Chronic pain (n=9)	Without pain (n=7)	p
HADS	Depression subscale (0–18)	4.25 ± 2.62 (0–9)	5.78 ± 2.33 (2–9)	2.29 ± 1.38 (0–4)	0.008**
	Anxiety Subscale (0–18)	5.25 ± 3.47 (1–13)	6.89 ± 3.62 (3–13)	3.14 ± 1.86 (1–7)	0.023**
	Total score (0–36)	9.5 ± 5.41 (1–20)	12.66 ± 4.89 (5–20)	5.42 ± 2.63 (1–9)	0.005**
FAB	FAB (0–18)	11.93 ± 3.84 (3–16)	11.67 ± 3.31 (6–16)	12.29 ± 4.42 (3–16)	0.536
SF-12	Physical Functioning (0–100)	42.79 ± 10.44 (25.58–57.06)	39.57 ± 9.45 (25.58–57.06)	46.94 ± 10.86 (25.58–57.06)	0.142
	Role Physical (0–100)	41.32 ± 11.58 (23.61–57.46)	37.71 ± 10.57 (23.61–57.46)	45.97 ± 11.89 (27.84–57.46)	0.174
	Bodily Pain (0–100)	45.32 ± 13.92 (21.66–57.73)	38.69 ± 14.57 (21.66–57.73)	53.86 ± 7.09 (39.69–57.73)	0.023**
	General Health (0–100)	44.14 ± 12.25 (23.90–63.66)	42.67 ± 14.09 (23.90–57.69)	46.04 ± 10.16 (33.84–63.66)	0.758
	Vitality (0–100)	49.68 ± 11.05 (29.39–68.74)	45.78 ± 10.99 (29.39–68.74)	54.68 ± 9.59 (39.23–68.74)	0.114
	Social Functioning (0–100)	42.44 ± 14.47 (21.32–56.90)	40.09 ± 14.37 (21.32–56.90)	45.46 ± 15.15 (21.32–56.90)	0.536
	Role Emotional (0–100)	48.80 ± 11.22 (14.70–56.28)	47.04 ± 14.18 (14.70–56.28)	51.08 ± 6.00 (40.69–56.28)	0.918
	Mental Health (0–100)	45.56 ± 13.81 (18.32–64.21)	39.35 ± 13.75 (18.32–58.47)	53.55 ± 9.61 (41.26–64.21)	0.042*

Abbreviation: HADS, The Hospital Anxiety, and Depression Scale; FAB, Frontal Assessment Battery; SF-12, 12-Item Short-Form Health Survey.

5.3 Quantitative sensory test's results

QST values in the off-DBS condition were not significantly different from the on-DBS in comparisons within the same body part (i.e., hand or trapezium) after correction for multiple comparisons. The index score i results were not different between the on- or the off-DBS conditions (Table 7).

When comparing changes between the more (trapezium) and less (hand) affected body regions in the off-DBS condition, we found that the pain rating to experimental pain cold stimulus (SuC) was significantly higher on the hand (43.6 $\pm$ 30.1 *vs.* 35.5 $\pm$ 31.4, p = 0.011), and similar findings were obtained in the on-DBS status in the hand (SuC: 53.6 $\pm$ 32.8) compared to the trapezium (42.2 $\pm$ 33.1, p = 0.021). Similarly, the VDT was significantly higher on the hand compared to the trapezium in the off-DBS status (7.5 $\pm$ 0.6 *vs.* 6.6 $\pm$ 1.0, p = 0.020), as well as in the on-DBS condition: 7.7 $\pm$ 0.7 *vs.* 6.4 $\pm$ 1.2, p = 0.002 for the hand and trapezium, respectively. In the on-DBS, WDT was significantly lower on the hand (33.2 $\pm$ 0.8) compared to the trapezium (34.3 $\pm$ 1.6, p = 0.007).

Table 7. Quantitative sensory test (QST) parameters. The table shows the results of following comparisons: (i) off *vs.* on-DBS for QST parameters in the hand (p-hand); (ii) off *vs.* on-DBS for QST parameters in the trapezium (p-trapezium); (iii) off *vs.* on-DBS for QST parameters index variables (p index); (iv) analysis of hand *vs.* trapezium for QST parameters in the off-DBS condition (p-off); and (v) analysis of hand *vs.* trapezium for QST parameters in the on-DBS condition (p-on). Results are presented as mean ± s.d. [(min-max)]. Significance set at *p < 0.05 and at **p < 0.025 for Bonferroni correction.

Variables	off-DBS			on-DBS			off *vs.* on-DBS			Hand *vs.* Trapezium	
	Hand	Trapezium	*i* Trapezium-Hand/Hand off##	Hand	Trapezium	*i* Trapezium-Hand/Hand on##	p hand	p trapezium	p *i*	p off	p on
CDT (°C)	30.68 ± 1.15 (27.9–31.8)	29.99 ± 1.77 (26.4–31.9)	-0.226 ± 0.040 (-0.13–0.01)	30.72 ± 0.76 (29.1–31.9)	30.1 ± 1.56 (28.7–31.9)	-0.020 ± 0.037 (-0.10–0.03)	0.975	0.900	0.796	0.083	0.061
WDT (°C)	33.52 ± 1.54 (32.3–37.4)	34.3 ± 1.76 (32.2–37.4)	0.023 ± 0.044 (-0.02–0.11)	33.25 ± 0.84 (32.4–35.3)	34.27 ± 1.61 (32.1–37.6)	0.030 ± 0.038 (-0.02–0.11)	0.682	0.979	0.796	0.155	0.007**
HPT (°C)	45.88 ± 2.71 (41.5–50)	44.95 ± 3.07 (38.95–49.25)	-0.016 ± 0.092 (-0.15–0.17)	45.99 ± 2.51 (42.35–49.8)	45.64 ± 3.49 (37.7–49.4)	-0.005 ± -0.088 (-0.18–0.16)	1.000	0.453	0.255	0.326	0.717
CPT (°C)	16.05 ± 7.68 (0.8–29.6)	13.5 ± 9.55 (0–26.1)	-0.133 ± 0.49 (-1–0.7)	16.56 ± 6.21 (5.3–24.45)	15.08 ± 9.44 (0–28.15)	-0.087 ± 0.498 (-1–0.79)	0.959	0.140	0.460	0.233	0.587
SuH (VAS)	39.81 ± 28.58 (2.5–90.5)	36.5 ± 28.29 (1.5–90.5)	-0.098 ± 0.344 (-0.91–0.33)	39.5 ± 28.71 (4–87.5)	48.25 ± 32.05 (2–93.5)	0.504 ± 1.229 (-0.92–4)	0.518	0.191	0.063	0.313	0.155
SuC (VAS)	43.62 ± 30.10 (2.5–87.5)	35.5 ± 31.4 (0–100)	-0.271 ± 0.343 (-1–0.39)	53.56 ± 32.83 (3–99)	42.21 ± 33.08 (0–100)	-0.143 ± 0.516 (-1–1.11)	0.083	0.233	0.496	0.011**	0.021**
MDT (g/mm^2)	1.77 ± 0.2 (1.7–2.3)	1.95 ± 0.49 (1.7–3.3)	0.876 ± 0.159 (0–0.43)	1.8 ± 0.4 (1.7–3.3)	1.91 ± 0.7 (1.7–4.5)	0.044 ± 0.122 (0–0.36)	0.655	0.783	0.336	0.059	0.180

Table 7. Quantitative sensory test (QST) parameters. (continuation)

Variables	off-DBS			on-DBS			off *vs.* on-DBS			Hand *vs.* Trapezium	
	Hand	Trapezium	*i* Trapezium-Hand/Hand off##	Hand	Trapezium	*i* Trapezium-Hand/Hand off##	p hand	p trapezium	p *i*	p off	p on
MPT (g/mm²)	104.02 ± 42.48 (25–137.3)	98.85 ± 48.33 (6.8–137.3)	-0.037 ± 0.341 (-0.83 - 0.56)	114.04 ± 36.42 (39.1–137.3)	117.01 ± 38.51 (31.6–137.3)	0.161 ± 0.730 (-0.72–2.51)	0.043	0.108	0.398	0.715	0.833
MH (VAS)	5.81 ± 8.5 (0–22)	6.69 ± 12.9 (0–51)	-0.003 ± 0.755 (-1–2)	7.94 ± 12.61 (0–45)	5.19 ± 12.01 (0–46)	-0.212 ± 0.405 (-1–0.09)	0.262	0.248	0.312	0.859	0.089
Mechanical dynamic allodynia (0–100)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	1.000	1.000	1.000	1.000	1.000
VDT (μm)	7.56 ± 0.62 (6–8)	6.62 ± 1.02 (5–8)	-0.115 ± 0.178 (-0.38–0.33)	7.69 ± 0.7 (6–8)	6.44 ± 1.2 (3–8)	-0.162 ± 0.154 (-0.5–0.17)	0.589	0.589	0.342	0.020**	0.002**

Abbreviations: #CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; SuH, pain rating to suprathreshold heat stimulation; VAS, Visual analogue scale 0–100 mm; SuC, pain rating to suprathreshold cold stimulation; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MH, mechanical hyperalgesia VDT, vibration detection threshold. ##Index to establish the difference between QST sites (hand versus trapezium) for each variable was created according to Equation 2.

5.4 Conditioned pain modulation's results

CPM values in the off-DBS state were not significantly different from the on-DBS (Table 8), but both on- (0.66 ± 1.99, p=0.0001) and off-DBS (0.20 ± 0.81, p=0.001) values were significantly higher (i.e., worse CPM) compared to reference data from healthy subjects ($-0.43 \pm 0{,}29$) (Table 8).

Table 8. Conditioned pain modulation's (CPM) results. The table shows the results of the following comparisons: (i) off *vs.* on-DBS for CPM variables (p-on *vs.* off), (ii) CPM of healthy volunteers *vs.* patients in the off-DBS condition (p HV *vs.* off), and (iii) in the on-DBS condition (p HV *vs.* on). Results are presented as mean ± s.d. (min–max). Significance set at *p < 0.05 and at **p < 0.025 after Bonferroni correction.

Variables	off-DBS	on-DBS	HV	p on *vs.* off	p HV *vs.* off	p HV *vs.* on
HPT (°C)	47.14 ± 2.36 (43.6–49.9)	47.03 ± 2.14 (42.7–49.6)	-	0.469	-	-
U-TS (VAS)	59.81 ± 35.64 (10–100)	57.5 ± 33 (9–100)	-	0.727	-	-
C-TS (VAS)	58.93 ± 35.17 (7–100)	45.75 ± 36.95 (0–100)	-	0.382	-	-
C-TS total duration	40.91 ± 11.96 (29.47–66.61)	42.13 ± 21.92 (26–115.02)	-	0.460	-	-
C-TS unpleasantness (VAS)[#]	70.67 ± 30.98 (13–100)	59.33 ± 38.32 (10–100)	-	0.182	-	-
CPM effect[##]	1.8 ± 22.10 (-34–50)	11.75 ± 40.68 (-86–97)	-	0.683	-	-
CPM[###]	0.20 ± 0.81 (-0.63–2.3)	0.66 ± 1.99 (-0.90–7.2)	-0.43 ± 0,29 (-0.96–0,35)	0.826	0.001**	0.0001**

Abbreviations: HV, healthy volunteers; TS, test stimulus; U-TS, unconditioned test stimulus; C-TS, conditioned test stimulus; CPM, conditioned pain modulation. [#]Conditioned-TS unpleasantness is the pain's VAS of the hand after water bath with ice blocks was finished; [##]''Raw'' CPM effects were calculated as (C-TS) – (U-TS); [###]CPM was calculated as a ratio: $\frac{C-TS-U-TS}{U-TS}$

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5.5 QST parameters comparisons between dystonic patients and HV

When compared to HV, both the MDT and MPT were higher in dystonic patients, regardless of the DBS conditions (Table 9). Curiously, the CPT and SuC were much higher in the patients while in the on-DBS condition. CPT reported a 54.8% increase, while SuC displayed a 95.7% gain when compared to HV.

Table 9. Comparison between patients and healthy volunteers concerning QST parameters. The table shows the results of the following comparisons: (i) HV *vs.* patients off-DBS for QST parameters in the hand (p HV *vs.* off); (ii) HV *vs.* patients on-DBS for QST parameters in the hand (p HV *vs*. on). Results are presented as mean ± s.d. (min–max). Significance set at *p < 0.05 and at **p < 0.025 for Bonferroni correction.

Variable	HV	Dystonic Off	Dystonic On	p HV vs. off	p HV vs. on
CDT (°C)	30.56 ± 0.88 (27.7–31.4)	30.68 ± 1.15 (27.9–31.8)	30.72 ± 0.76 (29.1–31.9)	0.171	0.897
WDT (°C)	33.51 ± 0.67 (32.4–35.1)	33.52 ± 1.54 (32.3–37.4)	33.25 ± 0.84 (32.4–35.3)	0.128	0.254
HPT (°C)	44.55 ± 3.35 (37.7–49.6)	45.88 ± 2.71 (41.5–50)	45.99 ± 2.51 (42.4–49.8)	0.402	0.491
CPT (°C)	10.70 ± 6.43 (0.5–22.3)	16.05 ± 7.68 (0.8–29.6)	16.56 ± 6.21 (5.3–24.5)	0.056	0.023**
SuH (VAS)	24.40 ± 23.27 (0.0–65.0)	39.81 ± 28.58 (2.5–90.5)	39.5 ± 28.71 (4.0–87.5)	0.073	0.080
SuC (VAS)	27.37 ± 27.83 (0.0–82.5)	43.62 ± 30.10 (2.5–87.5)	53.56 ± 32.83 (3.0–99.0)	0.086	0.019**
MDT (g/mm2)	0.04 ± 0.10 (0.0–0.4)	1.77 ± 0.2 (1.7–2.3)	1.8 ± 0.4 (1.7–3.3)	0.000**	0.000**
MPT (g/mm2)	80.96 ± 117.22 (1.4–300.0)	104.02 ± 42.48 (25.0–137.3)	114.04 ± 36.42 (39.1–137.3)	0.032*	0.023**
MH(VAS)	3.12 ± 8.73 (0–30)	5.81 ± 8.5 (0–22)	7.94 ± 12.61 (0–45)	0.196	0.184
Mechanical dynamic allodynia (0-100)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	1.000	1.000

Abbreviations: CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; SuH, pain rating to suprathreshold heat stimulation; VAS, Visual analogue scale 0–100 mm; SuC, pain rating to suprathreshold cold stimulation; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MH, mechanical hyperalgesia

5.6 Correlations analysis

We analyzed if on- or off- DBS CPM scores were correlated with BFM, SF-12, FAB and HADS' scores. We only found that on-DBS CPM values and BFM's disability scores were highly and positively correlated ($\rho = 0.598$, $p = 0.014$), while off-DBS CPM and the SF-12 vitality score were also highly, but negatively correlated ($\rho = -0.655$, $p = 0.008$), as observed in Figure 10. Other pre-planned correlation analyses were not significant.

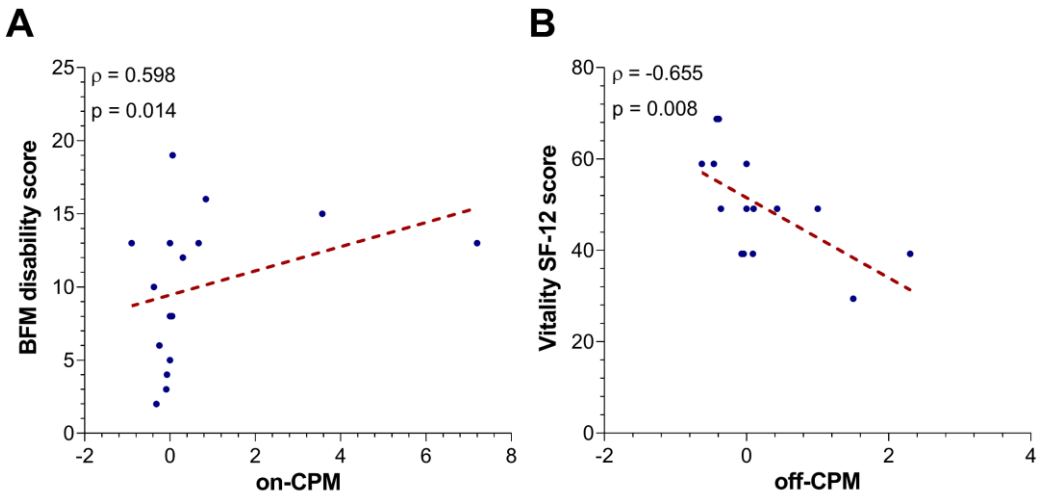

Figure 10. Significant correlation among tested scores and CPM. (A) A positive correlation was observed between CPM on the on-DBS state (on-CPM) and the BFM's disability score. (B) The vitality SF-12 score was associated with CPM when DBS was turned off (off-CPM), in which variables were inversely correlated. BFM: Burke-Fahn-Marsden scale; CPM: conditioned pain modulation; SF-12: 12-Item Short-Form Health Survey.

6 DISCUSSION

6.1 Pain is common in dystonic patients, even after DBS

In our sample, chronic pain is a common complaint in generalized/segmental dystonia patients, even after DBS. Patients with pain had more severe mood symptoms and worst QoL when compared to those without pain. Even after DBS treatment, 56.3% of patients had chronic pain.

Pain is a frequent complaint and impacts on the patient's QoL.[8, 74] Nevertheless, most studies on dystonia and pain have focused on cervical dystonia and other types of focal dystonia, reporting a high prevalence of pain (67–75%).[7, 8] Pain may be improved by common oral medication, as well as by botulinum toxin application and rehabilitation.[186]

GPi-DBS is an important part of the treatment of generalized and segmental dystonia of inherited or idiopathic etiology. Yet, few studies have reported pain-related outcomes after DBS and, those who did, usually also focus on cervical dystonia.[9] The papers that reported pain outcomes in these patients usually only use simple scales such as VAS.[9] Current evidence seems to implicate that pain response to treatment with DBS is dissociated from the motor response, although no study has systematically evaluated the association between the motor and pain outcomes of DBS.[9] In patients with inherited or idiopathic generalized dystonia, a randomized clinical trial with 40 patients showed a reduction (63%) of pain (VAS) in on-DBS patients, while the sham-stimulation control reported 0% change at 3 months, and was maintained both at 6 months and 5 years.[4, 9, 187] A series with 24 patients revealed a reduction of 53% in the pain symptoms after DBS.[9, 12]

When comparing patients with and without pain, their BFM motor score did not differ. Nevertheless, mental health subscores were worse in the chronic pain

subgroup. This is in line with studies in other diseases in which chronic pain has shown to be associated with worse depression and anxiety symptoms.[188-191]

6.2 DBS did not change sensory thresholds in dystonic patients, at least on a short-term on/off evaluation

We did not find a difference in sensory and pain thresholds when comparing both DBS status (on- versus off-DBS). Although there is evidence that pain improves after GPi-DBS, as discussed in section 6.1, this evidence has not been analyzed with further investigations.[9] Pain improvement may be due to motor improvement seen after DBS, but a recent systematic review of NMS' responses after DBS suggested appears to contradict this logical thought.[9]

Our hypothesis was that perhaps pain might have an improvement in these patients due, in part, to changes in sensory thresholds, as seen in other movement disorders such as PD.[15, 127] In PD, the pain relief seen after DBS did not correlate to the motor improvement after surgery.[15, 127]

Therefore, our aim with this study was to evaluate sensory thresholds responses to GPi-DBS in dystonic patients, something that has not been studied before in the literature. However, in our sample, turning on or off the DBS system had no significant effect on painful or non-painful sensory thresholds, on evoked pain ratings, or on the conditioned top-down modulation of pain. Perhaps the reason why this was a negative result is because of some of our study's limitations that will be described in detail further below.

