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Pain in Parkinson's disease and the role of the subthalamic nucleus

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Abstract

Pain is a frequent and poorly treated symptom of Parkinson's disease, mainly due to scarce knowledge of its basic mechanisms. In Parkinson's disease, deep brain stimulation of the subthalamic nucleus is a successful treatment of motor symptoms, but also might be effective in treating pain. However, it has been unclear which type of pain may benefit and how neurostimulation of the subthalamic nucleus might interfere with pain processing in Parkinson's disease. We hypothesized that the subthalamic nucleus may be an effective access point for modulation of neural systems subserving pain perception and processing in Parkinson's disease. To explore this, we discuss data from human neurophysiological and psychophysical investigations. We review studies demonstrating the clinical efficacy of deep brain stimulation of the subthalamic nucleus for pain relief in Parkinson's disease. Finally, we present some of the key insights from investigations in animal models, healthy humans and Parkinson's disease patients into the aberrant neurobiology of pain processing and consider their implications for the pain-relieving effects of subthalamic nucleus neuromodulation. The evidence from clinical and experimental studies supports the hypothesis that altered central processing is critical for pain generation in Parkinson's disease and that the subthalamic nucleus is a key structure in pain perception and modulation. Future preclinical and clinical research should consider the subthalamic nucleus as an entry point to modulate different types of pain, not only in Parkinson's disease but also in other neurological conditions associated with abnormal pain processing.

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Keywords

Parkinson's disease; pain; deep brain stimulation; subthalamic nucleus; nociception

Introduction

Pain is a common and increasingly recognized non-motor symptom of Parkinson's disease, and its prevalence is variably reported as between 40% and 85% and increases with disease progression.^{1,2} Pain in Parkinson's disease is multifactorial and has been classified into five main categories (musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, akathitic discomfort, and primary, or central, parkinsonian pain) based on clinical features and its presumptive anatomical basis.³

Dopaminergic transmission is involved in modulating nociception in Parkinson's disease, as pain has been associated with motor fluctuations⁴ and may respond to dopaminergic treatment.⁵ Yet, a recent large epidemiological study reported no difference of pain in 81% of Parkinson's disease patients between the ON and OFF medication state.² This result suggests that pain in Parkinson's disease might be uncoupled from the effect of dopamine on motor symptoms and optimization of dopaminergic treatment may only help a small proportion of patients.

In the past two decades, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an established and powerful treatment for subjects with Parkinson's disease experiencing severe motor complications.⁶ STN DBS might also be effective in treating pain, but it is unclear which type of pain may benefit and how neurostimulation might interfere with pain processing in Parkinson's disease.

The aim of this update is to shed light on how the STN can be an effective access point for modulation of neural systems subserving pain processing and perception in Parkinson's disease. This may provide insights into the neurobiological basis of different subtypes of pain and is crucial for understanding the mechanisms of action of STN DBS on pain, how these may differ from those of dopaminergic medications, and how they can be harnessed and improved as part of tailored therapies addressing specific pain subtypes. We hypothesize that while the effect on pain may in part relate to improvement of motor fluctuations, there is also a central component to pain in Parkinson's disease that may be modulated by STN DBS. Based on this hypothesis, here we explore the following research questions: (i) What is the evidence of abnormal central processing of pain in Parkinson's disease? (ii) What is the evidence for the efficacy of STN DBS in treating pain in Parkinson's disease and specifically for which subtypes of pain? and (iii) How may abnormal pain processing in Parkinson's disease be modulated by the STN?

We believe that points raised here may be relevant for understanding the neurobiological basis of pain in Parkinson's disease and developing tailored treatment of different subtypes of pain in Parkinson's disease, as well as being relevant to other neurological conditions characterized by abnormal pain processing.

