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REVIEW ARTICLE

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Deep brain stimulation of dorsal and ventral borders of the subthalamic nucleus in patients with Parkinson's disease: a systematic review

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ABSTRACT

Parkinson's disease patients experience motor signs and non-motor symptoms caused by the disease. Deep brain stimulation of the Subthalamic Nucleus (STN) itself or its ventral or dorsal borders is one of the treatment options indicated to treat the refractory symptoms of this disease. However, it is still unknown which edge, when stimulated, generates more beneficial effects for these patients, which is the objective of this systematic review. To answer this question, electronic and manual searches were conducted in five databases and gray literature to identify studies that answered the question in this review. The selection of studies, data extraction, and analysis of the risk of bias of the included studies were performed. In total, seven studies were included in this systematic review. Most studies presented a minimal risk of bias, and their main methodological limitation was related to the sample inclusion criteria. Stimulation of the dorsal or ventral borders of the STN resulted in improved motor signs of *Parkinson's* disease, with some of the studies tending towards the choice of dorsal border stimulation for better motor effects, while the improvement in non-motor symptoms and inhibitory control was due to stimulation of the ventral border. The findings of this systematic review suggest that the improvement in the motor signs of *Parkinson's* disease can be brought about by stimulating the dorsal or ventral borders of the subthalamic nucleus, whereas non-motor symptoms such as anxiety improve with stimulation of the ventral border.

Keywords: subthalamic nucleus; deep brain stimulation; Parkinson's disease; ventral thalamic nuclei; putamen.

INTRODUCTION

The subthalamus is located in the area between the thalamus and the hypothalamus, and its main components are the subthalamic nucleus and the uncertain zone[1]. The subthalamic nucleus (STN) has a biconvex shape and is exposed medially to the fibers of the internal capsule; it is located ventrally, inferiorly anterior, and slightly lateral to the zona incerta, as well as having various connections with the basal nuclei[1,2]. It can also be divided into three portions: dorsolateral, ventromedial, and medial. The first corresponds to the motor territory, as it acts in the indirect pathway of the motor circuit; the second to the associative, as it operates in the oculomotor circuit and the cognitive aspects of motor behavior; and the third to the limbic, as it acts in the motivational and emotional aspects of motor behavior[3,4]. Because it has these characteristics, the STN, along with some components of the basal nuclei, is considered one of the main targets of deep brain stimulation in the treatment of refractory symptoms of Parkinson's disease and this has shown excellent results[5], since the motor disorders caused by this disease stem from disturbances in the specific motor circuits related to these nuclei[6].

The pathophysiology of Parkinson's disease is based on dysfunction of the substantia nigra of the midbrain, which results in a decrease in dopamine in the nigrostriatal fibers. Consequently, the modulatory activity that these fibers exert on the direct and indirect pathways (motor circuit) is interrupted, which results in increased inhibition of the thalamic nuclei producing motor signs such as resting tremor, rigidity, and bradykinesia. In addition, in Parkinson's disease, the subthalamic nucleus exerts intense activity in the indirect pathway, which is a crucial factor in the production of signs and symptoms[7].

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Thus, the STN and its dorsal and ventral borders have been used as targets for deep brain stimulation[8], because as well as improving motor signals[9], stimulation of this nucleus relieves non-motor symptoms[10]. The study by Petry-Schmelzer et al.[10] demonstrated that deep brain stimulation of the ventral border and the sensorimotor subregion, as well as the associative subregion of the subthalamic nucleus, improved some of the non-motor signs and symptoms of Parkinson's disease, such as mood, apathy, attention, and memory. Baumann-Vogel et al.[11] observed that stimulation of the dorsal border of the subthalamic nucleus improved nocturnal sleep and daytime vigilance, without altering circadian rhythmicity, in patients with Parkinson's disease, demonstrating that the dorsal border is also one of the best targets for stimulation. Based on the beneficial effects brought about by stimulation of the dorsal or ventral border of the subthalamic nucleus, a study using stimulation of both borders in patients with Parkinson's disease described that selective stimulation of the dorsal as opposed to the ventral border is responsible for improving reactive inhibitory control of impulse responses[8].