6.3 Some sensory thresholds differ in areas with different severities of dystonia

We have observed that there are somatosensory abnormalities in dystonic areas (i.e., higher WDT). Our results also showed that body areas with more and

less dystonic symptoms had significant differences in sensory thresholds. Thermal tests assessing thinly myelinated A-δ and unmyelinated C-fibers, showed higher responses to experimental pain (cold) and lower detection thresholds for warm in the less dystonic area compared to the region where dystonia was more intense. For vibratory stimuli, detection thresholds were lower in the trapezium compared to the hand.

Few studies have used QST in dystonia and some have tried to compare areas with and without dystonic phenomenology, as listed in Table 10. Nevertheless, all studies have small samples and the largest one included different types of dystonia.[88]

Table 10. Studies that used QST in dystonia.

Study	Sample	DBS	Main Findings
Paracka et al. (2017) (79)	20 patients with inherited or idiopathic dystonia (8 with generalized dystonia; 5 with segmental dystonia with upper limb involvement and, 7 with cervical dystonia, CD).	no	• Decreased CDT, and allodynia on both hands (worse in the limb with dystonia); • CD: reduced CDT, WDT, increased allodynia (hand); • Increased CPT and allodynia (shoulder).
Suttrup et al. (2011) (80)	10 patients with idiopathic hand dystonia.	no	• Increased WDTs, CDTs, and MPT; • Increased WDTs and CDTs in the intraindividual comparison.
Lobbezoo et al. (1996) (81)	9 patients with CD.	no	• Pain-pressure thresholds two-time lower than HV.
Present study	16 patients with inherited or idiopathic dystonia (14 with generalized dystonia and 2 with segmental dystonia).	yes	• Increased MDT and MPT were higher in the patients, regardless of the DBS conditions; • Increased CPT and SuC in patients in the on-DBS condition.

Abbreviations: CDT, cold detection threshold; WDT, warm detection threshold; CD: cervical dystonia; CPT, cold pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; HV, healthy volunteers; SuC: pain rating to experimental pain cold stimulus.

However, many of the findings that compare different body parts need to be interpreted with caution because the two regions chosen for evaluation can be different in some aspects. For instance, the type of skin evaluated may be different. Some studies have shown that glabrous and non-glabrous (hairy) skin may have different sensory and pain thresholds.[192, 193]

6.4 Pain descending modulatory systems are abnormal in dystonic patients

We described, for the first time, that dystonic patients have an abnormally high CPM when compared to HV. The experience of pain depends not only on the quality and intensity of the peripheral stimulus but also on the status of pain modulatory systems.

CPM is one of the branches of the various top-down networks that modulate sensory and painful stimuli and is dependent on descending projections from the brainstem to the spinal cord, which is responsible for the creation of spatial contrast between two co-occurring nociceptive stimuli in two different body parts. In this way, the measured CPM changes can be seen as the nociceptive equivalent of the spatial discrimination threshold that has been so extensively described in focal or regional dystonia,[194-197] but less frequently reported in generalized dystonia, which is present in most of our patients.

Our data are in accordance with the theory proposed by Hallett, suggesting that both motor and NMS of dystonia would be related to a generalized inhibition loss with increased plasticity.[8, 198] This would explain the observed change in the pain modulatory system in dystonic patients, with worse spatial discrimination, and loss of counter-irritative nociceptive inhibition.

6.5 Some sensory thresholds in dystonic patients are different from those of HV

The patients had higher MDT and MPT (A-β fibers) in both DBS conditions, when comparing to HV, as well as, higher CPT and SuC (A-δ fibers) in the on-DBS.

Few studies have explored small-fiber sensory changes in dystonia, as seen in Table 10. Sample sizes were usually small, and QST measurements were

commonly based on reaction-time-dependent measurements, which may bias sensory assessment in motor disorders.[173]

One study found increased WDT, CDT, and MPT in the affected side of focal hand dystonia patients.[89] Another study found reduced CDT and WDT and enhanced dynamic mechanical allodynia in distant body parts (hands) and increased CPT and allodynia in the shoulder in patients with cervical dystonia.[88] In cervical dystonia, pain-pressure thresholds were twice as high as for HV.[90] In general, higher thermal detection thresholds have also been reported,[88] as well as abnormal A-δ-dependent heat evoked responses.[89]

These conflicting results might be related to the fact that, in some of these studies, the area chosen to perform QST was the same area where dystonia was localized,[89] while in others, it was the region less affected by the disease.[88] In some instances, one cannot ascertain the dystonic status of the region included in the QST study.[88]

Here we chose to study the less and more dystonic body regions to disentangle these variables. Also, this was the first study to use reaction-time independent QST methods for the determination of sensory detection thresholds. This analysis has a significant importance when studying diseases that cause motor impairment and bias the reaction time due to the motor deficits intrinsic to the pathology itself.

6.6 Are there any correlations between clinical characteristics and sensory thresholds in dystonia?

We found a positive correlation between BFM`s disability score and on-CPM values. This result indicates that impaired top-down modulatory descending pathway would be associated with the patient’s motor disability. We also observed a statistically significant negative correlation between off-CPM values and the vitality score in SF-12. This association indicates that, while DBS is off in

dystonic patients, the same impaired top-down pathway would be linked to patient's tiredness and feeling of burn-out.

Unfortunately, the literature displays no information in order to provide further views on these findings. Therefore, we solely provide an hypothesis that DBS may have a beneficial impact on dystonic patient`s vitality and disability.

6.7 Limitations

The present study has several limitations. The cross-sectional nature of pain and non-motor assessments precludes more in-depth interpretations of the correlations between pain, QoL, and motor symptoms, and might have failed to show potential changes seen after surgery (pain aggravation or improvement) that could have been detected by a prospective assessment.

Our sample has a higher male representation than expected, as shown in the introduction's epidemiology subsection. Some articles have shown the underrepresentation of women in clinical trials.[199, 200] Moreover, even in PD's trials, a condition where male's prevalence is higher than women's, women seem to be less present than expected.[201] Some studies have shown that pressure pain thresholds may differ regarding the subject's gender.[202] Another study indicated a difference in pain rating to thermal stimuli (higher in women), but no difference was noted on rated thermal intensity.[203]

Another critical point to mention is that some of our patients still had botulinum toxin injections as part of their treatment. Although we established a three-month period as inclusion criteria for this project, it's pharmacological effects could still bias our interpretation of some results.

Our small sample is another limitation to mention. Nevertheless, the other QST studies recruited a similar number of patients, and our sample differs from the other study because our patients had already undergone GPi-DBS treatment.

Also, despite the use of comprehensive sensory and pain assessments, including modulatory pain measurements and experimental pain, sessions were

performed after a relatively short period in the on and off conditions. Different from PD and essential tremor, where a few minutes of off-DBS may be enough to show some initial motor and non-motor phenomena, dystonic motor symptoms are known to have very robust therapeutic inertia after DBS shut down so that some patients might experience weeks without aggravations of motor symptoms.[5]

Our results suggest that the NMS of dystonia may also take a long time to appear after the end of stimulation by DBS, similar to what is known for motor symptoms. This information has apparent limitations for future on/off studies.

We chose to limit the wash-out period due to complications (including in extreme situations a theoretical risk of *status dystonicus*) that may arise when DBS is turned off in dystonia.[5] Therefore, technical limitation of a longer off-condition approach is that after the assessment, when stimulation is turned back on, patients would probably experience dystonia aggravation for a significant period, which imposes explicit ethical constraints.

7 CONCLUSION

According to the data presented in this dissertation, we may conclude the following points:

- No sensory and pain parameters were modified by acute short-lasting DBS's changes; therefore GPi-DBS does not seem to influence sensory thresholds in dystonic patients;
- Chronic pain is a common complaint in generalized/segmental dystonia patients, even after implantation of DBS;
- Patients with pain had more severe mood symptoms and worst QoL compared to those without pain;
- Some sensory changes were confirmed to differentially occur between the more and less affected dystonic limb;
- Some sensory thresholds are different in dystonic patients;
- CPM response in dystonic patients is abnormally high when compared to those of HV, suggesting an impairment of the conditioned top-down modulation of pain in dystonia;
- Alterations of CPM were correlated with QoL and motor symptoms.

These data support the integrative view proposing that motor and NMS of dystonia are part of a generalized lack of spatial discrimination in motor, sensory, and cognitive/affective loops.

ATTACHED FILES

ATTACHED FILE A — Ethics Commission's approval of the project.

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Avaliação prospectiva dos efeitos da estimulação cerebral profunda do globo pálido interno sobre a distonia primária: paralelo entre aspectos clínicos e neurofisiológicos envolvidos na evolução da doença

Pesquisador: rubens gisbert cury

Área Temática:

Versão: 6

CAAE: 48607515.5.0000.0068

Instituição Proponente: HOSPITAL DAS CLINICAS DA FACULDADE DE MEDICINA DA U S P

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.236.556

Apresentação do Projeto:

Nova documentação foi submetida.

Objetivo da Pesquisa:

Solicita a inclusão de novo grupo controle, já operado. Apenas procedimentos não invasivos serão utilizados.

Avaliação dos Riscos e Benefícios:

Sem alterações.

Comentários e Considerações sobre a Pesquisa:

A presença de outro controle aumentará a consistência da investigação, sem comprometer os riscos.

Considerações sobre os Termos de apresentação obrigatória:

Recomenda-se aplicar TCLE para este novo grupo, caso não exista TCLE prévio contemplando as atuais avaliações.

Recomendações:

Recomenda-se aplicar TCLE para este novo grupo, caso não exista TCLE prévio contemplando as atuais avaliações.

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_919306E2.pdf	11/05/2017 12:21:57		Aceito
Outros	AdendoClarice.pdf	11/05/2017 12:07:27	rubens gisbert cury	Aceito
Outros	Adendo2904.pdf	29/04/2016 13:17:50	rubens gisbert cury	Aceito
Outros	anuenciaeducacaofisica.pdf	17/04/2016 12:43:27	rubens gisbert cury	Aceito
Outros	Adendo.pdf	17/04/2016 12:41:02	rubens gisbert cury	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TERMODEASSENTIMENTO.docx	25/11/2015 10:10:05	rubens gisbert cury	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	31/10/2015 12:46:17	rubens gisbert cury	Aceito
Outros	Respostaaoparecer2.docx	31/10/2015 12:46:00	rubens gisbert cury	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoPesquisa.docx	31/10/2015 12:45:16	rubens gisbert cury	Aceito
Outros	cadastroprotocolo.pdf	26/08/2015 12:35:05	rubens gisbert cury	Aceito
Folha de Rosto	folharosto.pdf	26/08/2015 12:32:56	rubens gisbert cury	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 24 de Agosto de 2017

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador)

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

ATTACHED FILE B — Ethics Commission's approval of the project.

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação prospectiva dos efeitos da estimulação cerebral profunda do globo pálido interno sobre a distonia primária: paralelo entre aspectos clínicos e neurofisiológicos envolvidos na evolução da doença

Pesquisador: rubens gisbert cury

Área Temática:

Versão: 6

CAAE: 48607515.5.0000.0068

Instituição Proponente: Hospital das Clínicas da Faculdade de Medicina da USP

Patrocinador Principal: Financiamento Próprio

DADOS DA NOTIFICAÇÃO

Tipo de Notificação: Outros

Detalhe: inclusão do projeto de mestrado do adendo que não foi descrito no relatório de

Justificativa: São Paulo, dia 5 de fevereiro de 2018.

Data do Envio: 06/02/2018

Situação da Notificação: Parecer Consubstanciado Emitido

DADOS DO PARECER

Número do Parecer: 2.487.234

Apresentação da Notificação:

Citar aprovação do subprojeto: "Avaliação Quantitativa da Sensibilidade Geral em Regiões Corporais Padronizadas em Pacientes com Distonia Submetidos a Estimulação Cerebral Profunda do Globo Pálido Interno", que será o título da dissertação de Mestrado da neurologista Clarice Listik, sob orientação do Prof. Daniel Ciampi de Andrade no parecer de n° 2.236.556 referente a Emenda 2 do estudo.

Objetivo da Notificação:

Retificação de parecer de n° 2.236.556 da Emenda 2 para inclusão de subprojeto não citado na aprovação.

Avaliação dos Riscos e Benefícios:

Não se aplica.

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UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Comentários e Considerações sobre a Notificação:

Retificação de parecer de n° 2.236.556 da Emenda 2 para inclusão de subprojeto não citado na aprovação.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Conclusões ou Pendências e Lista de Inadequações:

Citar aprovação do subprojeto: "Avaliação Quantitativa da Sensibilidade Geral em Regiões Corporais Padronizadas em Pacientes com Distonia Submetidos a Estimulação Cerebral Profunda do Globo Pálido Interno", que será o título da dissertação de Mestrado da neurologista Clarice Listik, sob orientação do Prof. Daniel Ciampi de Andrade no parecer de n° 2.236.556 referente a Emenda 2 do estudo.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	NotClarice.pdf	06/02/2018 08:39:47	rubens gisbert cury	Postado
Outros	AdendoClarice.pdf	06/02/2018 08:40:08	rubens gisbert cury	Postado

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 06 de Fevereiro de 2018

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador)

ATTACHED FILE C — Ethics Commission's approval of the consent form.

USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação prospectiva dos efeitos da estimulação cerebral profunda do globo pálido interno sobre a distonia primária: paralelo entre aspectos clínicos e neurofisiológicos envolvidos na evolução da doença

Pesquisador: rubens gisbert cury

Área Temática:

Versão: 6

CAAE: 48607515.5.0000.0068

Instituição Proponente: Hospital das Clínicas da Faculdade de Medicina da USP

Patrocinador Principal: Financiamento Próprio

DADOS DA NOTIFICAÇÃO

Tipo de Notificação: Outros

Detalhe: Relator

Justificativa: São Paulo, dia 8 de fevereiro de 2018.

Data do Envio: 08/02/2018

Situação da Notificação: Parecer Consubstanciado Emitido

DADOS DO PARECER

Número do Parecer: 2.509.998

Apresentação da Notificação:

Os pesquisadores postaram na Plataforma Brasil em , a resposta aos questionamentos da CAPPesq e solicitam a inclusão de um grupo controle de 20 pacientes com distonia já previamente submetidos a Cirurgia para Estimulação Cerebral Profunda devido a refratariedade de seus quadro clínico. "Os participantes deste grupo controle serão submetidos a uma avaliação de sensibilidade (por meio das técnicas de avaliação quantitativa através das técnicas de teste de sensibilidade quantitativo e DNIC, que não acarretam qualquer risco à saúde do paciente e visam avaliar os limiares sensitivos por meio de um termo do e fibras de Von Frey) e aplicação de escalas de dor, qualidade de vida, depressão e ansiedade. A avaliação de sensibilidade será avaliada com o estimulado ligado e desligado por 30 minutos (procedimento habitual). Estas técnicas já foram aplicadas anteriormente pelo nosso grupo em pacientes com Doença de Parkinson da mesma

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maneira.

Aproveito para solicitar a inclusão do título " Avaliação Quantitativa da Sensibilidade Geral em Regiões Corporais Padronizadas em Pacientes com Distonia Submetidos a Estimulação Cerebral Profunda do Globo Pálido Interno", que será o título da dissertação de Mestrado da neurologista Clarice Listik".

Objetivo da Notificação:

Responder questionamentos e solicitar a inclusão de adendo.

Avaliação dos Riscos e Benefícios:

A avaliação da sensibilidade tem risco mínimo para o participante, restrito a um pequeno desconforto.

Comentários e Considerações sobre a Notificação:

A inclusão da avaliação da sensibilidade não altera os riscos dos participantes e pode ser útil para ele e o grupo avaliado.

Considerações sobre os Termos de apresentação obrigatória:

Foi anexado novo TCLE

Conclusões ou Pendências e Lista de Inadequações:

Os pesquisadores solicitam a inclusão de um adendo ao projeto de pesquisa para avaliar a sensibilidade de participantes já submetidos à cirurgia. Esta nova avaliação será utilizada por médico do serviço para dissertação de mestrado com o título " Avaliação Quantitativa da Sensibilidade Geral em Regiões Corporais Padronizadas em Pacientes com Distonia Submetidos a Estimulação Cerebral Profunda do Globo Pálido Interno".

Postaram na Plataforma Brasil os TCLE modificado, incluindo a avaliação da sensibilidade.

Os documentos e o adendo seguem as normas de ética em pesquisa e não há impedimentos éticos para a sua aprovação.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Outros	TCLE2.docx	08/02/2018 14:52:13	rubens gisbert cury	Postado

Endereço: Rua Ovídio Pires de Campos, 225 5º andar
Bairro: Cerqueira Cesar **CEP:** 05.403-010
UF: SP **Município:** SAO PAULO
Telefone: (11)2661-7585 **Fax:** (11)2661-7585 **E-mail:** cappesq.adm@hc.fm.usp.br

Outros	TERMODEASSENTIMENTO.docx	08/02/2018 14:52:19	rubens gisbert cury	Postado
Outros	AdendoClarice.pdf	08/02/2018 14:52:34	rubens gisbert cury	Postado

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 23 de Fevereiro de 2018

Assinado por:
ALFREDO JOSE MANSUR
(Coordenador)

ATTACHED FILE D — Patient consent form.

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP
TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1.NOME:.....
DOCUMENTO DE IDENTIDADE No: ..... SEXO: M □ F □
DATA NASCIMENTO: ...../...../.....
ENDEREÇO.....No.....APTO: .....
BAIRRO:..... CIDADE .....
CEP:.....TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL.....
NATUREZA (grau de parentesco, tutor, curador etc.).....
DOCUMENTO DE IDENTIDADE: ..... SEXO: M □ F □
DATA NASCIMENTO: ...../...../.....
ENDEREÇO: ..... No ..... APTO: .....
BAIRRO: ..... CIDADE: .....
CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA: Avaliação prospectiva dos efeitos da estimulação cerebral profunda do globo pálido interno sobre a distonia primária: paralelo entre aspectos clínicos e neurofisiológicos envolvidos na evolução da doença

2. PESQUISADOR: Rubens Gisbert Cury
CARGO/FUNÇÃO: Médico INSCRIÇÃO CONSELHO REGIONAL No 131445
UNIDADE DO HCFMUSP: ICHC

3. AVALIAÇÃO DO RISCO DA PESQUISA:
RISCO MÍNIMO □ RISCO MÉDIO □
RISCO BAIXO X RISCO MAIOR □

4.DURAÇÃO DA PESQUISA : 1 ano (mínima)[1]

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

1 – Você está sendo convidado a participar deste estudo, pois tem o diagnostico de distonia primária, sem controle adequado com as medicações que utiliza neste momento. Atualmente, para estas situações em que o tratamento medicamentoso não está sendo efetivo, é disponível um tipo de tratamento cirúrgico, já aprovado e realizado de forma rotineira na prática clínica. O tratamento

cirúrgico consiste na estimulação de áreas cerebrais que controlam o movimento e que estão alteradas por conta da distonia. Para isso é utilizado um tipo de estimulação cerebral implantável como um marca-passo implantado em um dos dois alvos aprovados para o tratamento da doença. O objetivo deste estudo é estudar as atividades cerebrais no núcleo globo pálido interno, que é o alvo da estimulação cerebral. Nos modelos convencionais, estimulamos o núcleo globo pálido interno com parâmetros pré-estabelecidos, baseados no alívio dos sintomas. A proposta do presente estudo é estudar as reais alterações que ocorrem no núcleo durante a estimulação, de tal forma que possamos melhorar os parâmetros esbalecidos, e consequentemente melhorar os sintomas.