Evidence for abnormal central pain processing in Parkinson's disease

Pain is a complex and multidimensional experience with both unpleasant sensory and emotional components.⁷ Different aspects of pain perception are thought to be processed in parallel streams in the CNS. In the brain, a 'lateral' pathway incorporates the lateral thalamic nuclei, primary and secondary somatosensory cortices and mediates the sensory-discriminative component of pain. A 'medial' pathway encompasses the periaqueductal grey matter, more medial thalamic nuclei, anterior cingulate and insular cortices and mediates the affective-motivational component.⁸ In the spinal cord, the dorsal horn is a key structure in which modulation of nociceptive signals is known to occur, for example via descending projections from brainstem monoaminergic nuclei.⁹

In this section, we examine experimental evidence in Parkinson's disease patients demonstrating both enhancement of quantitative measures of nociception and associated changes in brain activity. We also discuss how dopaminergic and non-dopaminergic neurotransmission is involved in modulating pain sensitization. Demonstrating that a central anomaly of pain perception and processing occurs in Parkinson's disease is crucial for understanding the anti-nociceptive effects of STN DBS and ultimately to speculate on the role of the STN in the pain network.

Insights from neurophysiological and neuroimaging studies

Psychophysical, spinal nociceptive reflex, laser-evoked potential (LEP) and functional neuroimaging studies have provided evidence for abnormal pain processing in Parkinson's disease.

Sensitization to noxious stimuli is a phenomenon common to many chronic pain conditions that can be reflected in reduced pain thresholds.¹⁰ A recent systematic review and meta-analysis concluded that there are significantly lower warm and cold thermal, mechanical and electrical pain thresholds tested with quantitative sensory testing (QST) in Parkinson's disease compared to healthy control subjects.¹¹ However, this phenomenon is also present in pain-free Parkinson's disease patients,^{12,13} suggesting that the presence of subclinical changes in pain pathways is only part of the spectrum of somatosensory abnormalities associated with the disease.¹⁴

The role of dopaminergic treatment in modulating nociceptive thresholds has been contradictory, with both increases¹⁵⁻¹⁷ or no change reported after levodopa¹⁸⁻²⁰ or apomorphine²¹ administration. Possible reasons for these discrepant findings include differences in drug regimens during ON medication testing as well as heterogeneous pain characteristics in Parkinson's disease patients. These ranged from pain-free subjects^{15,19} to those deemed to have central pain,¹⁷ to mixed groups of subjects with and without pain, sometimes of undefined subtype. One important potential confounding factor when interpreting QST studies in Parkinson's disease is the occurrence of cutaneous denervation,²² which provides an additional substrate for altered nociception of peripheral origin. Such small fibre neuropathy does not correlate with duration or severity of disease, and is structurally more severe on the most affected side.²³ Interestingly, a recent study proposed that small fibre neuropathy might predispose to central sensitization to peripheral

inputs in Parkinson's disease, as it correlates with enhanced perceived pleasantness to gentle touch in Parkinson's disease.²⁴

The nociceptive flexion reflex (NFR, also referred to as the RIII reflex) is an involuntary protective movement of a limb away from and in response to a noxious stimulus, as a result of activation of a spinal reflex arc.²⁵ Mirroring the changes seen in psychophysical studies, Parkinson's disease patients demonstrate a lower electrical stimulus intensity threshold for eliciting the NFR compared to healthy control subjects, which increases with levodopa administration.^{26,27} This phenomenon suggests a facilitation of the NFR within the spinal cord where the afferent somatosensory nociceptive inputs summate and lead to efferent motor neuron activation. A putative contributing mechanism might be the decreased inhibitory control from descending pain pathways modulating the dorsal horn. While the NFR in itself is unconscious and independent of pain perception, decreased descending modulation could provide a substrate for facilitation of nociceptive transmission through the spinal cord leading to enhanced conscious perception of pain. Such a mechanism is plausible but presumptive and should be tested in experimental studies linking the subjective experience of pain in Parkinson's disease with decreased descending control of spinal nociception.

One relatively consistent finding of electrophysiological and functional neuroimaging studies is the presence of abnormalities in brain regions implicated in the affective-motivational component of pain such as the anterior cingulate and insular cortices.

Specifically, LEP studies have shown reduced N2/P2 amplitudes in pain-free Parkinson's disease patients compared to healthy control subjects.^{19,28,29} In one series of studies, N2/P2 amplitudes were diminished even further in patients with lateralized muscular pain, but only with stimuli delivered to the painful side, and were not affected by levodopa administration.³⁰ In contrast to these findings, two studies reported increased¹⁷ or normal N2/P2 amplitudes³¹ in Parkinson's disease with different types of pain. The N2/P2 component of LEPs is generated by the anterior cingulate cortices perhaps with contributions from bilateral insula, likely expressing activity of the 'medial' pathway structures.³² One potential unifying explanation for the above findings is that N2/P2 amplitudes are increased specifically in subjects with central pain and temporarily reduced by conscious suppression of pain when subjects are asked to suppress a withdrawal response.^{19,28,30}