Other researchers, such as Gourisankar et al.[12] and Yokoyama et al.[13], showed different responses to stimulation of the dorsal and ventral borders of the STN. In the first study, it was observed that stimulation of the ventral border induced a greater improvement in rigidity and anxiety than stimulation of the dorsal border. In contrast, the second study showed that stimulation of the dorsal border caused a significantly greater improvement in rigidity and akinesia than stimulation of the ventral border.

Many other studies have been and are being conducted about deep brain stimulation of parts of the STN or its borders, but to date, no systematic review has been conducted to answer whether stimulation of the dorsal border causes better results than

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the ventral one. Therefore, this review aims to assess whether deep brain stimulation of the dorsal border of the subthalamic nucleus, compared to the ventral border, triggers better motor and non-motor results in patients with Parkinson's disease.

METHODS

Study design and protocol recording

This is a systematic review of the literature of primary studies with an observational, cross-sectional design. The project protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021272143, to guarantee transparency, and reproducibility and avoid duplication of effort.

Included were studies selected and examined by the reviewers that answered the systematic review's guiding question, published in all languages up to August 2021, with no date limitation, and that were conducted on human beings. In addition, studies were selected that used imaging exams to anatomically determine the parameters of centrality and dorsality of the STN.

The exclusion criteria were: 1) Articles that did not answer the systematic review question; 2) Conference or congress abstracts, posters, letter and review; 3) Articles that did not perform a comparison of stimulation of the dorsal and ventral edges of the subthalamic nucleus; 4) Articles in which the electrode contacts were located outside the subthalamic nucleus; 5) Articles that did not specify the location of the electrode contacts; 6) Unavailable full text in which the author did not respond to our contact attempts, three attempts in three weeks.

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Search strategies

The following databases were used for the bibliographic survey: PubMed; Cochrane Library, EMBASE, Lilacs, and SCOPUS. In addition, a search was conducted in Google Scholar and OpenGrey gray literature, as well as a manual screening of the list of references of each study included. Duplicate articles were removed using the EndNote X9® tool.

The search strategy developed for the Pubmed database was considered standard and was suitable for the other databases according to their criteria. The keywords used were: "Parkinson's Disease", "Idiopathic Parkinson's Disease", "Idiopathic Parkinson's Disease", "Parkinson," "subthalamic nucleus", "stimulation" "deep brain stimulation", "ventral" and "dorsal."

Research question

Does deep brain stimulation of the dorsal border of the subthalamic nucleus trigger better results than stimulation of the ventral border in patients with Parkinson's disease? The strategy adopted: PICOT (**P**articipants, **I**ntervention, **C**omparator, **O**utcome, and **T**ype of study). P: Patients with Parkinson's disease; I: Deep brain stimulation of the dorsal border of the subthalamic nucleus; C: Deep brain stimulation of the ventral border of the subthalamic nucleus; O: Motor and non-motor beneficial effects; T: Observational, cross-sectional studies (intervention clinical).

Selection of studies

The studies were selected in a paired and blinded manner by two reviewers (R1 and R2): MOG and JOG. The reviewers first examined the titles and abstracts of the

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articles in the databases and used Microsoft Excel to include the studies that met the inclusion criteria. These studies were included in a table containing: the title of the article, name(s) of author(s), year, place, objectives, methodology, results, reference, selection/exclusion, and reason for exclusion.

After selecting the titles and abstracts, the full texts were read and those that met the inclusion criteria were chosen for the next stage (data extraction). In all stages, the analyses of the two reviewers were compared and disagreements were resolved by a third reviewer (R3): LAL.

Data extraction

In the data extraction stage, R1 and R2 read the full texts of the selected articles and extracted the data manually, independently.

The data collected was included in a table made using the Microsoft Excel program, containing the title of the article, name(s) of the author(s) and year, location, objective, methods, sample, whether or not the medication was interrupted, duration of the disease, whether the stimulation was unilateral or bilateral, location of the stimulation, blinding, results and study design. The table containing the data collection is located under the results (Table 1).

Analysis of the risk of bias

Because the studies included in the review were observational intervention studies, we adapted the questions from the Cochrane Collaboration[14] in the RevMan tool by adding some questions from the Joanna Briggs Institute Critical questionnaire[15]. The questions related to the Cochrane Collaboration's randomized clinical trials were removed

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and added to the questions related to the cross-sectional studies questionnaire, which were included in this systematic review. Therefore, the risk of bias was assessed by adapting the two tools mentioned above.