2 – Descrição e Etapas do Estudo:
1. Avaliação Pré-operatória: Após entender e concordar em participar, serão realizados procedimentos rotineiros para verificar se você atende aos critérios para ser incluído no estudo. As avaliações específicas para esse estudo são:
Consulta com neurologista/neurocirurgião que anotará o histórico de sua doença e aplicará escalas clínicas e realizará um exame clínico e neurológico pormenorizado sem modificar as medicações ja utilizadas;
Exames de imagem: Ressonância magnética de crânio, Eletrocardiograma, Rx de torax;
Exames de sangue de rotina (preparatório para qualquer procedimento cirúrgico);
Após a avaliação inicial, se você preencher os critérios de inclusão, você será encaminhado para realização do tratamento cirúrgico.
2. Cirurgia: Você será solicitado a comparecer ao hospital no dia da internação em que será submetido ao procedimento cirúrgico. Deve permanecer internado por cerca de 6 a 7 dias (se não houver intercorrências) e retornar ao Hospital das Clínicas em cerca de 7 a 10 dias para consulta de retorno conforme será orientado por seu medico no dia da alta hospitalar. No momento da cirurgia você será encaminhado ao setor de Radiologia, onde fará um exame de tomografia do crânio após ser colocado o aparelho de estereotaxia (equipamento que acopla a imagem da tomografia e ressonância magnética para guiar a cirurgia. Logo depois será encaminhado ao centro cirúrgico e passará para a mesa cirúrgica com auxílio dos funcionários. A retirada de parte do cabelo e a limpeza detalhada do local da cirurgia serão realizadas para evitar infecção. Depois o Sr(a) será coberto com lençóis e adesivos estéreis. Todos os procedimentos que se seguem não devem causar dor. Sob anestesia geral, duas incisões no couro cabeludo seguidas de dois pequenos orifícios são realizados para que os eletródios responsáveis pela estimulação do alvo cerebral que determina a melhora dos sintomas sejam inseridos. O gerador de estímulos (semelhante a um marcapasso cardíaco) será implantado logo abaixo do osso da clavicula, em um dos lados da região peitoral, sendo necessária uma incisão de cerca de 7 cm. As conexões entre o gerador (marcapasso) e os eletródios cerebrais são inseridas por baixo da pele com um trajeto por trás da orelha, parte lateral do pescoço sem prejuízos estéticos
3. Acompanhamento Pós-operatório: No dia seguinte ao procedimento cirúrgico, e pelos próximos 4 dias, será registrada a atividade elétrica. Nesse momento, o paciente não passará por mais nenhuma intervenção cirurgica, apenas realizará atividades do dia-a-dia como andar, comer, e hábitos de higiene pessoal. O registro da atividade elétrica é feita por um dispositivo externo, não implantável, conectado ao estimaldor cerebral profundo, e através do eletroencefalograma. Você será deverá a retornar para consultas de acompanhamento no período pós-operatório mensalmente ou conforme a necessidade de cada paciente, segundo a orientação dos médicos assistentes pelo período mínimo de 1 ano. Neste acompanhamento pós-operatórios serão realizadas avaliações neurológicas e clínicas no Hospital das Clínicas. Algumas avaliações que serão feitas são:

- Avaliações de sensibilidade e dor, incluindo os testes de sensibilidade quantitativa também chamado de QST (feitas através de um aparelho que esquenta e esfria para testar os níveis de sensibilidade e de dor) e outro teste de sensibilidade e dor chamado DNIC (feito de maneira semelhante ao anterior, porém utilizando uma bacia com água e gelo).
- Testes cognitivos (avaliação de atenção, memória, entre outras);
- Testes de marcha (caminhada).

Alguns destes testes (os de sensibilidade e dor) são feitos com o aparelho ora ligado e ora desligado por cerca de 30 minutos há no máximo 2 horas).

3- Riscos Potenciais, Efeitos Golaterais e Desconforto:
1. Desconfortos e riscos comuns a qualquer cirurgia de implante de estimuladores cerebrais: Possibilidade (cerca de 4,5 a 7%) de infecção de couro cabeludo ou pele nos locais de manipulação cirúrgica e das membranas de envolvem o cérebro (meningites não contagiosas - risco menor que 1%) que devem ser tratadas com antibiótico e podem prolongar a internação. Possibilidade de complicação durante a anestesia geral relacionadas a alergias não conhecidas ou reações imprevisíveis aos anestésicos de uso rotineiro. Disfunções neurológicas temporárias não relacionadas à hemorragia, como perda de força em um lado do corpo, alterações da fala, confusão mental e desorientação no tempo e espaço no período após a cirurgia podem ocorrer em cerca de 10% dos casos. Inchaço temporário na face ou na fronte relacionados à fixação do aparelho estereotáctico ocorrem em 90% dos casos. Riscos de hemorragia cerebral (1,8 a 2,5%) com possível indução de prejuízo parcial ou total de funções cerebrais como movimentação do corpo, fala e movimento dos olhos. O risco de morte relacionados a procedimentos similares é de 0,5 a 1% das operações.
2. Desconfortos e riscos especificamente relacionados a este estudo: Risco de hemorragia cerebral estimado ser semelhante ao procedimento convencional. Riscos desconhecidos que possivelmente podem estar associados a este procedimento, mas não foram ainda observados. No entanto, estudos prévios semelhantes em animais e em humanos não os evidenciaram. Risco de ganho de peso e alteração de glicemia e colesterol no pós-operatorio tardio.

4 – Benefícios
Você provavelmente terá maior benefício de melhora dos sintomas da distonia (contrações musculares, posturas alteradas, dificuldade de marcha, dor) consequentemente ao implante de estimuladores cerebrais com a mais avançada técnica de cirurgia para distonia disponível no mundo. Além do benefício pessoal, as informações obtidas neste estudo poderão beneficiar, no futuro, outros pacientes com distonias de difícil controle com medicamentos, pois poderemos compreender melhor os mecanismos eletrofisiológicos presentes nesta doença, e aperfeiçoar as técnicas de estimulação. A participação nas avaliações pós-operatórias (avaliação de sensibilidade, dor, marcha) poderão contribuir no futuro com o entendimento das causas da distonia, bem como com o entendimento da evolução da doença.

5 – Garantia de acesso: em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é o Dr. Rubens Gisbert Cury, que pode ser encontrado no endereço Av Dr Enéias de Carvalho Aguiar, 255 Telefone(s) 11-26617877 ou celular 11-972838184. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5o andar – tel: 2661-6442 ramais 16, 17, 18 – e-mail:cappesq.adm@hc.fm.usp.br

6 – É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição.

7 – Direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente;

8 – Direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

9 – Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação.

10 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo " Avaliação prospectiva dos efeitos da estimulação cerebral profunda do globo pálido interno sobre a distonia primária: paralelo entre aspectos clínicos e neurofisiológicos envolvidos na evolução da doença"
Eu discuti com o Dr. Rubens Gisbert Cury sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante legal Data / /

Assinatura da testemunha Data / /
para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.

(Somente para o responsável do projeto)
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo Data / /

REFERENCES[1]

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Journal: Parkinsonism & Related Disorders
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Corresponding Author: Daniel CIAMPI DE ANDRADE
Co-Authors: Clarice Listik, M.D.; Rubens G Cury, MD, PhD; Valquiria A da Silva; Sara C Barbosa Casagrande, MD; Eduardo Listik, MSc, PhD; Naira Link, MD; Ricardo Galhardoni, PhD; Egberto R Barbosaa, MD, PhD; Manoel J Teixeira, MD, PhD;

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Submitted article “Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation”

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Corresponding Author: Professor Daniel CIAMPI DE ANDRADE, PhD, MD

Corresponding Author's Institution: Hospital das Clinicas, University of São Paulo, Brazil. Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, SP.

First Author: Clarice Listik, M.D.

Order of Authors: Clarice Listik, M.D.; Rubens G Cury, MD, PhD; Valquiria A da Silva; Sara C Barbosa Casagrande, MD; Eduardo Listik, MSc, PhD; Naira Link, MD; Ricardo Galhardoni, PhD; Egberto R Barbosaa, MD, PhD; Manoel J Teixeira, MD, PhD; Daniel C de Andrade, MD, PhD

Abstract: Introduction: Unlike motor symptoms, the effects of deep brain stimulation (DBS) on non-motor symptoms associated with dystonia remain unknown. The objective of this study was to assess the effects of DBS on evoked experimental pain and cutaneous sensory thresholds in a cross-over, double-blind on/off study and compare these results with those of healthy volunteers (HV).
Methods: Sixteen patients with idiopathic dystonia (39.9 ± 13 years old, n = 14 generalized) with DBS of the globus pallidus internus underwent a battery of quantitative sensory testing (QST) and assessment using a pain top-down modulation system (conditioned pain modulation, CPM). Results for the more and less dystonic body regions were compared in the on and off stimulation conditions. The patients' results were compared to age- and sex-matched HV.
Results: Descending pain modulation CPM response in dystonic patients (0.66±1.99) was abnormally high (defective) compared to HV (-0.43±0.29, p=0.0001). Cold pain threshold and cold hyperalgesia 54.8% and 95.7% higher in dystonic patients compared to HV. On-DBS CPM correlated with higher Burke-Fahn-Marsden (BFM) disability score (r=0.598; p=0.014). While sensory and pain thresholds were not affected by DBS on/off condition, pain modulation was remarkably low in dystonic patients and tended to be aggravated by DBS.
Conclusion: The analgesic effects seen after DBS does not seem to depend on short-duration changes in cutaneous sensory thresholds in dystonic patients, and may be related to changes in the central processing of nociceptive inputs.

Author Declaration

Parkinsonism & Related Disorders is committed to proper scientific conduct and the protection of animal and human research subjects. Submission of this manuscript implies compliance with the following ethical requirements. Please affirm that you are representing all of the authors in stating compliance with these policies by checking the box at the end of this section.

1. Studies with human subjects must have been conducted in accordance with the Declaration of Helsinki. All persons must have provided informed consent prior to being included in the study.

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3. Protocols with animal or human subjects must have been approved by the relevant local committee(s) charged with ensuring subject protection. Studies that entail pain or distress will be assessed in terms of the balance between the distress inflicted and the likelihood of benefit.

4. The authors declare that the manuscript is original, that it is not being considered for publication elsewhere, and that it will not be submitted elsewhere while still under consideration for Parkinsonism & Related Disorders or after it has been accepted by Parkinsonism & Related Disorders.

5. All authors have seen and approved the manuscript in the form submitted to the journal. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable.

6. All sources of financial support for the work have been declared in the Acknowledgements section of the manuscript. Any additional conflicts of interest must also be declared. Please include declarations of any consultancy or research funding received from relevant companies from three years prior to performance of the research until the time of manuscript submission. If the research is supported by internal funds, that should be stated as well.

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Highlights

- Sensory and pain thresholds do not differ in on- or off-DBS condition;
- Dystonic patients have altered sensory/pain thresholds regarding healthy controls;
- Dystonic patients have an abnormal descending modulatory system.

Abnormal sensory thresholds of dystonic patients are not affected by deep brain stimulation

Clarice Listik[a], Rubens Gisbert Cury[a], Valquiria Aparecida da Silva[b], Sara Carvalho Barbosa Casagrande[a], Eduardo Listik[c], Naira Link[b], Ricardo Galhardoni[b,d], Egberto Reis Barbosa[a], Manoel Jacobsen Teixeira[b], Daniel Ciampi de Andrade[a,b,e]

[a] *Movement Disorders Center, Department of Neurology, School of Medicine, University of São Paulo. Av. Dr. Enéas de Carvalho Aguiar, 255, 5th floor, São Paulo, SP, Brazil. P.O. Box: 05403-900.*

[b] *Pain Center, Neurosurgery Division, LIM 62, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil. Av. Dr. Enéas de Carvalho Aguiar, 255, 5th floor, São Paulo, SP, Brazil. P.O. Box: 05403-900.*

[c] *Department of Biochemistry of the Federal University of São Paulo, Rua Três de Maio, 100, São Paulo, SP, Brazil. P.O. Box: 04044-020.*

[d] *Federal University of ABC, São Bernardo do Campo; School of Medicine. Av. dos Estados, 5001, Santo André, SP. P.O. Box 09210-580.*

[e] *Pain Center, Instituto do Cancer do Estado de São Paulo. Dr. Arnaldo 251. São Paulo, SP, Brazil. P.O. Box: 01246-000.*

Emails: clarice.listik@gmail.com, rubens_cury@usp.br, valquiria.ase@gmail.com, drasaracasagrande@gmail.com, eduardo.listik@usp.br, naira.link@fm.usp.br, rgalhardoni@gmail.com, egbertob@8415.com.br, manoeljacobsen@gmail.com, ciampi@usp.br.

Corresponding author:

Daniel Ciampi de Andrade, M.D., Ph.D.
Address: Av. Dr. Enéas de Carvalho Aguiar, 255, 5º andar, sala 5084 – Cerqueira César 05403-900 – São Paulo – SP – Brazil.
Phone/ Fax: +55-11-2661-7152
E-mail: ciampi@usp.br

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ABSTRACT

Introduction: Unlike motor symptoms, the effects of deep brain stimulation (DBS) on non-motor symptoms associated with dystonia remain unknown. The objective of this study was to assess the effects of DBS on evoked experimental pain and cutaneous sensory thresholds in a cross-over, double-blind on/off study and compare these results with those of healthy volunteers (HV).

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Conclusion: The analgesic effects seen after DBS does not seem to depend on short-duration changes in cutaneous sensory thresholds in dystonic patients, and may be related to changes in the central processing of nociceptive inputs.

1 Introduction

Dystonia is a frequent movement disorder and impacts the patients' quality of life (QoL) [1]. Part of the challenges in dystonia is related to non-motor symptoms (NMS) [2, 3]. Chronic pain is one of the most disabling and frequent complaints in dystonia [1, 2].

Dystonic patients suffer from altered somatosensory integration and plasticity [4, 5]. It is believed that sensory abnormality and pain in dystonia are part of a more widespread (GABA-A/dopamine) loss of inhibition and increase in brain plasticity [1]. Even NMS improvement by motor symptom-directed therapies, such as botulinum toxin, occurs due to its uptake by sensory fibers and subsequent effects on Schwann cells in the dorsal horn of the spinal cord, speaking against a simple musculogenic mechanism [6]. Deep brain stimulation (DBS) targeting the *globus pallidus internus* (GPi) is a first-line treatment for refractory dystonia [7, 8], improving motor symptoms (43–65%) [9] together with pain improvement. It is thought that pain amelioration is a considerable drive of post-operative improvements in QoL [7, 8, 10]. Pain relief after deep brain stimulation (DBS) treatment is not thought to be simply due to the alleviation of motor symptoms [10], and could be due to increases in nociceptive thresholds, such as described in Parkinson's Disease (PD), or instead, by boosting top-down pain modulatory/inhibitory systems [11]. However, no study has assessed the mechanisms behind DBS effects on pain and sensory thresholds, nor evaluated pain modulatory systems in dystonia.

We report the first effort to dissect the analgesic effects of DBS in dystonia by measuring sensory and pain thresholds by quantitative sensory testing (QST), as well as pain descending modulatory responses by dynamic QST — a conditioned pain

modulation (CPM) paradigm, in a double-blind, crossover, on/off stimulation study with paired comparison with healthy volunteers (HV).

2 Methods

This study was conducted from November 2017 to April 2018 and approved by the Ethics Review Board (#48607515.5.0000.0068). All patients gave written informed consent.

2.1 Patients

Patients included had segmental/generalized dystonia of inherited/idiopathic [12] etiology who underwent GPi-DBS. Exclusion criteria were patients younger than 18 years old, those having received botulinum toxin injections over at least the preceding three months, who did not consent to participate, or those who could not have their DBS turned off.

2.2 Study design

Patients assessed under their usual treatment underwent a neurological examination and completed pain, mood, cognitive, and QoL questionnaires. Afterward, a double-blind, randomized controlled investigation (Figure 1A) was performed to assess the effects of DBS on sensory and pain thresholds using QST and pain descending modulation by CPM. Another switched the DBS between on/off (namely on-DBS or off-DBS, respectively), using www.randomizer.org. After a 30-minute wash-out, QST and CPM were performed again. Thus, patients were always evaluated with the same QST/CPM battery in the off and on-DBS condition.

QST parameters and CPM effect in dystonic patients were also compared to reference values obtained from age- and sex-matched HV from our lab's normative database [13].

2.3 Patients' clinical and functional status assessments

Patients were assessed by the motor and disability parts of the Burke-Fahn-Marsden (BFM) scale, with higher scores indicating worse dystonia and worse disability [14]. Previous disease and medication histories were obtained. Clinical and neurologic examinations were performed. Chronic pain was assessed in all patients. Oral medication was not changed during the evaluation. The hospital anxiety and depression scale (HADS) [15, 16], SF-12 quality of life questionnaire (QoL) (SF-12) [17], and the frontal assessment battery (FAB) were used to determine mood, QoL, and cognitive variables [18].

2.4 Outcome measures

2.4.1 Pain assessment scales

Below are the questionnaires used for pain assessment [11, 19]. These scales and questionnaires were applied only once, with patients under their usual treatment, thus, before the QST/CPM on/off study.

i. The Short-form McGill pain questionnaire (McGill) in which pain descriptors are categorized into three dimensions of pain: sensory, affective, and evaluative. There is an item for pain intensity by the visual analog scale (VAS, 0–100 mm, where 0 means no pain and 100 stands for maximal pain imaginable) [20];

ii. The Brief Pain Inventory (BPI) short-form gives two main scores: pain severity score, and pain interference score in daily activities [21];

iii. The *Douleur Neuropathique-4* (DN4) assesses a possible neuropathic component of the pain. Scores of ≥4 are considered positive [22];

iv. Neuropathic Pain Symptom Inventory (NPSI) evaluates different clusters of descriptors and varies from 0–10 [23].

2.4.2 Psychophysics assessment

2.4.2.1 QST

The tests performed were already extensively used [11, 19]. Briefly, stimuli were applied on the thenar eminence of the asymptomatic limb (i.e., no or less dystonic) and the skin over the most dystonic trapezium (Figure 1B). Mechanical detection thresholds (MDT) and mechanical pain thresholds (MPT) were measured using von Frey monofilaments (NC 17775; Bioseb, France) [11, 19]. Vibration detection threshold (VDT) was measured using a graduated tuning fork (Rydel-Seiffer tuning fork; Martin, Tuttlingen, Germany) [24]. Thermal thresholds were assessed using a TSA-2001 device (Medoc, Ramat Yshai, Israel) with a 20×35 mm thermode. For thermal detection thresholds (warm detection threshold, WDT; cold detection threshold, CDT), the forced-choice method [11, 19] was, again, used to avoid bias due to lower motor reaction time [11]. Heat and cold pain thresholds (HPT, CPT) were established through a method of limits (1°C/s from 32°C). Experimental pain was studied by suprathreshold heat (SuH) and cold (SuC) stimulations [11, 19]. Stimulations above (46°C and 48°C) and below (5°C and 10°C) heat and cold pain thresholds, respectively, were delivered for 2s and VAS scores were recorded.