On brain imaging, H₂¹⁵O PET in pain-free patients revealed increased cerebral blood flow in ipsilateral insular and prefrontal cortex, and contralateral anterior cingulate cortex in response to noxious cold stimuli, concomitant with reduced cold thermal pain thresholds.¹⁵ This pain-induced cortical activity was reduced by administration of levodopa. Functional MRI has shown reduced haemodynamic response to noxious contact heat in bilateral insulae and superior temporal gyri, and ipsilateral temporal pole and middle temporal gyrus compared to control subjects.³³ Furthermore, functional connectivity measures using functional MRI have shown reduced connectivity between the basal ganglia and the salience network (mainly comprising bilateral insulae and anterior cingulate gyri) during a noxious heat stimulus.³⁴

In summary, the large body of evidence describing increased pain sensitivity in the form of quantitative decreases in multimodal pain thresholds in Parkinson's disease is in keeping with altered central processing of nociceptive stimuli in the brain and spinal cord. This is present even in patients who do not report pain as a major symptom, suggestive of a subclinical deficit in such patients, and may be modulated by dopaminergic status. The observed abnormalities in pain-evoked cerebral activation in Parkinson's disease in electrophysiological paradigms and neuroimaging measures of cerebral metabolism, indicate alterations in processing within pain-related areas, even amongst patients with no clinical pain. It is possible that these abnormalities are part of the Parkinson's disease spectrum and contribute to a predisposition to abnormal pain perception.

Role of dopaminergic and non-dopaminergic pathways in Parkinson's disease-related pain

Dopaminergic projections from the ventral tegmental area to the nucleus accumbens, prefrontal cortex and cingulate cortex have a long-established role in central mechanisms of analgesia. Accordingly, degeneration of the meso-limbic pathway might underlie abnormal central pain processing in Parkinson's disease.³⁵

In rodents, enhancement of dopaminergic transmission, either pharmacologically or by direct stimulation of midbrain centres, increases nociceptive thresholds. Conversely, attenuation of dopaminergic signalling with drugs or experimental lesions has the opposite effect of decreasing nociceptive thresholds.^{36,37} The rat model in which dopaminergic pathways are selectively lesioned at the substantia nigra, striatum or medial forebrain bundle with the neurotoxin 6-hydroxydopamine (6-OHDA) has been extensively employed to model pain in Parkinson's disease (for a review, see Buhidma *et al.*³⁸) When lesioning the dopaminergic system with 6-OHDA, rodents manifested hypersensitivity to heat, mechanical, chemical or cold stimuli not only on the side showing motor impairment but also on the unaffected side,³⁸ suggesting a bilateral top-down control by dopaminergic neurons of pain processing.

Likewise, direct infusion of dopamine antagonists into the nucleus accumbens of the rat attenuates the effect of antinociceptive measures.^{39,40} In healthy humans, dietary depletion of dopamine precursors is associated with a greater affective component or perception of 'unpleasantness' in response to a noxious heat stimulus without affecting the sensory-discriminative aspects.⁴¹ In contrast, administration of levodopa to enhance dopaminergic transmission does not affect cold thermal pain or NFR thresholds.^{15,26} PET studies in healthy humans show increased striatal dopamine receptor occupancy following a noxious stimulus. In the more dorsal nigrostriatal projection this correlates with the sensory and affective qualities of the stimulus, while in the more ventral mesolimbic projection it is associated with negative affect and fear ratings.^{42,43}

Besides dopamine, other neurotransmitters might be involved in modulation of pain in Parkinson's disease, considering also that the neurodegenerative process involves multiple brain and brainstem nuclei.⁴⁴ Descending brainstem monoaminergic projections into the dorsal horn of the spinal cord are known to have pain modulating influences.⁹ Their degeneration may enhance the transmission of pain signals through the spinal cord and contribute to increased pain sensitivity at this level. In addition, loss of basal forebrain

cholinergic neurons in Parkinson's disease may impact upon the recognized role of acetylcholine in the modulation of pain perception.⁴⁵ In the endocannabinoid system, the rich expression of receptors in the basal ganglia undergoes changes in Parkinson's disease,⁴⁶ while reduction in endocannabinoid receptor density in pain-modulating regions such as the anterior cingulate cortex, as well as changes in endogenous opioid signalling in the dorsal horn, are associated with increased pain sensitivity following experimental parkinsonian lesions in rodents.^{47,48}