The adapted tool had nine questions and the answers could be "Yes", which indicates a minimal risk of bias, corresponding to the color green; "No", indicating an elevated risk of bias, corresponding to the color red and "Unclear", indicating an uncertain risk of bias, corresponding to the color yellow.

Summary and analysis of data

The results were presented in table format with a narrative summary.

RESULTS

The search of databases and gray literature generated 1,095 articles. Of these, 243 were duplicates, and when these were excluded, 852 articles remained. After reading the titles and abstracts of each study, 806 records were excluded because they did not fit the theme and, as a result, 45 articles were chosen and read in full. After reading the full texts, seven met the inclusion criteria (Figure 1). The data collected from the articles with the characteristics of each study to answer the question of interest is shown in Table 1.

Analysis of the risk of bias

Most of the studies presented a minimal risk of bias (Figures 2A and B). Four studies met all the methodological quality criteria, while three failed to meet any of the criteria. The main methodological limitation of these studies was related to the sample inclusion criteria, as they were not well defined. Two studies presented unclear

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information on the blinding of participants, three on the blinding of outcome assessment, performance bias, and detection respectively, and one study presented incomplete outcome data.

DISCUSSION

This systematic review aimed to assess whether deep brain stimulation of the dorsal border of the subthalamic nucleus would trigger better results than stimulation of the ventral border in patients with Parkinson's disease. Seven studies met the eligibility criteria and answered the guiding question. In general terms, it was noted that stimulation of both edges of the STN improves the motor signs of Parkinson's disease, such as tremor, gait, and balance[12,16,17]. However, two studies reported a significant improvement in motor performance through dorsal border stimulation[13,18]. Regarding the improvement of non-motor symptoms, such as anxiety, it has been found that stimulation of the ventral border is significantly better than the dorsal one[12], and stimulation of the ventral border improves global action stopping, which confirms the importance of the ventral part of the STN in modulating stopping control[19].

As mentioned above, some scholars argue that the STN can be divided into motor, associative, and limbic territories, each of which has a connection to certain parts of the brain. In the studies selected and presented in this review, the stimulation electrodes were on the dorsal and ventral borders of the STN in a dorsolateral to ventromedial arrangement. The fact that the improvement in motor symptoms was independent of the stimulation site corroborates the possibility that the motor connections are distributed more diffusely throughout the nucleus so that it does not preserve a clear segregation between the different functional modalities (sensorimotor, associative, and limbic)[20,21].

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On the other hand, as this improvement is acquired through different pathways and, in some of the selected studies, stimulation of the dorsal edge as opposed to the ventral edge improved motor signals, there is a possibility of functional segregation within the STN, which infers that stimulation may have influenced the indirect pathway of the motor circuit, in which the dorsolateral portion of the nucleus is involved[4,17].

The improvement in motor symptoms through stimulation of the dorsal border is in line with the report by Rodriguez-Oroz[22], in which the authors suggest that the neurons with activity related to voluntary movement and those involved in Parkinsonian tremor are the same and are found in the dorsal part of the STN. On the other hand, the fact that the improvement in motor signals is independent of the stimulation site is supported by the fact that the peak beta power in the STN, considered to be one of the characteristics of motor impairment in Parkinson's disease, is found in both the dorsal and ventral parts of the nucleus[23,24]. Reports in the literature indicate that stimulating sites where these motor/parkinsonian neurons are located and/or with the beta power peak results in improved motor signals[22,23].

Regarding the improvement of non-motor symptoms, such as anxiety, it can be said that stimulation of the ventral border stimulated the STN territories mentioned above, such as the ventromedial (associative) and medial (limbic) territories, thus influencing their connections with pallidal and nigral circuits, which act on the functions of the prefrontal, orbitofrontal and anterior cingulate cortexes, important in cognition, emotion, and behavior[3].

The selected studies reported that stimulation of the ventral border improves stop control. Stop control is based on the suppression of an already initiated manual response, and according to Aron and Poldrack[25], the STN is involved. The mechanism by which

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stimulation of the ventral border acts on this effect can be explained by modulations of the hyper direct and indirect pathways. Hyperdirected cortical projections to the STN could be involved in providing a rapid global inhibitory signal to pause or interrupt all ongoing action plans, thus allowing more time to respond. In this way, stimulation of the ventral part of the STN could modulate the input of these cortical projections and result in improved agility in stopping an action that has already begun in patients with Parkinson's disease[19].