2.4.2.2 CPM

Dynamic QST, CPM (Figure 1C), was explored with a painful thermal test stimulus (set at 5°C above HPT for 5s) applied to the left anterior thigh. This was performed both before (unconditioned test stimulus), and after (conditioned test stimulus) the delivery of a painful conditioning stimulus at the contralateral upper limb - immersion in 4°C water until pain reached a VAS of at least 60/100 mm (i.e., cold pressor test) [13, 19]. CPM is based on the modulatory effect that a painful *conditioning* stimulus (i.e., the upper limb immersion in cold water) has on a painful *test* stimulus applied in a different body segment (i.e., heterotopic). Thus, it is calculated as the change in pain intensity, measured by VAS, by the subtraction of the conditioned test stimulus and the unconditioned test stimulus. Therefore, normal individuals have negative CPM values, as a normal response is to have a lower pain intensity after the painful conditioning stimulus is delivered.

2.5 Statistical Analysis

Data were expressed as mean ± standard deviation (min–max). Non-normal data were evaluated using the Wilcoxon non-parametric test. Bonferroni correction was used to adjust to multiple analysis. Correlation analyses were performed by Spearman's correlation. The following comparisons were made: i) Over the less affected body region (hand) – off *vs.* on-DBS for each QST parameter; ii) Over the more affected body region (trapezium) – off *vs.* on-DBS for each QST parameter; iii) In the off-DBS condition – hand *vs.* trapezium for each QST parameter; iv) In the on-DBS condition – hand *vs.* trapezium for each QST parameter; v) CPM effect (off *vs.* on-DBS condition); vi) In the on- and off-DBS QST and CPM effect was compared to HV's.

A subanalysis was performed comparing the QoL, BFM, FAB, and HADS scales between patients with and without chronic pain using the Mann-Whitney test for

independent samples. QST/CPM analyses were correlated with BFM, pain intensity (BPI), HADS, and SF-12 scores. All statistical calculations were performed using the Statistical Package for the Social Sciences software (SPSS, version 20.0.0; SPSS Inc., Chicago, IL, USA) and statistical significance was set at $p<0.05$).

3 Results

3.1 Sample description

Sixteen patients, with 39.9±13.8 (18–61) years, were included (n=14 generalized, n=2 segmental; 4 women). Family history of dystonia was present in 25.0% of the patients, and 43.8% had consanguinity. Seven patients underwent genetic analyses: DYT1, n=2; DYT6, n=3; and DYT16, n=2. Age at dystonia onset was 17.8±14.9 (4–54).

Patients were evaluated after 3.7±3.8 (0.31–12.26) years after DBS surgery. They had a total BFM motor score of 48.0±21.1 (20–78) and a disability score of 10.0±5.0 (2–19) (Supplementary Table 1). Nine patients (56.3%) reported current chronic pain, defined as pain that lasts or recurs for longer than three months [25]. Only one reported the presence of chronic pain before dystonia development. The BPI pain severity index was 3.3±1.9 (0.0–6.2), and its pain interference in daily activities was 2.4±2.7 (0.0–8.7) (Supplementary Table 2). Two patients had a positive DN4 (both with a score of 4). Four patients (25.0%) had anxiety scores higher than 8.0, and none had major depression (score >9.0) on the HADS. SF-12's bodily pain ($p=0.023$) and mental health ($p=0.042$) subscores were significantly worse in patients with chronic pain compared with pain-free dystonic patients (Supplementary Table 1). Also, patients with chronic pain had worse total ($p=0.005$), depression ($p=0.008$), and anxiety ($p=0.023$) scores in the HADS (Supplementary Table 1).

3.2 Sensory and modulatory pain assessment

QST values in the off-DBS condition were not significantly different from the on-DBS in comparisons within the same body part (hand or trapezium, Table 1).

When comparing changes between the more (trapezium) and less (hand) affected body regions in the off-DBS condition, we found that the pain rating to experimental pain cold stimulus was significantly higher on the hand (43.6±30.1 *vs.* 35.5±31.4; p=0.011), and similar findings were obtained in the on-DBS status in the hand (SuC: 53.6±32.8) compared to the trapezium (42.2±33.1; p=0.021). Similarly, the VDT was significantly lower on the trapezium compared to the hand in the off-DBS status (7.5±0.6 *vs.* 6.6±1.0, p=0.020; respectively), as well as in the on-DBS conditions: 7.7±0.7 *vs.* 6.4±1.2, p=0.002 for the hand and trapezium, respectively. In the on-DBS, WDT was significantly lower on the hand (33.2±0.8) compared to the trapezium (34.3±1.6; p=0.007; respectively).

Concerning the less affected body region (hand), both the MDT and MPT were higher in dystonic patients compared to HV, regardless of the DBS conditions (Table 2). CPT and experimental pain cold stimulus (SuC) (i.e., cold hyperalgesia) were significantly higher in dystonic patients while in the on-DBS condition. CPT was 54.8% higher, while SuC was 95.7% higher when compared to HV.

CPM values in the off-DBS state were not significantly different from the on-DBS (Table 3), but both on- and off-DBS values were significantly higher (i. e. worse CPM) compared to reference data from HV (Table 3).

We found a correlation between on-DBS CPM and BFM disability score (r=0.598, p=0.014), with off-DBS CPM and the SF-12 vitality score (r=-0.655, p=0.008). Other pre-planned correlation analyses were not significant.

4 Discussion

We found that chronic pain is a common complaint in dystonic patients, even after DBS. Patients with pain had more severe mood symptoms and worst QoL. Even in the body area less affected by dystonia, patients presented cold allodynia and hyperalgesia, as well as a significant A-β and A-δ dependent deficits related to mechanical detection and pain thresholds. Since cold hyperalgesia and allodynia depend on central alterations in sensory processing, these data suggest that dystonic patients have both peripheral and central sensory abnormalities occurring even in unaffected body regions.

We also found that the more affected dystonic body region (i.e. skin over the trapezium) presented more altered sensory integration results (i.e. higher WDT, lower cold hyperalgesia) when compared to the less affected hand.

Although this may be, in part, due to the difference between glabrous and non-glabrous skin or due to intrinsic discriminatory threshold differences between the hand and the shoulder, these results were relatively consistent and did not occur in other sensory thresholds, suggesting an actual abnormality related to the dystonic state. Turning on or off the DBS had no significant effect on painful or non-painful sensory thresholds, on evoked pain ratings or conditioned top-down modulation of pain.

In our sample, 56.3% of patients had chronic pain even after DBS treatment. Pain is a frequent complaint and impacts a patient's QoL [1, 3]. Nevertheless, most studies on dystonia and pain have focused on cervical dystonia and other focal dystonias, with a high prevalence of pain (67–75%) [1, 2]. In patients with inherited/idiopathic generalized dystonia, a randomized clinical trial with 40 patients showed reduction in pain (VAS) in on-DBS patients *versus* no change in sham-

stimulation (63% *vs.* 0%, p<0.001) at 3 months, which was maintained at 6 months and 5 years [7, 10, 26].

We found that among patients with pain, two fulfilled the DN4 screening test for neuropathic pain. The current diagnostic criteria for neuropathic pain imply that pain be located in an area of sensory deficits caused by a disease or lesion to the somatosensory system. While we have found that there are somatosensory abnormalities in dystonic areas (i.e. higher WDT), the task to ascertain that dystonic patients have a lesion of disease directly causing these abnormalities remains to be determined.

We found a higher MDT and MPT (A-β fibers) in both DBS conditions, as well as, higher CPT and SuC (A-δ fibers) in the on-DBS state compared to HV. Few studies have explored small-fiber sensory changes in dystonia. The sample sizes were usually small, and QST measurements were commonly based on reaction-time-dependent measurements, which may bias sensory assessment in motor disorders [19].

One study found increased WDT, CDT, and MPT in the affected side of focal hand dystonia patients [27]. Another study reported reduced CDT and WDT and enhanced dynamic mechanical allodynia in distant body parts (i.e. hands) and increased CPT and allodynia in the shoulder in patients with cervical dystonia [5]. In cervical dystonia, pain-pressure thresholds were twice as high as for HV [28]. In general, higher thermal detection thresholds have also been reported [5], as well as abnormal A-β-dependent heat evoked responses in dystonic patients when compared to HV [27]. These conflicting results might be related to the fact that, in some of these studies, the body area chosen to perform QST was the same where dystonia was located [27], while in others it was the region less affected by the disease [5]. In some instances, one cannot ascertain the dystonic status of the region included in the QST study [5]. Here we chose to study the less and more dystonic body regions to disentangle these variables. Also,

this was the first study to apply reaction-time independent QST methods for the determination of sensory detection thresholds. This analysis has a significant importance when studying diseases that cause motor impairment that can bias the reaction time due to the motor deficits intrinsically associated with the studied pathology. To our knowledge, this is the first attempt to evaluate DBS's effect on sensory and pain thresholds, and we found no effect between the on- and off-DBS status.

We described, for the first time, that dystonic patients have an abnormally high (i.e. defective) pain modulatory function. The experience of pain depends not only on the quality and intensity of the peripheral stimulus but also on the status of pain modulatory systems. CPM assesses one of the branches of the various top-down networks that modulate sensory and painful stimuli and is dependent on descending projections from the brain cortex and brainstem to the spinal cord, which is responsible for the creation of spatial contrast between two co-occurring nociceptive stimuli in two different body parts. Our CPM changes could be seen as the nociceptive equivalent of the spatial discrimination threshold that has been so extensively described in dystonia [29]. Such differences were less frequently explored in generalized dystonia, which was present in most of our patients. Our data are in accordance with the theory proposed by Hallett [4], suggesting that both motor and NMS of dystonia would be related to an inhibition loss with increased plasticity [1, 4]. This would explain defective QST parameters seen even on the less affected body region in dystonic patients compared to HV. Also, it would justify the deficits found when comparing the more and less affected body areas in patients. Furthermore, pain modulatory system was highly defective in dystonic patients, with worse loss of counter-irritation nociceptive modulation, where

facilitation occurred instead of inhibition. Our findings, which shows that altered CPM was strongly correlated with dystonic disability scores, further support this view.

The present study has limitations. The cross-sectional nature of pain and non-motor assessments precludes more profound interpretations on the correlations between pain, QoL, and motor symptoms, and might have failed to show potential changes seen after surgery. Also, sessions were performed after a relatively short period in the on- and off-DBS condition; therefore, despite the use of many thresholds, modulatory pain measurements, and assessments; most of the on/off comparisons were not significant. Different from PD, in which a short period without DBS stimulation may be enough to reveal initial motor and non-motor phenomena; dystonic motor symptoms are known to have very robust therapeutic inertia after DBS activation or shut down so that some patients might experience weeks without changes of motor symptoms [30]. It is possible that NMS of dystonia may also take a long time to build after the end of stimulation by DBS, similar to what is known for motor symptoms. By submitting patients to more extended off-DBS time, patients could experience dystonia aggravation for a significant period, even after stimulation is resumed, imposing explicit ethical constraints for on/off DBS studies [8]. This information is original and may have important implications for the design of future on/off studies

5 Conclusion

We have shown that in a sample of patients with predominant generalized dystonia under DBS, a significant proportion of individuals still have pain. Alterations of CPM were correlated with QoL and motor symptoms, according to the literature. Some sensory changes were confirmed to occur differentially between the more and less affected dystonic limb, and were worse in patients compared to HV; while no sensory

parameters were modified by acute short-lasting DBS changes. These data support the integrative view, which proposes that motor and NMS of dystonia are part of a generalized lack of spatial discrimination in motor, sensory, and cognitive/affective loops.

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Figure Captions

Figure 1. Cross-sectional and double-blind randomized evaluation using QST and CPM. (A) Patients underwent a clinical assessment (cross-sectional study) using the following validated tools and questionnaires: Burke-Fahn-Marsden scale, Neuropathic Pain Symptom Inventory, *Douleur Neuropathique-4*, Brief Pain Inventory, short-form McGill Pain Questionnaire, Frontal Assessment Battery, the Hospital Anxiety and Depression Scale and SF-12 Quality of Life Questionnaire. Afterward, a double-blind, randomized controlled study was performed to assess the effects of deep brain stimulation on sensory and pain thresholds using QST and CPM. An unblinded researcher maintained or changed the DBS status (on-DBS or off-DBS respectively), as previously randomized. After a 30-minute wash-out, QST and CPM were performed. (B) The QST battery was applied in the thenar eminence of the asymptomatic [(no dystonia)/less symptomatic (less dystonic)] limb (hand) and in the most affected (most dystonic) trapezium. (C) The CPM battery was done with a thermal test stimulus applied to the left anterior thigh. The unconditioned test stimulus was the pain intensity measured by the Visual Analog Scale (VAS, 0—100 mm) to a stimulus set at 5 °C above the heat pain threshold (HPT) applied for 5 s (VAS 1). The conditioned test stimulus was the pain intensity (VAS 2) to the same stimulus described above while the patients submerged their right hand in a 4 °C water bath with ice blocks and cold water (painful conditioning stimulus). CPM effect is calculated as follows: [VAS 2] – [VAS 1], as the expected response in healthy volunteers is VAS 1 > VAS 2, it is usually a negative number.

Abbreviations: QST: Quantitative Sensory Test; CPM: Conditioned pain modulation.

Table 1

Table 1. Quantitative Sensory Test (QST) values on the more (trapezium) and less (hand) affected body region and in the on- and off-DBS conditions. The table shows the results of the following comparisons: (i) off *vs.* on-DBS for QST parameters in the hand (p-hand); (ii) off *vs.* on-DBS for QST parameters in the trapezium (p-trapezium); (iii) analysis of hand *vs.* trapezium for QST parameters in the off-DBS condition (p-off); and (iv) analysis of hand *vs.* trapezium for QST parameters in the on-DBS condition (p-on). Results are presented as mean ± standard deviation (min–max). Significance set at *p < 0.05 and at **p < 0.025 for Bonferroni correction.

Variable	off-DBS		on-DBS		off *vs.* on-DBS		Hand *vs.* Trapezium	
	Hand	Trapezium	Hand	Trapezium	p-hand	p-trapezium	p-off	p-on
CDT (°C)	30.68 ± 1.15 (27.9–31.8)	29.99 ± 1.77 (26.4–31.9)	30.72 ± 0.76 (29.1–31.9)	30.1 ± 1.56 (28.7–31.9)	0.975	0.900	0.083	0.061
WDT (°C)	33.52 ± 1.54 (32.3–37.4)	34.3 ± 1.76 (32.2–37.4)	33.25 ± 0.84 (32.4–35.3)	34.27 ± 1.61 (32.1–37.6)	0.682	0.979	0.155	0.007**
HPT (°C)	45.88 ± 2.71 (41.5–50)	44.95 ± 3.07 (38.95–49.25)	45.99 ± 2.51 (42.35–49.8)	45.64 ± 3.49 (37.7–49.4)	1.000	0.453	0.326	0.717
CPT (°C)	16.05 ± 7.68 (0.8–29.6)	13.5 ± 9.55 (0–26.1)	16.56 ± 6.21 (5.3–24.45)	15.08 ± 9.44 (0–28.15)	0.959	0.140	0.233	0.587
SuH (VAS)	39.81 ± 28.58 (2.5–90.5)	36.5 ± 28.29 (1.5–90.5)	39.5 ± 28.71 (4–87.5)	48.25 ± 32.05 (2–93.5)	0.518	0.191	0.313	0.155
SuC (VAS)	43.62 ± 30.10 (2.5–87.5)	35.5 ± 31.4 (0–100)	53.56 ± 32.83 (3–99)	42.21 ± 33.08 (0–100)	0.083	0.233	0.011**	0.021**
MDT (g/mm^2)	1.77 ± 0.2 (1.7–2.3)	1.95 ± 0.49 (1.7–3.3)	1.8 ± 0.4 (1.7–3.3)	1.91 ± 0.7 (1.7–4.5)	0.655	0.783	0.059	0.180
MPT (g/mm^2)	104.02 ± 42.48 (25–137.3)	98.85 ± 48.33 (6.8–137.3)	114.04 ± 36.42 (39.1–137.3)	117.01 ± 38.51 (31.6–137.3)	0.043	0.108	0.715	0.833
MH (VAS)	5.81 ± 8.5 (0–22)	6.69 ± 12.9 (0–51)	7.94 ± 12.61 (0–45)	5.19 ± 12.01 (0–46)	0.262	0.248	0.859	0.089
Mechanical dynamic allodynia (0-100)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	1.000	1.000	1.000	1.000
VDT (µm)	7.56 ± 0.62 (6–8)	6.62 ± 1.02 (5–8)	7.69 ± 0.7 (6–8)	6.44 ± 1.2 (3–8)	0.589	0.589	0.020**	0.002**

Abbreviations: CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; SuH, pain rating to suprathreshold heat stimulation; VAS, Visual analogue scale 0–100 mm; SuC, pain rating to suprathreshold cold stimulation; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MH, mechanical hyperalgesia; VDT, vibration detection threshold

Table 2

Table 2: Comparison between patients and healthy volunteers concerning hand QST parameters. The table shows the results of the following comparisons: (i) HV *vs.* patients off-DBS for QST parameters in the hand (p HV *vs.* off); (ii) HV *vs.* patients on-DBS for QST parameters in the hand (p HV *vs.* on). Results are presented as mean ± standard deviation (min–max). Significance set at *$p < 0.05$ and at **$p < 0.025$ for Bonferroni correction.