Overall, evidence in humans and animal models has shown that reduction in dopaminergic neurotransmission is associated with increased pain sensitivity. Dopaminergic denervation thus provides a plausible substrate for altered central pain processing in Parkinson's disease, though pathological changes in non-dopaminergic neurotransmitter systems seem also to be implicated. Both these findings link Parkinson's disease pathology to pain generation and point to interventions aimed at modulating a dysfunctional pain network as a strategy to treat pain in Parkinson's disease.

How effective is STN DBS in treating pain and modulating pain processing in Parkinson's disease?

Several observational studies on small cohorts of patients (total number = 324) have described significant improvement in global measures of pain in Parkinson's disease patients who have undergone STN DBS (Table 1). Improvement in global pain scores after STN DBS ranged between 28% and 84% compared to the preoperative baseline.

Table 1 summarizes the details from these studies, including the experimental conditions and the subtype of pain tested. Although the majority of them were observational, uncontrolled and performed on small samples, and many did not examine specific pain subtypes, STN DBS appears to be effective in improving most types of pain. Limited data are available on the role of preoperative levodopa challenge in predicting the postoperative change of pain. Either a positive⁵⁵ or no correlation⁵⁶ have been reported.

Better control of motor symptoms by STN DBS might determine improvement of fluctuation-related and dystonic pain.^{49,50,54,56,60} In addition, reduction of musculoskeletal and dystonic pain has been correlated with the decrease in rigidity and dyskinesia after surgery,⁵⁴ suggesting that the effect on pain might be mediated by the improvement in motor symptoms and motor fluctuations by STN DBS. However, a few clinical studies did not find any correlation between the change in pain and the variation of motor response induced by STN stimulation either in an acute challenge test or by chronic neurostimulation.^{56,57,59,61} The effect on clinically defined central pain is even more controversial with reports of either improvement^{50,53,62} or no change.^{54,56,59}

QST following STN DBS has been used to examine central pain processing and has yielded inconsistent findings in seven investigations encompassing a total of 128 participants, which are summarized in Table 2. Four studies reported increase in pain thresholds in Parkinson's disease patients when on compared to off stimulation, for both mechanical and thermal stimuli.^{16,52,53} One further study showed increased mechanical pain thresholds with STN

stimulation at 60 Hz rather than at the patients' usual higher therapeutic frequencies, though the authors did not account for medication status.⁶⁵ In contrast, others have found no acute stimulation-related modulation of pain thresholds, though some described an increase in non-noxious thermal sensitivity via a reduction in temperature detection thresholds.^{51,63,64} One study showed a correlation between increased pain threshold and acute DBS-mediated motor improvement⁵²; however, another with similar methodology did not demonstrate this relationship.¹⁶

Table 2 highlights how variability in disease features (range of disease duration; inclusion of pain-free subjects), experimental conditions (medication and stimulation status; body site tested) and pain modality tested (all or a specific one) might account for such discrepancies. Insights from pain threshold studies suggest that STN might differently modulate pain thresholds when patients were stratified according to the presence of pain and its subtype. Accordingly, increase of heat pain threshold by STN DBS was demonstrated only in Parkinson's disease with central pain, but not in pain-free patients.⁵³ Furthermore, an important con-founder is whether or not data were retrieved from the most affected Parkinson's disease body side, and from a painful or a pain-free site. Finally, all studies have challenged pain thresholds under an acute stimulation condition (off stimulation versus on stimulation) but none of them have compared these with preoperative values, especially in subjects who experienced pain before DBS. Such a study design should be pursued in order to demonstrate whether the anti-nociceptive action of STN DBS is a chronic effect of neuromodulation on central pain processing.

In summary, while STN DBS may exert some of its pain-relieving effects via improvement in motor function, it can modulate quantitative pain thresholds, cerebral activity and pain-evoked responses of cortical areas responsible for pain processing, which may account for an effect on pain unrelated to motor symptoms or fluctuations.

How may abnormal pain processing in Parkinson's disease be modulated by STN?