In the literature there are several reports of the effects of stimulation of the ventral and dorsal parts of the STN in humans, as in the study by Greenhouse et al.[26], when comparing the effects of stimulation directed at the STN using dorsal and ventral electrodes contacts, they observed that stimulation of the ventral contact led to a general increase in positive affect. However, stimulation of the ventral part of the STN can also cause some harm, as in the three cases reported by Zoon et al.[27], patients with apathy related to stimulation of the ventral part of the STN improved when stimulation was switched to the dorsal part of the nucleus. Also, about stimulation of the dorsal part of the STN, Van Wouwe et al.[8] found an improvement in the ability to inhibit response impulses in patients with Parkinson's disease, providing evidence that circuits in the dorsal part of the nucleus play a fundamental role in motor suppression.

The benefits provided by the ideal choice of the part of the STN to be stimulated are many and can contribute to a better quality of life for patients with Parkinson's disease.

Conclusion

This systematic review showed that stimulation of the dorsal or ventral borders of the subthalamic nucleus provides comparable results for motor signs, with some of the

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studies tending to choose dorsal border stimulation for better effects. Regarding non-motor symptoms, stimulation of the ventral border provided better results in the treatment of anxiety, as well as improving stop control. However, there is still a lack of studies comparing stimulation of both borders with electrodes positioned only on the borders of the STN, stimulating structures beyond.

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Figure 1: PRISMA flowchart.