Variable	HV	Dystonic Off	Dystonic On	p HV *vs.* off	p HV *vs.* on
CDT (°C)	30.56 ± 0.88 (27.7–31.4)	30.68 ± 1.15 (27.9–31.8)	30.72 ± 0.76 (29.1–31.9)	0.171	0.897
WDT (°C)	33.51 ± 0.67 (32.4–35.1)	33.52 ± 1.54 (32.3–37.4)	33.25 ± 0.84 (32.4–35.3)	0.128	0.254
HPT (°C)	44.55 ± 3.35 (37.7–49.6)	45.88 ± 2.71 (41.5–50)	45.99 ± 2.51 (42.4–49.8)	0.402	0.491
CPT (°C)	10.70 ± 6.43 (0.5–22.3)	16.05 ± 7.68 (0.8–29.6)	16.56 ± 6.21 (5.3–24.5)	0.056	0.023**
SuH (VAS)	24.40 ± 23.27 (0.0–65.0)	39.81 ± 28.58 (2.5–90.5)	39.5 ± 28.71 (4.0–87.5)	0.073	0.080
SuC (VAS)	27.37 ± 27.83 (0.0–82.5)	43.62 ± 30.10 (2.5–87.5)	53.56 ± 32.83 (3.0–99.0)	0.086	0.019**
MDT (g/mm^2)	0.04 ± 0.10 (0.0–0.4)	1.77 ± 0.2 (1.7–2.3)	1.8 ± 0.4 (1.7–3.3)	0.0001**	0.0001**
MPT (g/mm^2)	80.96 ± 117.22 (1.4–300.0)	104.02 ± 42.48 (25.0–137.3)	114.04 ± 36.42 (39.1–137.3)	0.032*	0.023**
MH(VAS)	3.12 ± 8.73 (0–30)	5.81 ± 8.5 (0–22)	7.94 ± 12.61 (0–45)	0.196	0.184
Mechanical dynamic allodynia (0-100)	0 ± 0 (0–0)	0 ± 0 (0–0)	0 ± 0 (0–0)	1.000	1.000

Abbreviations: CDT, cold detection threshold; WDT, warm detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; SuH, pain rating to suprathreshold heat stimulation; VAS, Visual analogue scale 0–100 mm; SuC, pain rating to suprathreshold cold stimulation; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MH, mechanical hyperalgesia

Table 3

Table 3. Conditioned pain modulation (CPM) parameters. The table shows the results of the following comparisons: (i) off *vs.* on-DBS for CPM variables (p-on *vs.* off), (ii) CPM of HV *vs.* patients in the off-DBS condition (p HV *vs.* off), and (iii) in the on-DBS condition (p HV *vs.* on). Results are presented as mean ± standard deviation (min–max). Significance set at *p < 0.05 and at **p < 0.025 for Bonferroni correction.

	off-DBS	on-DBS	HV	p on *vs.* off	p HV *vs.* off	p HV *vs.* on
HPT (°C)	47.14 ± 2.36 (43.6–49.9)	47.03 ± 2.14 (42.7–49.6)	—	0.469	—	—
U-TS (VAS)	59.81 ± 35.64 (10–100)	57.5 ± 33 (9–100)	—	0.727	—	—
C-TS (VAS)	58.93 ± 35.17 (7–100)	45.75 ± 36.95 (0–100)	—	0.382	—	—
C-TS total duration	40.91 ± 11.96 (29.47–66.61)	42.13 ± 21.92 (26–115.02)	—	0.460	—	—
C-TS unpleasantness (VAS)[#]	70.67 ± 30.98 (13–100)	59.33 ± 38.32 (10–100)	—	0.182	—	—
CPM effect[##]	1.8 ± 22.10 (-34–50)	11.75 ± 40.68 (-86–97)	—	0.683	—	—
CPM[###]	0.20 ± 0.81 (-0.63–2.3)	0.66 ± 1.99 (-0.90–7.2)	-0.43 ± 0,29 (-0.96–0,35)	0.826	0.001**	0.0001**

Abbreviations: HV, healthy volunteers; TS, test stimulus; U-TS, unconditioned test stimulus; C-TS, conditioned test stimulus; CPM, conditioned pain modulation;
[#]Conditioned-TS unpleasantness is the pain's VAS of the hand after water bath with ice blocks was finished;
[##]''Raw'' CPM effects were calculated as (C-TS) – (U-TS);
[###]CPM was calculated as a ratio: [(C-TS) – (U-TS)]/[U-TS].

Figure 1

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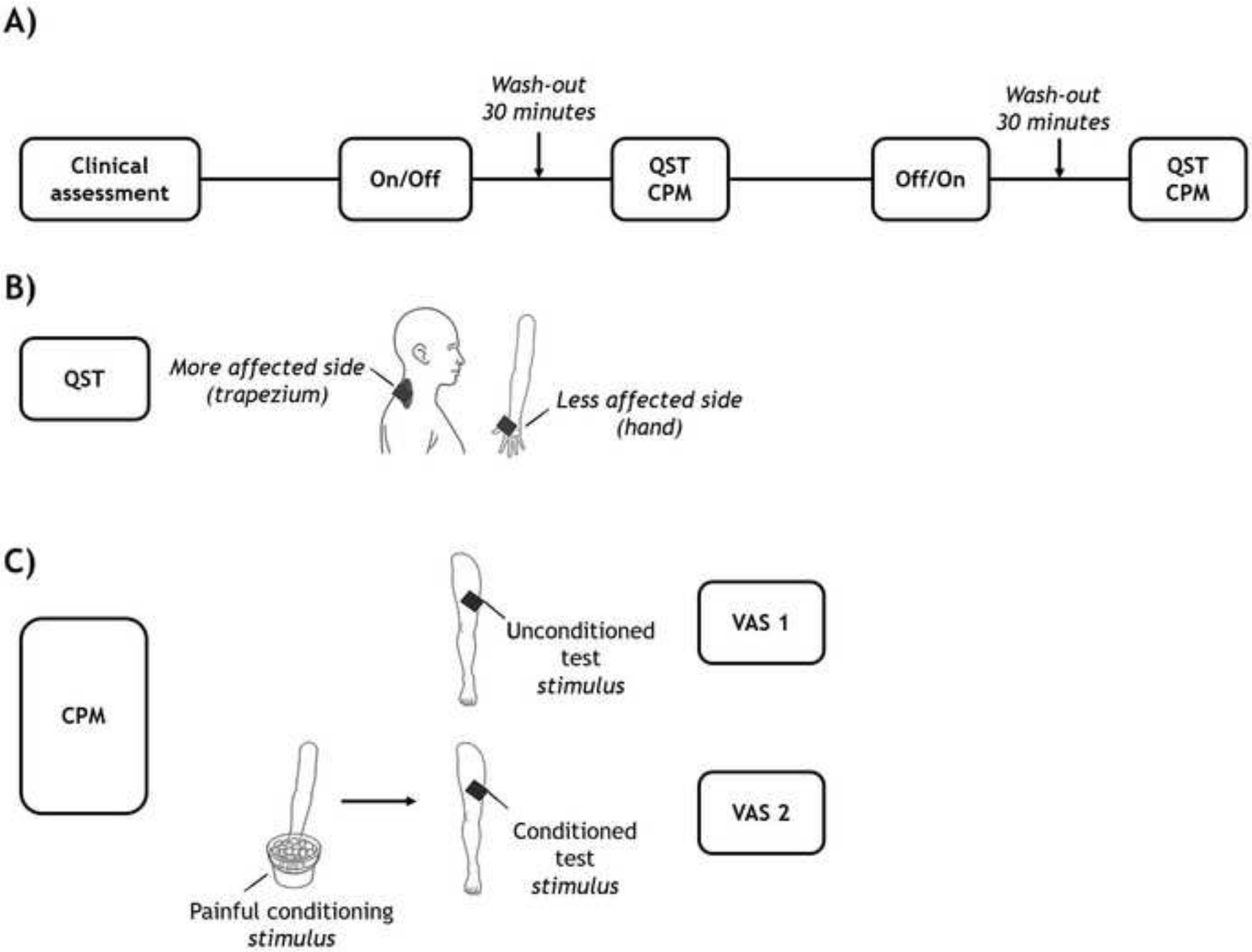

Submitted article “Thirty Years of Dystonia Research: a Bibliometric Analysis”

ARQUIVOS DE
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Thirty Years of Dystonia Research: a Bibliometric Analysis

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Keyword:	Movement Disorders, Dystonia, Bibliometric analysis

Thirty Years of Dystonia Research: a Bibliometric Analysis

Trinta Anos de Pesquisa em Distonia: uma Análise Bibliométrica

Clarice Listik[a] *; Eduardo Listik[b] *; Rubens Gisbert Cury[a]; Egberto Reis Barbosa[a]; Manoel Jacobsen Teixeira[c]; Daniel Ciampi de Andrade[a, c]

*The authors share equal contribution.

[a] *Movement Disorders Center, Department of Neurology, Universidade de São Paulo. Avenida Dr. Enéas Carbalho de Aguiar, 255, São Paulo, SP, Brazil. P.O. Box: 05402-000. clarice.listik@gmail.com; rubens_cury@usp.br; egbertob@8415.com.br*

[b] *Department of Biochemistry, Universidade Federal de São Paulo. Rua Três de Maio, 100, São Paulo, SP, Brazil. P.O. Box: 04044-020. eduardo.listik@usp.br*

[c] *Pain Center, Instituto do Cancer do Estado de São Paulo. Avenida Dr. Arnaldo, 251, São Paulo, SP, Brazil. P.O. Box: 01246-000. manoeljacobsen@gmail.com; ciampi@usp.br*

Corresponding Author:

Clarice Listik, M.D.

Address: Av. Dr. Enéas de Carvalho Aguiar, 255, 5º andar, sala 5084 – Cerqueira César 05403-900 – São Paulo – SP – Brazil.

Phone/ Fax: +55-11-2661-7152

E-mail: clarice.listik@gmail.com

ABSTRACT

Dystonia is a rare and impactful disease. The bibliometric analysis is crucial to evaluate the most influent journals, authors, and countries in a given research field. It also enables for people unfamiliar with the topic to become aware of its most discussed works and authors. **Objective:** This study aimed to bibliometrically analyze how dystonia has been researched over the thirty past years. **Methods:** We used the Scopus database for article retrieval and, after an assessment of pertinence, the 100 most cited articles in dystonia research from the last 30 years were selected. Variables such as authors, article title, journal and its impact factors, both country and affiliation of the corresponding author were retrieved. All publications were thematically categorized and divided into primary (original) and secondary (reviews, editorials, opinions) research articles. **Results:** The United States and Europe are the sources of 92% of our sample. The most cited articles were published in *Neurology* (13%), *Nature Genetics* (12%), *Annals of Neurology* (11%), *Brain* (10%) and *Movement Disorders* (8%). Most of them were from *Columbia University* and the *National Institutes of Health* (each with 6%). The most prolific authors were S. B. Bressmann (14 articles, 4294 citations), S. Fahn (10 articles, 3603 citations) and J. Jankovic (11 articles, 2930 citations). The most cited categories were *Genetics*, *Pathophysiology,* and *Treatment*. **Conclusion:** This data may help clinicians with less familiarity with dystonia to know the top articles and assist future researches.

Keywords: Movement Disorders; Dystonia; Bibliometric analysis

RESUMO

Distonia é uma doença rara e impactante. A análise bibliométrica é essencial para avaliar periódicos, autores e países mais influentes num dado campo de pesquisa. Ela também permite que pessoas pouco familiarizadas com o tópico se tornem cientes dos trabalhos e autores mais discutidos. **Objetivo:** Este estudo teve como intuito analisar bibliometricamente como a distonia vem sendo estudada nos últimos trinta anos. **Métodos:** Nós utilizamos o banco de dados Scopus para buscar na literatura e, após avaliar a pertinência do conteúdo, os 100 artigos mais citados em distonia nos últimos trinta anos foram selecionados. Variáveis como autores, título do artigo, periódico e seus fatores de impacto, país e afiliação do autor de correspondência; foram avaliadas. Todas as publicações foram categorizadas por temas e divididas em artigos de pesquisa primária (originais) ou secundária (revisões, editoriais, opiniões). **Resultados:** Os Estados Unidos e a Europa são fontes de 92% da nossa amostra. Os artigos mais citados são publicados na *Neurology* (13%), *Nature Genetics* (12%), *Annals of Neurology* (11%), *Brain* (10%) e *Movement Disorders* (8%). A maioria destes estudos foi realizada na Universidade de Columbia e no *National Institutes of Health* (cada um com 6%). Os autores mais prolíficos foram S. B. Bressmann (14 artigos, 4294 citações), S. Fahn (10 artigos, 3603 citações) e J. Jankovic (11 artigos, 2930 citações). As categorias mais citadas foram Genética, Fisiopatologia e Tratamento. **Conclusão:** Estes dados podem auxiliar indivíduos com menor familiaridade em distonia em conhecer os artigos mais destacados no campo, de modo a auxiliar futuras pesquisas.

Palavras-chave: Distúrbios do Movimento; Distonia e Análise Bibliométrica

1 INTRODUCTION

Dystonia is characterized by abnormal movement and/or postures caused by sustained or intermittent muscle contractions.[1] It is a rare disease, but it dramatically impacts the patients' and family's quality of life impinging significant limitations to even the most common day-to-day activities.[2]

The bibliometric analysis is essential for evaluation of the most influent journals, authors, and countries in a given research field.[3] It helps to have an overall assessment of what has been the main focus in this field and indicates needs, directions, and deficiencies.[4] It is also a simple way to present the most discussed works and authors to people outside the field.

Different themes have been assessed in this manner, such as Parkinson's disease,[5] neurocritical care,[3] essential tremor,[4] back pain,[6] neurorehabilitation,[7] deep brain stimulation.[8] Dystonia was previously analyzed in this manner, although it focused on the categorical panorama of the selected sample and compared it to the essential tremor data profile.[4] This study also applied the Web of Sciences as a database.

We report the 100 most cited articles in dystonia in the last thirty years and consider both author information, their affiliation, and the main country in which the research was associated with. We also analyze the most cited journals and their impact factors. All these data were considered both in primary research articles or secondary research ones (reviews, editorials, and opinions).

2 MATERIALS AND METHODS

Search protocol

For the article selection, the search "TITLE(dystonia)" was inserted in Elsevier's Scopus in May 2019. Publications were restricted to the last thirty years (i.e., since 1989), and the 100 most cited were used in this study. For impact factor (IF) analysis, the 2017 IF and the

5-year IF of the journals were obtained from InCites Journal Citation Reports (Clarivate Analytics) at the same time. The *h* index from authors was acquired from Scopus.

Bibliometric Analysis

From the sample, the collected variables included: all authors, article title, journal and its impact factors, both country and affiliation of the corresponding author. Publications were also divided into primary and secondary research articles, in which the latter included reviews, editorials, and opinions. Primary research articles were also categorized under the following themes: classification, clinical characteristics, epidemiology, genetics, medications, pathophysiology, surgery, and non-pharmacological treatment.

3 RESULTS

General results

The search resulted in 6604 articles with a mean of 19.9 citations (0–762). The top 100 articles had ranged from 153 to 762 citations (mean of 247.6). The top ten had a mean of 582 citations (393–762), as seen in Table 1, in which the most cited was from Ozelius et al.,[9] from the United States, with 762 citations, a primary research article.

Journals and Impact Factor

The 100 most cited articles were found in 29 different journals, in which the ten journals with most citations in this topic are exhibited in Table 2

. These ten journals had 71 of the top 100 articles and summed up 18562 of the 24761 citations in all these articles. *Neurology* and *Annals of Neurology* had the most articles in this list, each with 13; however, the most cited journals were *Neurology* (3153) and *Nature Genetics* (2850). Both these two journals had only primary research articles, and *Annals of Neurology*

had only one secondary research article. Figure 1 shows a relation of the 5-year impact factor *vs.* total citation in our sample.

Country and Affiliation

The analyzed articles were from a total of 11 countries. Aside from Japan and Australia, all of them are from North America or Europe, as seen in Table 3. Next to half of the sample were from the USA (47) with 11193 citations, while 37 of these publications represented primary research articles (8924 citations). Europe has a total of 45 articles (11644) in the top 100, in which Germany had the most prevalent production within our sample: 13 articles with 3222 citations, 12 of those are of primary research material (3067 citations).

We could observe 58 different affiliations in our list. United States institutions, such as the *Harvard University, Columbia University*, and *National Institutes of Health,* did prevail as the most cited ones. The *Harvard University* had 1485 citations within 5 publications, and *Columbia University* had 1299 citations in 6 publications.

Authors

Data were inspected by first author production and any co-author placement (Table 4). In the first author analysis, the most cited author was J. Jankovic (*h*-index of 126), which had 5 publications with 1276 citations, 4 of which were from primary research (1076 citations). M. Vidailhet (*h*-index of 66) was the second most cited, with 3 publications and a total of 1143 citations, followed by L. J. Ozelius (*h*-index of 63), with 2 first-author articles, 964 citations.

For any co-author placement analysis, the most cited author was S. B. Bressman (*h*-index of 68), with 14 publications and 4294 citations, which 11 were from primary research in a total of 2930 citations. The second most cited was S. Fahn (*h*-index of 90) with 10 articles (3603 citations) followed by J. Jankovic (*h*-index of 126) with 11 articles (2930 citations).

Categories

The categorized primary research articles revealed that the category with most publications in the top 100 is *Genetics*, with 23 articles and 5901 citations, followed by *Pathophysiology*, with 21 articles and 5030 citations. The primary research material summed a total of 84 publications in the top 100 most cited, and 16 secondary research articles included 14 reviews, 1 editorial and 1 opinion, totalizing 4258 citations, as shown in Table 5.

4 DISCUSSION

Our bibliometric analysis found that 10 journals withheld more than two-thirds of the top 100 articles and about 75% of this total sample citation. Dystonia research is mainly published in *Neurology*, *Nature Genetics*, *Annals of Neurology*, *Brain,* and *Movement Disorders*, although 16 journals had at most two publications in the field.

Besides Australia, all countries within our sample were from the Northern Hemisphere, and all of them from developed countries. The USA exhibits almost half this production, with 47% of all articles in the sample, and 45% of citations. Germany, the second most prolific country, revealed 13% of articles in this list, and 13% of total citations. France, in sequence, has 8% of total articles, and 10% in the number of citations. This context reveals that, although some countries may possess a smaller number of articles in the top 100, they can have a more significant impact.

The authors with most citations are, in order, S. B. Bressmann (*h*-index 68), S. Fahn (*h*-index 90), J. Jankovic (*h*-index 126) and M. Hallett (*h*-index 155). We conclude that S. Fahn may participate in the most impactful set of articles, as he appears in 10% of articles in our sample, and has 15% of citations.

Primary research articles corresponded to 84% of the articles, summing up to 83% of total citations, revealing that dystonia still has many areas to incorporate knowledge. The

categories with most articles are *Genetics* (27%), *Pathophysiology* (25%), and *Treatment* (17% in *Surgery*, 19% in *Medication*). However, the most cited were articles concerning dystonia *Surgery* with a mean of 281.4 citations per paper.

Our study has some limitations, as we used a single database to obtain our sample. However, Scopus has 20% greater coverage than Web of Science.[3, 10] Google Scholar has typically a broader data spectrum; nevertheless, it generally includes non-articles, theses, books, thus being inaccurate.[10, 11] Additionally, recently published articles, usually, have fewer citations, which can undervalue their importance.

The top cited dystonia publications are concentrated in a handful of scientific journals. These productions originate, mainly, from the United States and Europe and generally focus on themes such as *Genetics*, *Pathophysiology,* and *Treatment*. This data may help clinicians with less familiarity with dystonia to know the top articles in the field and assist future researches.

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FIGURE LEGENDS

Figure 1. Scatter-plot showing the number of citations within the 100 most cited articles in dystonia research *vs.* the journal's 5-year impact factor.

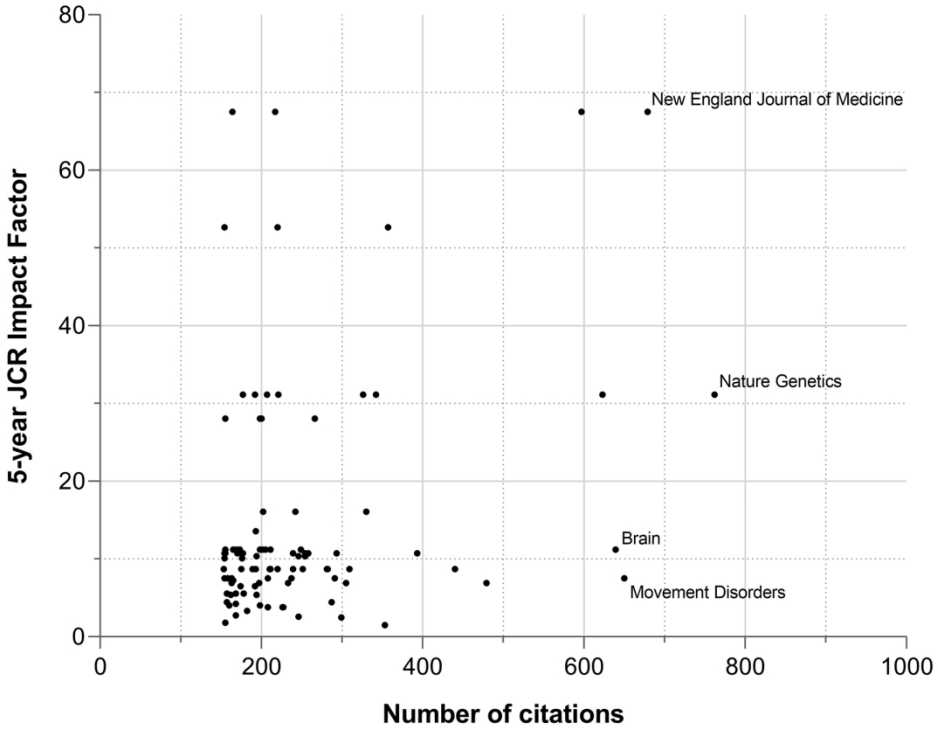

Figure 1. Scatter-plot showing the number of citations within the 100 most cited articles in dystonia research vs. the journal's 5-year impact factor.

161x125mm (300 x 300 DPI)

Table 1. Top ten cited publications in dystonia

First author	Title	Year	Journal	Country	Citations
Ozelius L.J.	The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein	1997	Nature Genetics	USA	762
Vidailhet M.	Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia	2005	New England Journal of Medicine	France	679
Albanese A.	Phenomenology and classification of dystonia: A consensus update	2013	Movement Disorders	Italy	650
Berardelli A.	The pathophysiology of primary dystonia	1998	Brain	Italy	639
Ichinose H.	Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene	1994	Nature Genetics	Japan	623
Kupsch A.	Pallidal deep-brain stimulation in primary generalized or segmental dystonia	2006	New England Journal of Medicine	Germany	597
Fahn S.	Classification of dystonia.	1998	Advances in neurology	USA	558
Ridding M.C.	Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia	1995	Journal of Neurology, Neurosurgery and Psychiatry	UK	479
Byl N.N.	Cerebellothalamocortical connectivity regulates penetrance in dystonia	1996	Neurology	USA	440
Vitek J.L.	Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study	1999	Annals of Neurology	USA	393

Table 2. Ten most cited journals in dystonia

Journal	Number of articles (primary research)	Number of citations (primary research)	2017 IF	5-Year IF
Neurology	13 (13)	3153 (3153)	8.055	8.716
Nature Genetics	8 (8)	2850 (2850)	27.125	31.156
Annals of Neurology	13 (12)	2819 (2561)	10.250	10.748
Brain	11 (9)	2521 (1677)	10.848	11.202
Movement Disorders	7 (4)	1861 (849)	8.324	7.523
New England Journal of Medicine	4 (3)	1657 (1493)	79.290	67.513
Journal of Neurology. Neurosurgery and Psychiatry	5 (5)	1377 (1377)	7.144	6.923
Lancet Neurology	4 (2)	819 (464)	27.144	28.055
Neuron	3 (3)	774 (774)	14.319	16.076
Lancet	3 (3)	731 (731)	53.254	52.665

Table 3. Most cited countries in dystonia research (top 100 selection)

Region/Countries	Number of articles (primary research)	Number of citations (primary research)
North America	**53 (43)**	**12299 (10030)**
USA	47 (37)	11193 (8924)
Canada	6 (6)	1106 (1106)
Europe	**45 (39)**	**11644 (9655)**
Germany	13 (12)	3222 (3067)
France	8 (8)	2386 (2386)
United Kingdom	9 (9)	2322 (2322)
Italy	9 (4)	2543 (709)
Netherlands	3 (3)	547 (547)
Switzerland	2 (2)	446 (446)
Norway	1 (1)	178 (178)
Asia	**1 (1)**	**623 (623)**
Japan	1 (1)	623 (623)
Oceania	**1 (1)**	**175 (175)**
Australia	1 (1)	175 (175)

Table 4. Ten most cited authors in dystonia research for publications in the top 100 regarding (i) first authorship and (ii) any co-authorship placement.

		Author	Number of articles (primary research)	Number of citations (primary research)	*h* index
First author	1	J. Jankovic	5 (4)	1276 (1076)	126
	2	M. Vidailhet	3 (3)	1143 (1143)	66
	3	L. J. Ozelius	2 (2)	964 (964)	63
	4	A. Albanese	2 (0)	848 (0)	63
	5	P. Coubes	2 (2)	644 (644)	32
	6	A. Barardelli	1 (0)	639 (0)	71
	7	H. Ichinose	1 (1)	623 (623)	45
	8	N. N. Byl	2 (2)	622 (622)	40
	9	J. L. Vitek	2 (1)	601 (393)	61
	10	A. Kupsch	1 (1)	597 (597)	63
Any co-author placement	1	S. B. Bressman	14 (11)	4294 (2930)	68
	2	S. Fahn	10 (7)	3603 (2930)	90
	3	J. Jankovic	11 (9)	2930 (2080)	126
	4	M. Hallett	9 (4)	2687 (917)	155
	5	M. F. Brin	8 (8)	2479 (2479)	72
	6	L. J. Ozelius	8 (8)	2326 (2326)	63
	7	A. L. Benabid	5 (5)	2194 (2194)	88
	8	C. D. Marsden	5 (3)	1856 (659)	150
	9	D. De Leon	5 (5)	1706 (1706)	28
	10	A. E. Lang	6 (5)	1608 (958)	128

Table 5. Most cited categories in dystonia

Article category	Number of publications	Number of citations
Primary Research	**84**	**20503**
Genetics	23	5901
Pathophisiology	21	5030
Surgery	14	3940
Medication	16	3555
Clinical characteristics	7	1534
Epidemiology	1	226
Classification	1	163
Treatment (non-pharmacological)	1	154
Secondary Research	**16**	**4258**
Review	14	3807
Editorial	1	258
Opinion	1	193

Submitted article “Deep Brain Stimulation Treatment In Dystonia: A Bibliometric Analysis”

ARQUIVOS DE
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DEEP BRAIN STIMULATION TREATMENT IN DYSTONIA: A BIBLIOMETRIC ANALYSIS

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Keyword:	Bibliometric, deep brain stimulation, dystonia

DEEP BRAIN STIMULATION TREATMENT IN DYSTONIA: A BIBLIOMETRIC ANALYSIS

ESTIMULAÇÃO CEREBRAL PROFUNDA NO TRATAMENTO DA DISTONIA: UMA ANÁLISE BIBLIOMÉTRICA

Clarice Listik[a], M.D.*; Eduardo Listik[b], M.Sc.*; Rubens Gisbert Cury[a], M.D., Ph.D.; Egberto Reis Barbosa[a] M.D., Ph.D.; Manoel Jacobsen Teixeira[c], M.D., Ph.D.; Daniel Ciampi de Andrade [a,c], M.D., Ph.D.

* These authors contributed equally to this work

[a] *Movement Disorders Center, Department of Neurology, Universidade de São Paulo, São Paulo, SP, Brazil. Av. Dr. Enéas de Carvalho Aguiar, 255, 5th floor, São Paulo, SP, Brazil. P.O. Box: 05403-900.*

[b] *Department of Biochemistry, Universidade Federal de São Paulo, São Paulo, SP, Brazil.Rua Três de Maio, 100, São Paulo, SP, Brazil. P.O. Box: 04044-020.*

[c] *Pain Center, Instituto do Cancer do Estado de São Paulo, São Paulo, SP, Brazil. Av. Dr. Arnaldo 251. São Paulo, SP, Brazil. P.O. Box: 01246-000.*

Emails: clarice.listik@gmail.com, eduardo.listik@usp.br, rubens_cury@usp.br, egbertob@8415.com.br, manoeljacobsen@gmail.com, ciampi@usp.br.

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Corresponding Author:

Clarice Listik, M.D.
Address: Av. Dr. Enéas de Carvalho Aguiar, 255, 5º andar, sala 5084 – Cerqueira César
05403-900 – São Paulo – SP – Brazil.
Phone / Fax: +55-11-2661-7152
E-mail: clarice.listik@gmail.com

ABSTRACT

Background: Dystonia is a heterogeneous disorder that, when refracted to medical treatment, may have a favorable response to deep brain stimulation (DBS). A practical way to have an overview of a research domain is through a bibliometric analysis, as it makes it more accessible for researchers and others outside the field to have an idea of its directions and needs.

Objectives: To analyze the 100 most cited articles in the use of DBS for dystonia treatment in the last thirty years.

Methods: The research protocol was performed in June 2019 in Elsevier's Scopus, by retrieving the most cited articles regarding DBS in dystonia and we analyzed authors, year of publication, country, affiliation, and targets of DBS.

Results: Articles are mainly published in *Movement Disorders* (19%), the *Journal of Neurosurgery* (9%), and *Neurology* (9%). European countries offer significant contributions (57% of our sample). *France* (192.5 citations/paper) and *Germany* (144.1 citations/paper) have the highest citation rates of all countries. The *United States* also contributes to 31% of the articles, with 129.8 citations/paper. The publications are focused on *General outcomes* (46%), followed by *Long-term outcomes* (12.5%), and *Complications* (11%), and the leading type of dystonia researched is *idiopathic or inherited, isolated, segmental or generalized dystonia*, with 27% of articles and 204.3 citations/paper.

Conclusion: DBS in dystonia research is mainly published in a handful of scientific journals and focused on the outcomes of the surgery in idiopathic or inherited, isolated, segmental or generalized dystonia, and with *globus pallidus internus* as the main DBS target.

Keywords: Bibliometric, deep brain stimulation, dystonia.

RESUMO

Introdução: Distonia é uma doença heterogênea que, quando refratária ao tratamento medicamentoso, pode ter uma resposta favorável à estimulação cerebral profunda (ECP). Uma forma prática de ter uma visão desta área de pesquisa é por meio de análise bibliométrica, pois permite aos pesquisadores e terceiros a terem uma ideia das tendências e necessidades desta área.

Objetivos: Analisar os 100 artigos mais citados sobre o tratamento da distonia pelo uso de ECP nos últimos trinta anos.

Métodos: O protocolo de pesquisa foi realizado em Junho de 2019 através do Scopus da Elsevier, em que se obteve os artigos mais citados na área de tratamento de distonia com ECP. Analisaram-se variáveis como autores, ano de publicação, país, afiliação, e alvos de ECP.

Resultados: Os artigos foram principalmente publicados na *Movement Disorders* (19%), no *Journal of Neurosurgery* (9%), e na *Neurology* (9%). Países europeus contribuem significativamente (57% da amostra). *França* (192,5 citações/artigo) e *Alemanha* (144,1 citações/artigo) possuem as mais altas taxas de citações. Os *Estados Unidos* também contribuem para 31% dos artigos da amostra (129,8 citações/artigo). As publicações focaram em *Desfechos gerais* (46%), seguido de *Desfechos a longo prazo* (12,5%), e *Complicações* (11%). O principal tipo de distonia pesquisada foi distonia *generalizada ou segmentar, idiopática ou hereditária, isolada*, abrangendo 27% dos artigos e 204,3 citações/artigo.

Conclusão: A pesquisa de ECP na distonia é publicada em seletos periódicos científicos, e foca nos desfechos da cirurgia, nas distonias generalizadas ou segmentares, idiopáticas ou hereditárias, isoladas, sendo o *globus pallidus internus* o principal alvo da ECP.

Palavras-chave: Bibliometria, estimulação cerebral profunda, distonia

1. INTRODUCTION

Dystonia is a heterogeneous movement disorder characterized by sustained or intermittent muscle contractions leading to abnormal movements and postures. [1] It can be classified by their clinical characteristics, including body distribution (focal, segmental, multifocal, generalized or hemidystonia) and associated features (isolated or combined); and etiology (idiopathic, inherited or acquired). [1] The treatment of dystonia is aimed at providing symptomatic relief for the motor symptoms, improving pain, and avoiding musculoskeletal complications such as joint contractures. [2] Medical treatment is usually limited to the side effects and has small symptomatic relief. [3] Botulinum toxin is a good option for focal dystonia; however, in generalized and segmental dystonia, it may have a limited effect due to its dose limits. When refractory to these approaches, deep brain stimulation, usually targeting the *globus pallidus internus* (GPi), has a response in idiopathic or inherited isolated segmental or generalized dystonia that varies between 43–65%. [2] GPi is the most common target; however, initially, thalamic targets were used. [2] Recently, the *subthalamic nucleus* (STN) is also being considered a viable target. [4, 5]

A practical way to identify which are the most influential authors, journals, and countries in a particular field is through a bibliometric analysis. [6] It makes it more accessible for researchers and others outside the field to have an overview of its directions and needs. [7] The literature does present bibliometric analysis on various themes, such as neurocritical care, [6] back pain, [8] essential tremor, [7] Parkinson's disease, [9] and deep brain stimulation. [10]

We analyzed the 100 most cited articles in the use of DBS for dystonia treatment in the last thirty years. We evaluated author information, their affiliation, and the country of the corresponding author. Additionally, we investigated which were the most cited journals and their impact factors, the used DBS targets (when applicable), and the dystonia classification (also, when applicable). Articles were divided into primary or secondary (i.e., reviews and guidelines) articles.

2. METHODS

Search protocol

The used database for article selection was Elsevier's Scopus, and the search protocol was performed in June 2019. The exact input was *TITLE("dystonia" AND ("DBS" OR "Deep brain stimulation")) OR ABS("dystonia" AND ("DBS" OR "Deep brain stimulation")) AND PUBYEAR > 1988*. This terminology translated to publications which possessed the terms *dystonia* and *DBS* or *deep brain stimulation* in either the article's title or abstract and have been published in the last thirty years (i.e., since 1989). After screening the search results based on pertinence, the 100 most cited were used in this study. Impact factor (IF) data of journals were retrieved from InCites Journal Citation Reports (Clarivate Analytics), and both 2017 IF and 5-year IF were collected. Lastly, the *h* index of authors was obtained from Scopus, as well.

Bibliometric Analysis

After selecting the 100 most cited articles, we obtained additional information regarding these publications within our sample. At first, all the authors, year of publication, journal and its impact factor, country, and affiliation of the corresponding author were retrieved. All articles were also categorized, when mentioned, regarding the targets of DBS. The publications were divided into primary researches (i.e., original articles) and secondary researches, such as reviews, and guidelines; the classification of dystonia, if applicable; and into specific themes, such as: complications, outcomes, pathophysiology, physiology, surgical approach, targets, ethics, types of stimulation and treatment. Categorized articles in *outcomes* were further classified into: general aspects, long-term outcomes, dystonic tremor outcomes, and predictors of outcome.

3. RESULTS

General results

Our search led to 337 hits ranging from 0 to 679 citations (mean of 30.2). The 100 most cited articles have a mean of 130.4 citations (70–679), and the top 10, a mean of 311.2 (203–679), which have been detailed in Table 1. The most cited article was from Vidailhet and collaborators (2005). [11]

Journals and Impact Factor

A complete distribution of the presented articles within the 100 most cited in "DBS in dystonia" according to their number of citations and journal's 5-year impact factor can be seen in Figure 1. *Movement Disorders* (2017 IF = 8.324) accounts for 19 of the articles in our sample, summing up 2071 citations, and 12 articles were from primary research (1262 citations). *New England Journal of Medicine* (2017 IF = 79.260) was the second most cited journal while having only 2 articles in the top 100, both of them from primary research; they were cited 1276

times. The *Journal of Neurosurgery* was the third most cited journal, with 9 publications, all of them from primary research. This material accounted for 1247 citations.

Country and Affiliation

All of the corresponding author countries in our samples were from the Northern Hemisphere, as seen in Figure 2. They were divided primarily in Europe and North America, but also in Asia. "DBS in dystonia" research is highly prevalent in Europe, which accounted for 57 articles in our sample. *Germany*, *France,* and the *United Kingdom* display a large production of material. *Germany* accounted for 25 articles (3203 citations), 18 from primary research (2438 citations). *France* summed up to 15 articles (2647 citations), 12 from primary research (2309). Moreover, the *United Kingdom* had 10 articles (1086 citations), in which 8 were from primary research. The *United States* was another country in which publications were majorly present. The country has the most articles than any other in the sample: 31 articles (3834 citations), 19 from primary research (2466 citations).

As seen in Table 2, the most prolific affiliations are the *University of Sorbonne* (France), the *Kiel University* (Germany), and the *University of Montpellier* (France). The three institutions account for 16% of the 100 most cited articles in "DBS in dystonia." Both *University of Sorbonne* and *Kiel University* display 5 articles, although the first has 4 primary research publications, and the latter 2. However, the total citations from the *University of Sorbonne* are 1300 (1221 from primary research), and the *Kiel University* 1036 (696 from primary research). The *University of Montpellier* has 6 articles, all of them from primary research, summing up 789 citations.

Year

Although we researched articles since 1989, the most cited ones were only included from 1999 on, as seen in Figure 3. After then, all years, until 2014, had highly cited publications,

with a peak from 2005–2007, in which 33% of our sample's articles reside, summing up to 39% of total citations.

Authors

The three most cited *first* authors were *M. Vidailhet* (*h* index of 66), *A. Kupsch* (*h* index of 63) and *J. Volkmann* (*h* index of 61), as seen in Table 3. The three altogether represent 18% of all citations in our sample. *M Vidailhet* displayed 4 articles (1222 citations), 3 from primary research (1143 citations). *A Kupsch* has a single highly cited, primary research article with 597 citations. Lastly, *J. Volkmann* had a total of 4 articles (547 citations), 2 of which were from primary research (256 citations).

Another analysis was performed according to any placement of authors during publications. In this analysis, the most cited authors were *P. Pollak* (*h* index of 83), *J. Volkmann* (*h* index of 61) and *A. L. Benabid* (*h* index of 88). *P. Pollak* appeared in 7 articles (1646 citations), 6 from primary research (1520 citations). *J. Volkmann* was included in 9 publications (1625 citations), 5 of which are primary research articles (1334 citations). *A. L. Benabid* was in 6 articles (1568 citations), 5 of which were from primary research (1442 citations).

Categories

The articles were then categorized, as displayed in Table 4. Primary research articles accounted for 72% of our samples. The most present categories were articles that discussed general *Outcomes* from DBS, which included 33 articles (5044 citations). We separated from these general overviews, the ones that investigated the *Long-term Outcomes* (more than 18 months), which was the second most discussed topic (9 articles, 1327 citations). The third most present category was *Complications*, which had 8 articles summing 996 citations.

The other 28 articles in our sample were from secondary research; most of them were Reviews, and only one a Guideline. Most of the secondary researches focused on *Treatment*

aspects using DBS (13 articles, 1508 citations), and other minor focus were given to *Pathophysiology* (3 articles, 388 citations) and general *Outcomes* (3 articles, 294 citations).