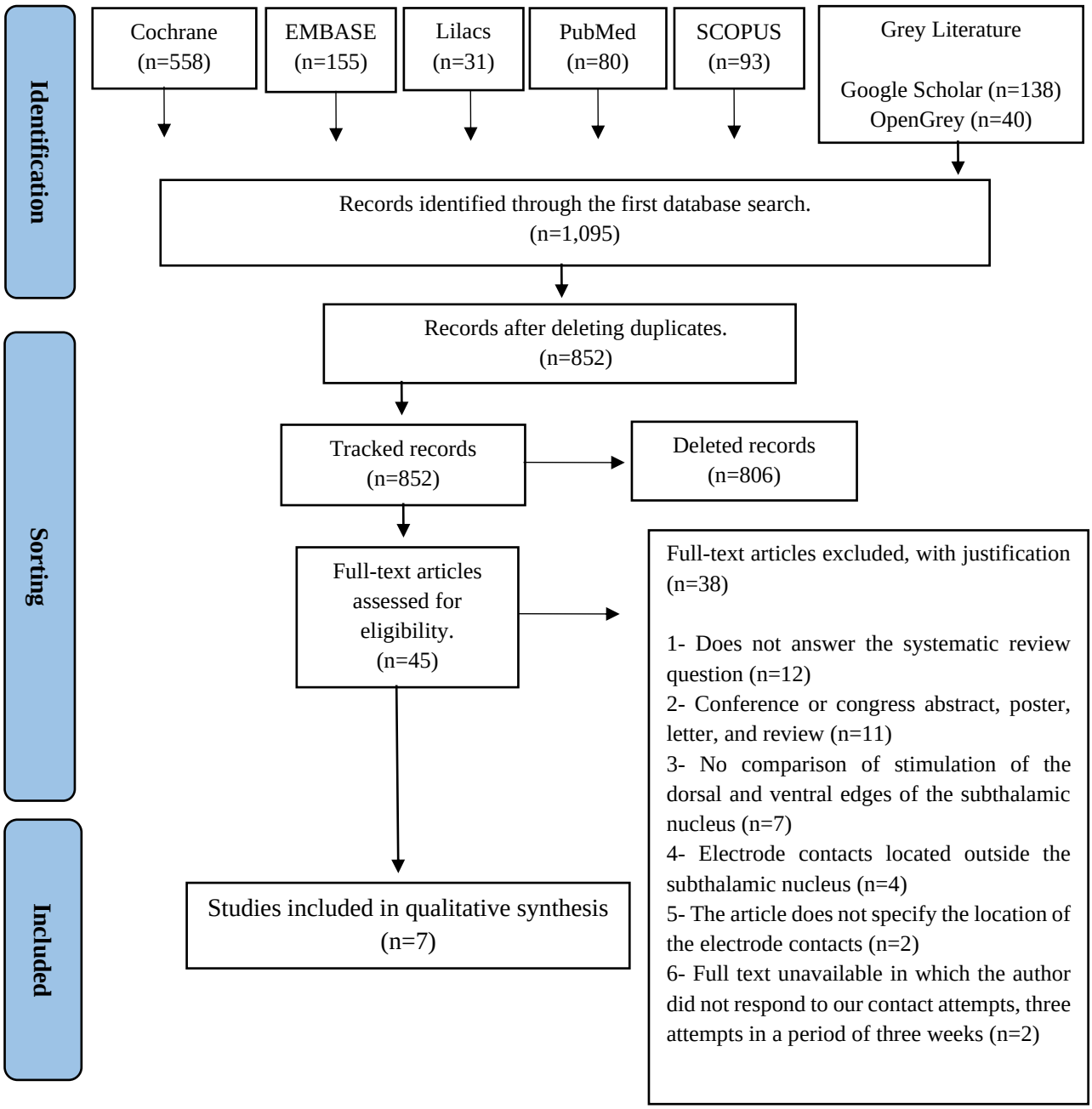
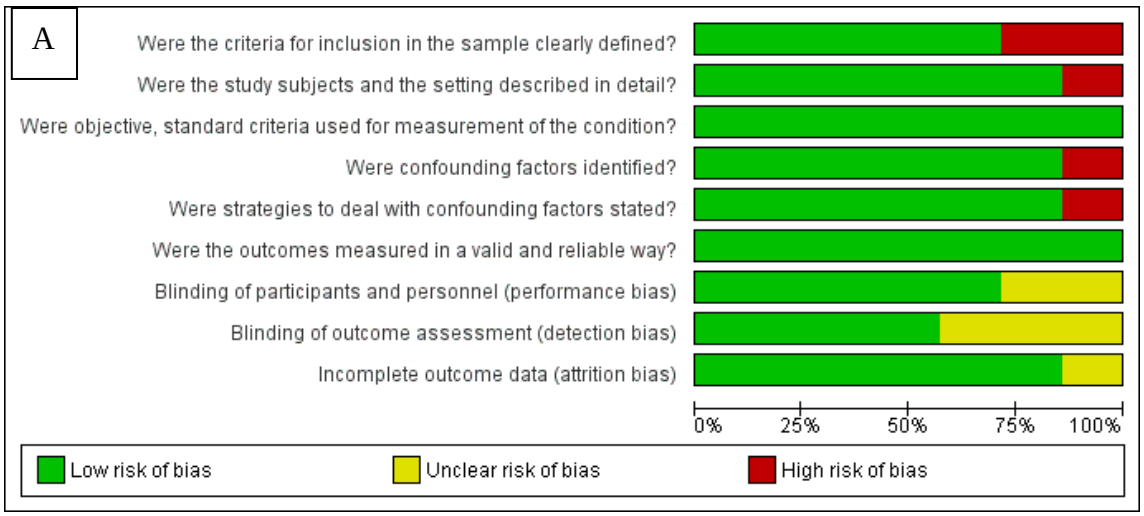