DBS Targets

As reported in Figure 4, we detailed how DBS targets were applied in the different publications listed in the 100 most cited articles in "DBS in dystonia." There were 31 articles in which this analysis was not applicable, as the target was either not mentioned, neither DBS treatment was specified in a general manner. Without a doubt, the most mentioned target was the GPi, which appeared in 60 articles (8255 citations), 54 of which being from primary research (7662 citations). Thalamic targets were, then, the most present ones. In total, 10 articles mentioned thalamic targets: 5 of which did not specify a precise target, 3 focused on the *Ventral intermediate nucleus* (VIM), 1 on the *Ventrolateral thalamic nucleus* (VLp), and 1 on the *Ventral-oralis complex* (Vo). The total citations for thalamic targets were 1126. Additionally, 7 articles were focusing on the *Subthalamic nucleus* (STN, 663 citations), 5 of which were from primary research (461 citations). One primary research article focused on the *Caudal Zona Incerta* (cZi) and had 143 citations.

Dystonia classification

In the most cited articles, the description of dystonia classification was only observed in primary articles (Table 5). A fraction of them (18, under *Miscellaneous*) did present different kinds of dystonia in the study. The most common dystonia investigated was *idiopathic or inherited, isolated, segmental or generalized dystonia*, which presented 16 articles (3269 citations), followed by *idiopathic, isolated, focal dystonia*, with 11 publications (1238 citations).

4. DISCUSSION

Our analysis indicated that the 10 most cited journals in DBS in dystonia accounted for almost three-quarters of all articles and citations in our sample. They are majorly published in *Movement Disorders* (19%), the *Journal of Neurosurgery* (9%), *Neurology* (9%), *Brain* (8%) and *The Lancet Neurology* (7%). However, the journals with most cited articles were the *New England Journal of Medicine* (average of 638 citations per paper), *The Lancet Neurology* (152.1 citations/paper), the *European Journal of Neurology* (146.5 citations/paper).

DBS in dystonia is mainly researched in the Northern Hemisphere. In the top 100 most cited articles in this theme, there were no countries outside of it. European countries offer significant contributions (57% of our sample). *France* and *Germany* have the highest citation rates of all countries. When considering primary research articles, *France* displays 192.5 citations/paper, and *Germany* 144.1 citations/paper. The *United States* also contributes to 31% of the articles, with 129.8 citations/paper.

Most primary research articles focus on *General outcomes* (46%), followed by *Long-term outcomes* (12.5%), and *Complications* (11%). Few publications in our sample tried to find *Predictors of outcome* (2.8%) or compared different *Targets* (1.4%). When we analyzed the used DBS targets for dystonia treatment, the classic *GPi* corresponded to 77% of the publications, *STN*, which is a hopeful new option of treatment, [4, 5, 56] totalized 9%, and thalamic targets 13%, though mainly used for dystonic tremor. [56, 57]

As expected, most articles analyzed *idiopathic or inherited, isolated, segmental or generalized dystonia* (27% with an average of 204.3 citations/paper), which is the most studied kind of dystonia and has, usually, the most improvement after DBS treatment. [58] *Idiopathic, isolated, focal dystonia* is also highly prevalent (18.5%, 112.6 citations/paper) in our sample.

Similarly to other bibliometric analysis, our study has limitations. Scopus possesses greater coverage and specificity when compared to Web of Science and Google Scholar;

however, we employed it as a single database for article retrieval. [6, 59, 60] Moreover, articles published after 2014 did not occur in our sample, possibly because more recent articles are still accumulating citations. Nevertheless, this context does not undervalue their potential.

DBS in dystonia research is mainly focused on selected, Northern Hemisphere, countries. They are mostly published in a handful of scientific journals and mainly focusing on outcomes of the surgery, with GPi as DBS target, and in idiopathic or inherited, isolated, segmental or generalized dystonia. This bibliometric analysis might assist unfamiliar researchers and practitioners in obtaining an overview of this particular domain.

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FIGURE LEGENDS

Figure 1. Bubble chart showing the number of citations within the 100 most cited articles in DBS in dystonia research *vs.* the journal's 5-year impact factor. The size of the bubble represents the number of publications within each journal.

Figure 2. Geographical heat map representing citations per country of the corresponding author.

Figure 3. Chronological incidence of (A) articles and (B) citations per year in the top most cited publications regarding DBS in dystonia since 1989.

Figure 4. Pie charts indicating the distribution of (A) articles and (B) citations for different DBS targets.

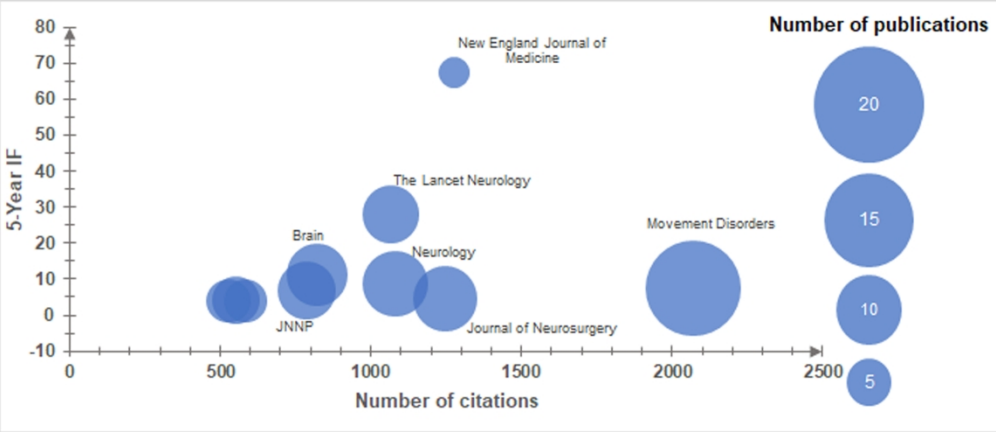

Figure 1. Bubble chart showing the number of citations within the 100 most cited articles in DBS in dystonia research vs. the journal's 5-year impact factor. The size of the bubble represents the number of publications within each journal.

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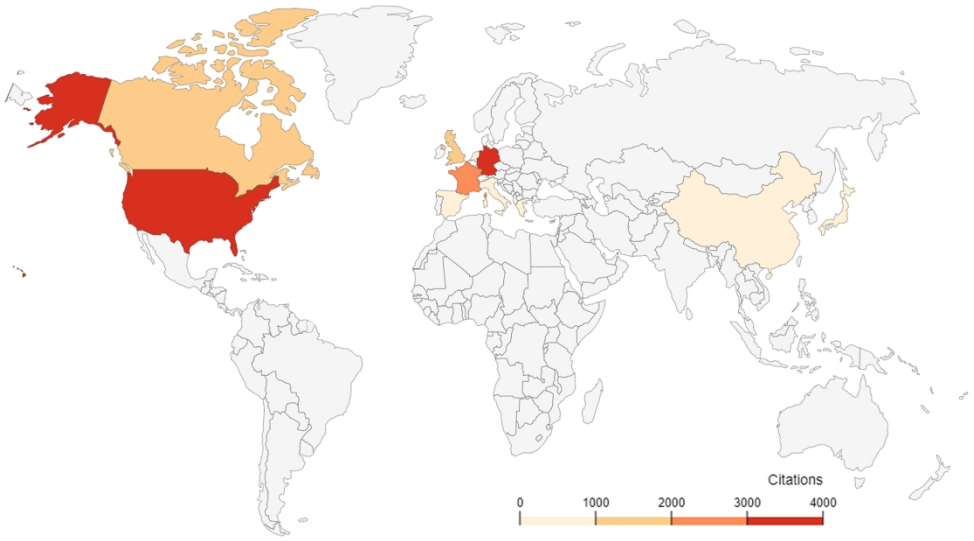

Figure 2. Geographical heat map representing citations per country of the corresponding author.

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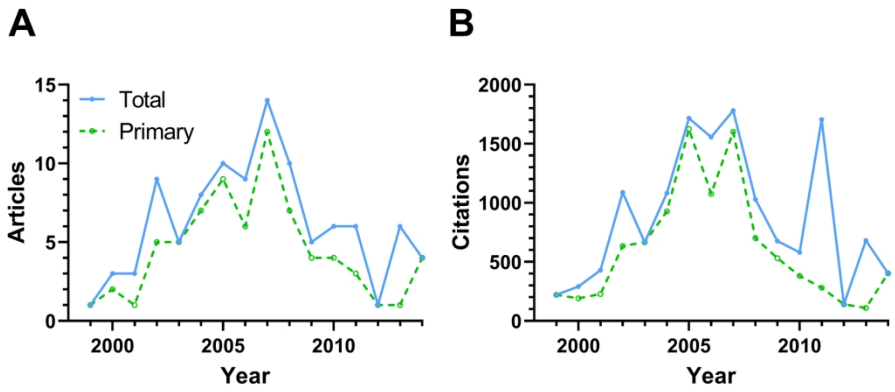

Figure 3. Chronological incidence of (A) articles and (B) citations per year in the top most cited publications regarding DBS in dystonia since 1989.

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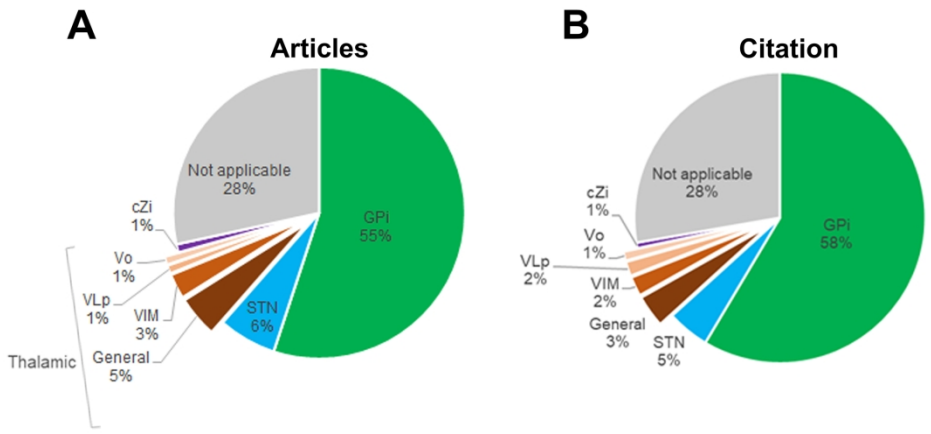

Figure 4. Pie charts indicating the distribution of (A) articles and (B) citations for different DBS targets.

209x96mm (300 x 300 DPI)

Table 1. Top ten cited publications in DBS in dystonia.

First author	Title	Year	Journal	Country	Citations
Vidailhet M.[11]	Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia	2005	New England Journal of Medicine	France	679
Kupsch A.[12]	Pallidal deep-brain stimulation in primary generalized or segmental dystonia	2006	New England Journal of Medicine	Germany	597
Coubes P.[13]	Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: Long-term results	2004	Journal of Neurosurgery	France	287
Vidailhet M[14]	Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study	2007	Lancet Neurology	France	266
Vercueil L.[15]	Deep brain stimulation in the treatment of severe dystonia	2001	Journal of Neurology	France	227
Kumar R.[16]	Globus pallidus deep brain stimulation for generalized dystonia: Clinical and pet investigation	1999	Neurology	USA	220
Albanese A.[17]	EFNS guidelines on diagnosis and treatment of primary dystonias	2011	European Journal of Neurology	Italy	214
Volkmann J.[18]	Introduction to the programming of deep brain stimulators	2002	Movement Disorders	Germany	213
Okun M.S.[19]	Management of referred deep brain stimulation failures: A retrospective analysis from 2 Movement Disorders Centers	2005	Archives of Neurology	USA	206
Beric A.[20]	Complications of deep brain stimulation surgery	2002	Stereotactic and Functional Neurosurgery	USA	203

Table 2. Most cited affiliations in DBS in dystonia research with at least 2 articles in top 100.

Affiliation	Country	Number of articles (primary research)	Number of citations (primary research)
University of Sorbonne	France	5 (4)	1300 (1221)
Kiel University	Germany	5 (2)	1063 (696)
University of Montpellier	France	6 (6)	789 (789)
Heidelberg University	Germany	6 (4)	748 (505)
Baylor College of Medicine	USA	5 (1)	685 (142)
University of California	USA	6(5)	674 (548)
University of Oxford	United Kingdom	5 (4)	537 (449)
University of Milan	Italy	3 (1)	519 (107)
University of Toronto	Canada	4 (4)	507 (507)
Mount Sinai School of Medicine	USA	4 (4)	483 (483)
University Medicine Berlin/Humboldt University	Germany	4 (4)	382 (382)
University of Grenoble	France	2 (2)	299 (299)
Colorado Neurological Institute	USA	2 (1)	294 (220)
University of Florida	USA	2 (2)	285 (285)
University of Würzburg	Germany	2 (2)	256 (256)
University College London	United Kingdom	2 (1)	245 (124)
University Health Network	Canada	2 (2)	239 (239)
University of Cologne	Germany	2 (1)	194 (118)
University of Bonn	Germany	2 (2)	179 (179)
Imperial College London	United Kingdom	2 (2)	161 (161)

Table 3. Ten most cited first authors and all authors in DBS in dystonia research.

Type of authorship	First author	Number of articles in the top 100 (primary research)	Number of citations (primary research)	*h* index
First authorship	M. Vidailhet[11, 14, 21, 22]	4 (3)	1222 (1143)	66
	A. Kupsch[12]	1 (1)	597 (597)	63
	J. Volkamnn[18, 23-25]	4 (2)	547 (256)	61
	J. K. Krauss[26-29]	4 (2)	514 (271)	50
	J. Jankovic[30-32]	3 (0)	424 (0)	126
	A. Albanese[17, 33]	2 (0)	412 (0)	63
	P. Coubes[13, 34]	2 (2)	363 (363)	32
	J. L. Ostrem[35-37]	3 (2)	354 (228)	31
	L. Cif[38-40]	3 (3)	294 (294)	20
	R. Kumar[16, 41]	2 (1)	284 (220)	44
Any authorship	P. Pollak[11,14,15,21,42-44]	7 (6)	1646 (1520)	83
	J. Volkmann[12, 18, 23-25, 42-45]	9 (7)	1625 (1334)	61
	A. L. Benabid[11, 14, 15, 21, 46, 47]	6 (5)	1568 (1442)	88
	L. Vercueil[11, 14, 15, 46-49]	7 (5)	1524 (1322)	25
	G. H. Schneider[12, 24, 25, 43, 45, 50-53]	9 (9)	1430 (1430)	47
	M. Vidailhet[11, 14, 21, 22, 47, 49]	6 (5)	1372 (1293)	66
	A. Kupsch[12, 24, 25, 43, 45, 51-53]	8 (7)	1356 (1356)	63
	J. K. Krauss[17, 24, 26-29, 33, 50, 54, 55]	10 (6)	1302 (647)	50
	Y. Agid[11, 14, 21, 49]	4 (3)	1221 (1023)	121
	C. Ardouin[11, 14, 21, 40, 49]	4 (4)	1221 (1221)	26

Table 4. Most cited categories in DBS in dystonia.

Article category			Number of publications	Number of citations
Primary Research			**72**	**9709**
Original articles	Complications		8	996
	Outcome	General	33	5044
		Dystonic Tremor	3	315
		Long-term	9	1327
		Predictors	2	272
	Pathophysiology		8	861
	Physiology		2	179
	Surgical approach		5	483
	Surgical approach/Physiology		1	157
	Targets		1	75
Secondary research			**28**	**3329**
Review	Ethics		1	79
	Outcome	General	3	294
		Predictors	3	278
	Pathophysiology		3	388
	Physiology		1	213
	Targets		2	281
	Treatment		13	1508
	Types of stimulation		1	74
Guidelines	Treatment		1	214

Table 5. Citation and publication profile according to the type of dystonia in the 100 most cited articles in DBS in dystonia research.

Dystonia classification	Number of articles (primary research)	Number of citations (primary research)
Idiopathic or inherited, isolated, segmental or generalized dystonia	16 (16)	3269 (3269)
Idiopathic, isolated, focal dystonia	11 (11)	1238 (1238)
Acquired dystonia	7 (7)	759 (759)
Combined dystonia	5 (5)	416 (416)
Dystonia associated with other neurological or systemic manifestations	2 (2)	250 (250)
Miscellaneous	18 (18)	2133 (2133)
Not applicable	41 (13)	4973 (1644)

Published article “Targeting the hot spot in a patient with essential tremor and Parkinson’s disease: Tractography matters”

Clinical Neurology and Neurosurgery 174 (2018) 230–232

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Case Report

Targeting the hot spot in a patient with essential tremor and Parkinson's disease: Tractography matters

Clarice Listik[a], Natally Santiago[b], Paul Rodrigo Reis[b], Fabio Godinho[b], Kleber Duarte[b], Manoel Jacobsen Teixeira[b], Egberto Reis Barbosa[a], Rubens Gisbert Cury[a,*]

[a] Movement Disorders Center, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil
[b] Neurosurgery Division, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil

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Tractography
Zona incerta

ABSTRACT

Introduction: Thalamic ventralis intermedius deep brain stimulation (VIM-DBS) is generally effective in treating refractory tremor in Parkinson's disease (PD) and in essential tremor (ET), but some patients do not respond well due to side effects or from loss of the effect of stimulation over time. The caudal zona incerta (ZI) has emerged as a promising target in ET, and the effects of ZI-DBS on PD tremor are less studied. Here, we describe a rare situation in which both ET and PD coexist in a 72-year-old male referred for ZI-DBS due to refractory tremor. The aim of this study was to evaluate whether there was a difference in the area stimulated to improve each type of tremor and whether tractography could improve and predict motor outcome.

Methods: Two months after the surgery, in order to define which of the cathodes was the most effective towards improving the tremor and parkinsonian symptoms, a double-blinded, monopolar evaluation was conducted on both hemispheres separately. Once the best contact and parameters were defined, the volume of tissue activation (VTA) was represented spatially for each type of tremor and, finally, the image model was fused with the tractography.

Results: For both types of tremor, the hot spot stimulated region achieved the dentato-rubro-thalamic tract (DRTT) at the higher fiber density region. The DRTT fibers were asymmetrical between the right and left hemispheres.

Conclusion: Regardless of the type of tremor, DRTT can be the most effective region for stimulation. Tractography should be considered when planning the surgical target since the DRTT is not always symmetrical, and the reconstruction of the VTA together with the tractography can greatly improve the DBS programming, and, probably, the patient's outcome to the stimulation.

1. Introduction

Essential tremor (ET) and Parkinson's disease (PD) are common disorders in which the tremor can be disabling and is frequently associated with poor quality of life. When the tremor is refractory to pharmacological intervention, surgical treatment with deep brain stimulation (DBS) is an established, effective option [1]. In ET, the most popular target is the thalamic subnucleus ventralis intermedius (VIM). In PD, the globus pallidum and the subthalamic nucleus are usually targeted, and the VIM can be an option in the tremor-dominant PD [2].

Although VIM-DBS is generally effective in treating tremor in PD and in ET, some patients do not respond well, either due to side effects or from loss of the effect of stimulation over time (tolerance). Recent studies have pointed to the caudal zona incerta (ZI) as a promising target in ET, probably because of convergence of fiber bundles contained in this region (including the dentato-rubro-thalamic tract, DRTT), with similar outcomes of VIM and possibly fewer side effects. It is possible that the stimulation of axon, and not of nuclei, may reach more neurons, altering tremor oscillations in a more efficacious manner. The ZI is part of the posterior subthalamic area (PSA) which is located ventral to VIM and between the red nucleus and the STN. The PSA also includes, the Forel's fields, the lemniscus and the prelemniscal radiations.

The effects of ZI-DBS on PD tremor are less studied, but some studies

* Corresponding author at: Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084 – Cerqueira César, 05403-900, São Paulo, SP, Brazil.
E-mail addresses: clarice.listik@usp.br (C. Listik), natallysantiago@hotmail.com (N. Santiago), paulrodrigo.sp@itelefonica.com.br (P.R. Reis), fabiogodinho@hc.fm.usp.br (F. Godinho), kleber.duarte@hc.fm.usp.br (K. Duarte), manoeljacobsen@hc.fm.usp.br (M.J. Teixeira), egbertob@hc.fm.usp.br (E.R. Barbosa), rubens_cury@usp.br (R.G. Cury).

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Published article “PUS3 mutations are associated with intellectual disability, leukoencephalopathy, and nephropathy”

CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

PUS3 mutations are associated with intellectual disability, leukoencephalopathy, and nephropathy

Anderson Rodrigues Brandão de Paiva, MD, David S. Lynch, MD, PhD, Uirá Souto Melo, PhD, Leandro Tavares Lucato, MD, PhD, Fernando Freua, MD, Bruno Della Ripa de Assis, MD, Isabella Barcelos, MD, Clarice Listik, MD, Diego de Castro dos Santos, MD, Lúcia Inês Macedo-Souza, PhD, Henry Houlden, MD, PhD, and Fernando Kok, MD, PhD

Correspondence
Dr. de Paiva
arbrandaopaiva@gmail.com

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Mutations in *PUS3*, which encodes a highly conserved enzyme responsible for post-transcriptional modification of tRNA, have been shown in a single family to be a cause of nonsyndromic intellectual disability (ID).[1] In this study, we used whole-exome sequencing (WES) to identify biallelic mutations in *PUS3* associated with syndromic ID with dysmorphic features, white matter disease (WMD), and renal abnormalities in a nonconsanguineous family from Brazil.

Clinical findings

We evaluated 2 sisters (figure, A) who had ID, renal abnormalities, diffuse WMD, and dysmorphic features. Their brother was similarly affected and died at age 22 years of complications of renal disease. The parents were nonconsanguineous from Northeast Brazil and Southern Italy. We obtained approval from the institutional ethics committee and written informed consent from family members.

The first patient (P1; III-3; figure, A) was noted to have global developmental delay after age 1 year. As a child, she could understand short sentences, but expressive language was limited to monosyllables. She was diagnosed with profound ID but was independent in basic activities of daily living (ADLs). She had 2 focal dyscognitive seizures with secondary generalization, at age 18 and 23 years, responsive to carbamazepine. At age 37 years, asymptomatic proteinuria and reduced creatinine clearance were detected. At 44 years, she developed psychosis, with prominent auditory and visual hallucinations and episodes of aggression. Physical examination revealed her to be on the 10th centile for height, weight, and head circumference and to have genu valgum. In addition, neurologic examination revealed dysarthria, pseudobulbar affect, with impaired gait and balance.

The second patient (P2; III-6; figure, A) also presented with short stature, neurodevelopmental delay, and dysmorphic features. She was diagnosed with acute nephritis at age 6 months and coeliac disease at age 5 years. She also developed generalized phenobarbital responsive seizures. She was able to walk and could complete ADLs with assistance. At age 20 years, she developed nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS) with mesangial granular deposits and positive IgM and C3 immunofluorescence. She did not respond to steroids and developed end-stage renal failure requiring hemodialysis. Physical examination revealed that she was on the 3rd centile for height, weight, and head circumference and to have gray

From the Neurogenetics Unit (A.R.B.d.P., F.F., B.D.R.d.A., I.B., C.L., D.d.C.d.S., F.K.), Neurology Department, Hospital das Clínicas da Universidade de São Paulo, Brazil; Department of Molecular Neuroscience (D.S.L., H.H.), UCL Institute of Neurology, London, UK; Leonard Wolfson Experimental Neurology Centre (D.S.L., H.H.), UCL Institute of Neurology, London, UK; Human Genome and Stem Cell Research Center (U.S.M., L.I.M.-S., F.K.), Department of Genetics and Evolutionary Biology, Instituto de Biociências, Universidade de São Paulo, Brazil; and Neuroradiology Section (L.T.L.), Hospital das Clínicas da Universidade de São Paulo, Brazil.

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Published article “Deep Brain Stimulation in Patients with Isolated Generalized Dystonia Caused by PRKRA Mutation”

Movement Disorders
CLINICAL PRACTICE

Deep Brain Stimulation in Patients with Isolated Generalized Dystonia Caused by *PRKRA* Mutation

Sara Carvalho Barbosa Casagrande, MD,[1] Clarice Listik, MD,[1] Daniel Boari Coelho, PhD,[2] Joao Carlos Papaterra Limongi, MD, PhD,[1] Luis Augusto Teixeira, PhD,[2] Manoel Jacobsen Teixeira, MD, PhD,[3] Egberto Reis Barbosa, MD, PhD,[1] and Rubens Gisbert Cury, MD, PhD[1,*]

Dystonia is defined by sustained or intermittent involuntary contractions leading to abnormal movements and postures, with a heterogeneous etiology and a complex pathophysiology. Advances in genetics have allowed the identification of several monogenic forms of dystonia.[1] Recently, a novel form of recessively inherited dystonia characterized by early-onset generalized dystonia-parkinsonism (DYT16) has been described caused by a mutation in the *PRKRA* gene,[2] responsible for 4.5% of the idiopathic dystonia cases in a Brazilian cohort.[3] The management of DYT16 is challenging.

Deep brain stimulation (DBS) of globus pallidus internus (GPi) is an established treatment for dystonia, but the outcomes vary regarding the underlying cause and genetic subtype.[4] Here we describe the effect of GPi-DBS in 2 DYT16 patients.

Case 1: A 35-year-old man developed phonation difficulties and hand dystonia at age 6. Over time, the movements spread to his neck and trunk, leading to extreme side-bending, without parkinsonism. Treatment attempts with anticholinergics, levodopa, and botulinum toxin showed poor responses. At 4 years before the current presentation, a unilateral palidotomy was performed with mild improvement.

Case 2: A 16-year-old woman presented at age 7 with dystonia in her right leg followed by her trunk, neck, and speech. No parkinsonism was observed. Conventional oral medications and botulinum toxin injections have been tried with mild response.

As a result of refractory symptoms, bilateral GPi-DBS was proposed after both patients signed the written informed consents. This study was approved by the local ethics committee. A neuropsychological assessment was made showing significant improvement in anxiety and depression symptoms. The patients were assessed by the Burke–Fahn–Marsden Dystonia Rating Scale before and 6 months after surgery and by the Patient's Global Impression of Change Scale postoperatively. Wireless accelerometers and a rigid surface were used to assess gait and balance control, respectively.

The Burke–Fahn–Marsden Dystonia Rating Scale motor/disability scores improved 42%/50% in case 2 and 49%/57% in case 2, respectively (Video S1). In the gait analysis, time to complete the walk decreased after DBS in both patients. Case 1 showed smaller values of wrist and head acceleration during walking after DBS, showing improved gait stability. Analysis of the quiet stance indicated improved balance in both patients as registered by the center of pressure. Speech was not affected by stimulation. No adverse effects were reported (detailed in Fig. 1).

To date, only a single case of DYT16 with DBS performed as treatment was described superficially without prospective assessment.[5] Several factors are thought to be good predictors of DBS response, including age of onset, characteristics such as phasic dystonia, leads location, and stimulator settings.[4] The current evidence suggests that genetic screening may provide useful information regarding the selection of potential DBS candidates.[4] Some studies have suggested that patients with *TOR1A* mutations respond to GPi-DBS more consistently, whereas patients with DYT-*THAP1* have more variable outcomes.

In the era of individualized DBS for movement disorders, a deeper understanding of the outcomes regarding the genetic status in dystonia is crucial, as preoperative screening could provide valuable prognostic information. Moreover, considering the possibility of higher *PRKRA* mutation prevalence than is currently known,[3] it seems reasonable to study new therapies to optimize the results for refractory cases.

Our series is the first prospective study of GPi-DBS response in patients with a *PRKRA* mutation. Although robust conclusions are limited because of the small number of cases, our observation supports GPi-DBS as a treatment option for DYT16.

[1]*Movement Disorders Center, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil;* [2]*Human Motor Systems Laboratory, School of Physical Education and Sport, University of São Paulo, São Paulo, Brazil;* [3]*Neurosurgery Division, Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil*

***Correspondence to:** Dr. Rubens Gisbert Cury, Av. Dr. Enéas de Carvalho Aguiar, 255, 5° andar, sala 5084, Cerqueira César, 05403-900, São Paulo, SP, Brazil; E-mail: rubens_cury@usp.br

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Observership certificate

RETA LILA WESTON INSTITUTE OF NEUROLOGICAL STUDIES
DIRECTOR OF RESEARCH

Professor: Thomas Warner PhD FRCP

To Whom It May Concern

Re: Dr Clarice Listik
Faculdade de medicina da universidade de São Paulo (sao paulo's university medical School)

This is to certify that Dr Clarice Listik undertook clinical training in the Movement Disorders Group at the National Hospital for Neurology and Neurosurgery, UCLH in London under my direct supervision for the period of one month October 2019.

Dr Listik attended brain cuts in the Queen Square Brain Bank and research lectures including Gowers rounds, Clinco-pathological conferences and video sessions, ataxia, neurogenetics, dbs clinics and weekly meetings at the Institute of Neurology.

Faithfully yours

12th November 2019

Thomas Warner
Professor of Neurology

University College London • UCL Queen Square Institute of Neurology • 1 Wakefield Street • London WC1N 1PJ
Tel: +44 (0)20 7679 4246 Fax: +44 (0)20 7278 4993
weston-inst@ucl.ac.uk
www.ucl.ac.uk/rlweston-inst

Curriculum vitae

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Clarice Listik

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Resumo informado pelo autor

Possui graduação em Medicina pela Universidade de São Paulo (2013) e Residência Médica na área de Neurologia pelo Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC-FMUSP (2017). Fellow de Distúrbios de Movimento no HC-FMUSP em fevereiro de 2018 e em Neurogenética com término em fevereiro de 2019 na mesma instituição. É atualmente mestranda do Departamento de Neurologia do HC-FMUSP e acompanha os ambulatórios de Distúrbio de Movimento no HC-FMUSP e de Neurocirurgia Funcional (Estimulação Cerebral Profunda - ECP, da sigla em inglês DBS) para Distúrbios de Movimento no IPQ-FMUSP.

(Texto informado pelo autor)

Nome civil

Nome Clarice Listik

Dados pessoais

Nome em citações bibliográficas LISTIK, C.;LISTIK, CLARICE

Sexo Feminino

Cor ou Raça Não desejo declarar

Filiação Sergio Listik e Marcia Listik

Nascimento 30/09/1988 - São Paulo/SP - Brasil

Carteira de Identidade 372511910 SSP - SP - 30/01/2014

CPF 382.385.158-66

Passporte FM440034

Endereço residencial Rua Afonso Celso n 1629 conj 42
Vila Mariana - São Paulo
04119062, SP - Brasil
Telefone: 11 55849961
Celular 11 995999142

Endereço eletrônico
E-mail para contato : dra.clarice.listik@gmail.com
E-mail alternativo clarice.listik@gmail.com

Formação acadêmica/titulação

2014 - 2017 Especialização - Residência médica .
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC FMUSP, Brasil
Título: Neurologia

2008 - 2013 Graduação em Medicina.
Universidade de São Paulo, USP, Sao Paulo, Brasil

Formação complementar

2017 Fellow Neurogenética. .
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC FMUSP, Brasil

2017 - 2018 Fellow Distúrbios do Movimento. .
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC FMUSP, Brasil
Palavras-chave: extrapiramidal, disturbios do movimento

2016 - 2016 Observership. .
Cleveland Clinic Foundation, CCF, Cleveland, Estados Unidos

Áreas de atuação

1. Medicina
2. Neurologia
3. Distúrbios do Movimento

Idiomas

Inglês Compreende Bem , Fala Bem , Escreve Bem , Lê Bem

Francês Compreende Pouco , Fala Pouco , Escreve Pouco , Lê Pouco

Português Compreende Bem , Fala Bem , Escreve Bem , Lê Bem

Prêmios e títulos

2017 Título de Especialista em Neurologia, Academia Brasileira de Neurologia - ABN

2013 Prêmio Professor Edmundo Vasconcelos, Faculdade de Medicina da Universidade de São Paulo

2012 Prêmio de 3º lugar - Prêmio de melhor tema livre na qualidade de AUTOR/APRESENTADOR, 5º Encontro de Neurocirurgiões Jovens do Estado de São Paulo e 1º Congresso Brasileiro de Abordagens

2011 Prêmio na Categoria Protocolo de estudo estrutural e aplicações clínicas, V Workshop CInAPCe

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Palavras-chave: dystonia, DBS, pain
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2. **LISTIK, C.**
Lesão medular trato específica após choque elétrico de alta voltgem sem alteração na ressonância magnética, 2016. (Congresso,Apresentação de Trabalho)
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3. **LISTIK, C.**; VIEIRA, G.; CASTRO, B. M.; PASSOS, J. A.; OTADUY, M. C. G.; CASTRO, L. H. M.; AMARO JR., E.; ARANTES, P. R.
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Language and memory fMRI behaviour analysis in left temporal lobe epilepsy, 2011. (Congresso,Apresentação de Trabalho)
Referências adicionais: Brasil/Inglês. Meio de divulgação: Impresso Categoria PÔSTER; Local: São Paulo; Cidade: São Paulo; Evento: V Workshop CInAPCe; Inst.promotora/financiadora: CInAPCe

Eventos

Eventos

Participação em eventos

1. **Convenção Nacional dos Departamentos Científicos da ABN -**

NEURODC19, 2019. (Congresso)
GPI–DBS DOES NOT AFFECT SENSORY THRESHOLDS IN INHERITED/ IDIOPATHIC DYSTONIA.

2. Apresentação de Poster / Painel no(a) **Convenção Nacional dos Departamentos Científicos da ABN - NEURODC19**, 2019. (Congresso)
GPI–DBS DOES NOT AFFECT SENSORY THRESHOLDS IN INHERITED/ IDIOPATHIC DYSTONIA.

3. **Convenção Nacional dos Departamentos Científicos da ABN - NEURODC19**, 2019. (Congresso)
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4. Apresentação de Poster / Painel no(a) **XII CONGRESSO PAULISTA DE NEUROLOGIA**, 2019. (Congresso)
GPi DBS does not affect sensory thresholds in hereditary/idiopathic dystonia.

5. Apresentação de Poster / Painel no(a) **2nd Pan American Parkinson's Disease and Movement Disorders Congress**, 2018. (Congresso)
Targeting the right spot in a patient with essential tremor and Parkinson's disease: does the tractography matter?.

6. Apresentação de Poster / Painel no(a) **XXVIII Congresso Brasileiro de Neurologia**, 2018. (Congresso)
TARGETING THE RIGHT SPOT IN A PATIENT WITH ESSENTIAL TREMOR AND PARKINSON'S DISEASE: DOES THE TRACTOGRAPHY MATTER?.

7. **11° Curso de CONDUTAS EM NEUROLOGIA**, 2016. (Outra)
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8. **2° Curso de EMERGÊNCIAS NEUROLÓGICAS**, 2016. (Outra)
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9. **BCTRIMS 17th Annual Meeting**, 2016. (Congresso)
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10. **Curso Pré-Congresso com tema em Neuroinfecção - XXVII Congresso Brasileiro de Neurologia**, 2016. (Congresso)
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11. Apresentação de Poster / Painel no(a) **XXVII Congresso Brasileiro de Neurologia**, 2016. (Congresso)
Lesão medular trato específica após choque elétrico de alta voltgem sem alteração na ressonância magnética.

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13. **1° Curso de EMERGÊNCIAS NEUROLÓGICAS**, 2015. (Outra)
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14. **V Simpósio de Neuroimunologia da Santa Casa de São Paulo – 18 anos de CATEMEM**, 2015. (Simpósio)
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15. **BCTRIMS 15th Annual Meeting**, 2014. (Congresso)
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16. **32º CONGRESSO MÉDICO UNIVERSITÁRIO DA FMUSP**, 2013. (Congresso)
.

17. **31º Congresso Médico Universitário da FMUSP**, 2012. (Congresso)
.

18. **34º Congresso Brasileiro de Epilepsia e da Reunião Anual da Sociedade Brasileira de Neurofisiologia Clínica**, 2012. (Congresso)
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19. **5º Encontro de Neurocirurgiões Jovens do Estado de São Paulo e 1º Congresso Brasileiro de Abordagens Neurocirúrgicas**, 2012. (Congresso)
.

20. **5º Encontro de Neurocirurgiões Jovens do Estado de São Paulo e 1º Congresso Brasileiro de Abordagens Neurocirúrgicas,**, 2012. (Congresso)
Desempenho comportamental no exame de Ressonância Magnética funcional para linguagem na epilepsia do lobo temporal.

21. Apresentação de Poster / Painel no(a) **5º Encontro de Neurocirurgiões Jovens do Estado de São Paulo e 1º Congresso Brasileiro de Abordagens Neurocirúrgicas,**, 2012. (Congresso)
Desempenho comportamental no exame de Ressonância Magnética funcional para linguagem na epilepsia do lobo temporal.

22. **6ª Jornada de Obstetrícia e Ginecologia da FMUSP, do 6º Encontro de Ex-Residente de Obstetrícia e Ginecologia da FMUSP**, 2012. (Simpósio)
.

23. **Congresso Cirurgião ano 6 – Atualização em Cirurgia Geral, Emergência e Trauma**, 2012. (Congresso)
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24. **Curso A Psiquiatria da Clínica Cotidiana no XXX Congresso Médico Universitário da Faculdade de Medicina da Universidade de São Paulo**,

2011. (Congresso)
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25. Apresentação de Poster / Painel no(a) **V Workshop CInAPCe**, 2011. (Congresso)
Language and memory fMRI behaviour analysis in left temporal lobe epilepsy.

26. **V Workshop CinAPCe**, 2011. (Congresso)
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27. **VIII Congresso Paulista de Neurologia**, 2011. (Congresso)
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28. **Workshop Emergências Clínicas no XXX Congresso Médico Universitário da Faculdade de Medicina da Universidade de São Paulo**, 2011. (Congresso)
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Desempenho comportamental no exame de Ressonância Magnética funcional para linguagem na epilepsia do lobo temporal.

30. **15º Congresso Brasileiro Multidisciplinar Multiprofissional em Diabetes es**, 2010. (Congresso)
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31. **2° Encontro Internacional de Tecnologia e Inovação para Pessoas com Deficiência**, 2010. (Encontro)
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32. **III Uptodate in Multiple Sclerosis**, 2010. (Outra)
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33. **Curso de Emergências Clínicas no XXVIII Congresso Médico Universitário da Faculdade de Medicina da Universidade de São Paulo**, 2009. (Congresso)
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Artigos completos publicados em periódico	5
Capítulos de livros publicados	3
Apresentações de trabalhos (Congresso)	6

Eventos	
Participações em eventos (congresso)	26
Participações em eventos (simpósio)	3
Participações em eventos (encontro)	1
Participações em eventos (outra)	5

Página gerada pelo sistema Currículo Lattes em 19/12/2019 às 21:46:39.