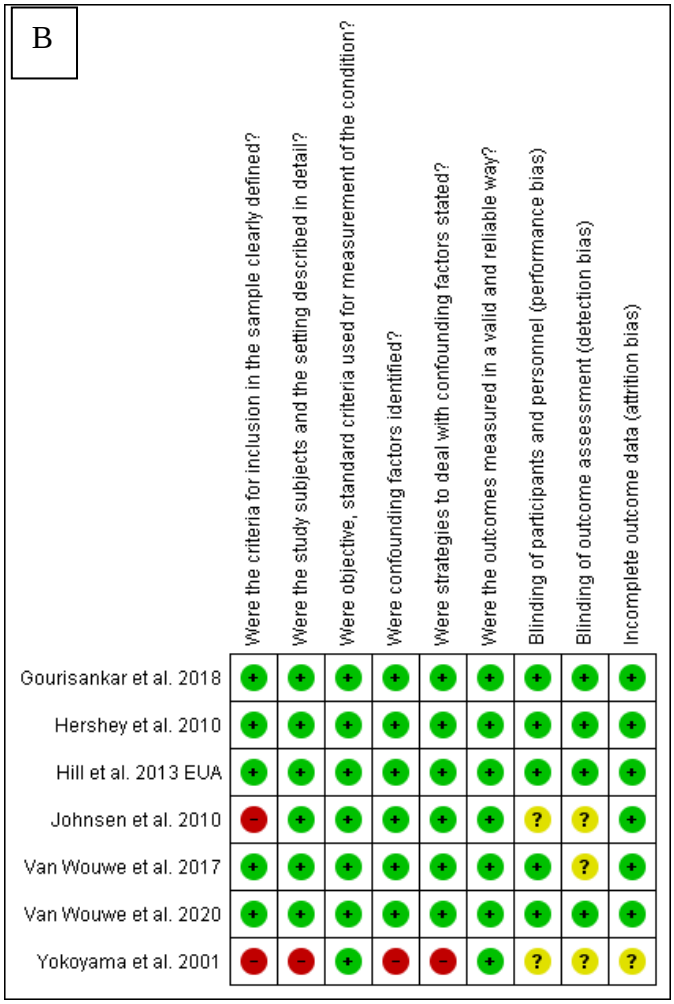


Figure 2: Analysis of the risk of bias of the included studies.





RevMan tool (The Cochrane Collaboration, 2019). Note: Green - low risk of bias; Red - high risk of bias; Yellow - uncertain risk of bias.

Table 1: Characteristics of the included studies.

Author/Year/ Country	Methods	Sample	Have you stopped your medication?	Duration of illness (average)	Stimulation site on the STN	Blinding	Conclusion	Study design
Gourisankar et al. 2018 EUA	The voltage, frequency, and pulse width were 2.5 V, 185 Hz, and 60 µs, respectively, for most of the participants. In 14 participants the voltage was reduced to 1.6-2.3 V. Motor symptoms were assessed with the UPDRS III-motor and cognition through spatial delay response and Go/No-Go tasks	74 patients with Parkinson's disease (50 men and 24 women with an average age of 62)	YES (00 hours before the morning of the study)	12.4 years	Bilateral stimulation, in the STN contralateral to the most affected side of the body. The ventral contact was within 2mm of the ventral border and the dorsal contact was within 2mm of the dorsal border. All this in the dorsal posterolateral STN	Of the patients and evaluators, no control group, the same patients underwent the two interventions (dorsal and ventral border stimulation).	Stimulation of the ventral border of the STN improved anxiety and rigidity more than dorsal; stimulation of the dorsal or ventral border of the STN improved motor function, anxiety, valence, and apathy.	Cross-sectional observational study (clinical intervention)
Hershey et al. 2010 EUA	Frequency of 185 Hz, amplitude of 2.5 V, and 60µs pulse width. Motor and cognitive measures were performed: 1) both stimulators switched off; 2i) unilateral dorsal contact; and 3i) unilateral ventral contact. Motor symptoms were measured using the motor subscale (part III) of the UPDRS and response inhibition was measured with the Go-No-Go.	10 patients with Parkinson's disease (9 men and 1 woman with an average age of 56.5 years)	YES (the night before the study)	Average of 14.1 years	The patients recruited had bilateral stimulation, but the stimulation was unilateral. Two contacts were selected: one at 2mm from the dorsolateral STN and the other at 2mm from the ventral STN.	Patients and evaluators were blinded, but there was no control group, as the same patients underwent both interventions (stimulation of the dorsal border and stimulation of the ventral border of the STN).	Stimulation of the ventral region of the STN, but not the dorsal, impaired oriented behavior by suggesting a prepotent motor response, while stimulation of both regions of the STN improved motor performance.	Cross-sectional observational study (clinical intervention)
Hill et al. 2013 EUA	Frequency of 185 Hz, amplitude of 2.5 V, and 60µs pulse width. Assessment of motor function in each stimulation condition included 1) administration of the UPDRS-III 2) gait analysis and 3) balance analysis. Pairwise comparisons for dorsal STN stimulation vs stimulation off and ventral STN stimulation vs stimulation off were performed for each variable such as regional cerebral blood flow, gait, and balance.	37 patients (19 men and 11 women with an average age of 64 years). 7 of the 37 participants were excluded from the analyses due to visible tremors or excessive electromyography activity during all PET scans in one or more stimulation conditions.	YES (withdrew the drug for more than 8 hours the night before the tests)	14.3 years	The patients recruited had bilateral stimulation, but the stimulation was unilateral and contralateral to the most affected side of the body	Patients and evaluators were blinded, but there was no control group, as the same patients underwent both interventions (stimulation of the dorsal border and stimulation of the ventral border of the STN).	Dorsal and ventral STN stimulations do not differentially affect gait or balance and are only minimally different in their effects on selected regions of blood flow. In both cases, stimulation-induced decreases in regional cerebral blood flow were associated with improvements in gait speed.	Cross-sectional observational study (clinical intervention)
Johnsen et al. 2010 Denmark	Gait analysis was conducted on 17 of the 22 patients with and without stimulation. Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale Part III. 152 Hz frequency, 3.4 V amplitude, and 60µs pulse width.	22 patients with Parkinson's disease (13 men and 9 women with an average age of 61.5 years). 4 patients were excluded	YES	-	Bilateral stimulation in the STN or medial to the edges of the nucleus. 27 were in the dorsal half and 7 in the ventral half. Of the active contacts in the dorsal half, 15 were anterior and 12 were posterior. In the inferior half, one contact was anterior and six were posterior.	-	Stimulation of the dorsal half of the STN improves balance and gait performance on the contralateral side of the body significantly better than stimulation of the ventral half.	Cross-sectional observational study (clinical intervention)
vanWouwe et al. 2017 EUA	Frequency 125.5, amplitude 2.6 (in the left STN) and 2.4 (in the right STN) and 59µs pulse width (in the right STN) and 61.7µs pulse width (in the right STN). After the cognitive test, the UPDRS was administered	11 patients with Parkinson's disease (6 men and 5 women with an average age of 58.9 years)	YES (withdrawal of levodopa 24 hours before the test and of agonists 48 hours before the test)	12.9 years	Bilateral stimulation	Patients were blinded and there was no control group, as the same patients underwent both interventions (dorsal and ventral border stimulation).	Stimulating the dorsal sub-region of the STN as opposed to the ventral sub-region improves reactive inhibitory control of impulse responses in Parkinson's disease patients removed from the influence of dopaminergic drugs. Stimulation of the STN subregions did not improve motor symptoms	Cross-sectional observational study (clinical intervention)
vanWouweet al. 2020 EUA	One group of participants completed two sessions of the stop signal task, once with bilateral stimulation of the dorsal part of the STN and once in ventral contacts. The other group of participants performed the stop signal task without stimulation (one session). Frequency 130 Hz and pulse width 60µs.	24 patients with the disease, 14 men and 10 women. 12 participated in the dorsal and ventral border stimulation procedure and 12 participated in the condition WITHOUT stimulation	YES (withdrawal of Levodopa 24 hours before the test and agonists 48 hours before the test)	Group with stimulation - 13.83. group without stimulation - 10.92	Bilateral stimulation	Patients were blinded and underwent two interventions (stimulation of the dorsal border and stimulation of the ventral border of the STN).	Stimulation in the ventral subregion of the STN improves global action arrest relative to stimulation in the dorsal subregion of the STN. This provides new causal evidence that the modulatory effect of stimulation on stop control depends on the STN subregion and confirms the importance of the ventral STN in modulating stop control.	Cross-sectional observational study (clinical intervention)
Yokoyama et al. 2001 Japan	Patients were assessed using separate subsets of UPDRS scores. Frequency 143.6, amplitude 2.2, and pulse width 68.1 µs.	10 patients with Parkinson's disease (1 man and 9 women). Average age not informed	YES (8-10 hours before the test)	-	Contact-0 was located near the ventral edge of the STN; contact-1 inside the STN; contact-2 dorsal edge of the STN; contact-3 above the STN, above the AC-PC plane.	-	The most significant improvement in Parkinsonian symptoms was obtained by stimulation of the dorsal border of the STN. Stimulation at points slightly above the dorsal border also produced an improvement in Parkinsonian symptoms. Stimulation of the ventral border caused no improvement	Cross-sectional observational study (clinical intervention)

STN - Subthalamic nucleus; UPDRS III - Unified Parkinson's Disease Rating Scale III; PET - Positron Emission Tomography; Go-No-Go Test; Simon Task - participants make quick reactions based on the color of a circle that appears to the left or right of a central fixation point.

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