If abnormal processing of pain is a major mechanism mediating nociception in Parkinson's disease, one hypothesis is that STN may represent an effective access point for modulation of basal ganglia circuits influencing pain processing and perception.

The STN is commonly segmented anatomically and functionally into sensorimotor, associative and limbic subregions based on its connectivity within parallel basal ganglia–thalamocortical circuits.⁶⁶ The posterolateral sensorimotor part is typically targeted by DBS to improve motor symptoms,⁶⁷ whereas the more anterior and medial parts are connected to cortical regions subserving associative and limbic functions, respectively.⁶⁸ Multiple cortical areas including somatosensory and limbic regions are involved in pain processing and the stimulation field of DBS is unlikely to be confined to a single STN subregion, given the degree of topographical overlap.⁶⁹ STN DBS can induce widespread changes in glucose metabolism in sensorimotor, associative and limbic cerebral cortical regions, including those responsible for pain processing.⁷⁰ Furthermore, stimulation of STN is associated with a reduction in cerebral cortical haemodynamic responses to noxious heat in primary

somatosensory cortex and insula in patients with central pain.⁵³ The neuromodulation by STN of networks mediating pain processing was also demonstrated in 6-OHDA lesioned parkinsonian rats in which stimulation-induced changes in neuronal firing in single units were recorded in anterior cingulate cortex, periaqueductal grey and sensory thalamus.⁷¹

As the effects of STN DBS can be seen in multiple pain-related cortical areas, it is conceivable that specific territories of STN are involved in pain processing. Indeed, phasic responses to noxious stimuli can be seen in neuronal populations in STN during intraoperative microelectrode recordings in Parkinson's disease patients.⁷² Such responses are also seen in physiological conditions in the rat and are enhanced in 6-OHDA lesioned parkinsonian rats, suggesting Parkinson's disease-related changes in the way nociceptive information is handled by the STN.⁷³ In both the rodent model⁷⁴ and humans with Parkinson's disease,⁶⁵ low frequency (50/60 Hz) DBS has proved to increase pain thresholds compared to high frequency stimulation. A similar dissociation between low and high frequency stimulation for controlling axial and segmental signs, respectively,⁷⁵ is well-known for motor symptoms and suggests the activation of different neuronal populations within the STN.

Yet, how and whether different STN territories may contribute to the therapeutic effect on pain remains a knowledge gap to be addressed. Excessive neuronal synchronization in the beta frequency band within motoric regions of the basal ganglia has been consistently associated with bradykinesia and rigidity,⁷⁶ and desynchronization has been pointed out as a mechanism of DBS.⁷⁷ Studies of local field potentials recorded from implanted DBS electrodes demonstrate changes in low beta-band synchrony evoked by noxious stimuli in the globus pallidus and STN,^{72,78} suggesting that STN neurons responding to nociceptive stimuli might be also excessively synchronized.

The sources of nociceptive inputs to the STN include pathways to the basal ganglia from the spinal cord as well as transcortical pathways via pain-related regions of cerebral cortex.⁷⁹ These pathways and others involved in central processing of pain in Parkinson's disease are summarized in Fig. 1. The STN is also connected to brainstem nuclei involved in pain processing, such as the pedunculopontine nucleus (PPN)⁸⁰ and the pontine parabrachial nucleus.⁷³ PPN is implicated in a wider brainstem network mediating antinociception,^{81,82} potentially acting via cholinergic projections to descending monoaminergic nuclei in the rostral ventromedial medulla.^{83,84} Its cholinergic neurons can show strong responses to nociceptive inputs.⁸⁵

Recent work in the rat has also highlighted the parabrachial nucleus as an important relay for nociceptive signals to the STN.⁷³ This rostral pontine nucleus is known to provide nociceptive inputs to the amygdala, which is involved in the affective dimension of pain⁸⁶ and influences the descending modulation of pain by monoaminergic neurons of the rostral ventromedial medulla.⁸⁷ The parabrachio-amygdaloid pathway runs in parallel with parabrachio-subthalamic fibres, traverses the STN and could potentially be modulated by STN DBS.⁷³

In summary, neural substrates of pain processing are present in the STN as well as in important fibres of passage in its vicinity, and there is evidence that these are pathologically enhanced in Parkinson's disease patients and rodent models of Parkinson's disease. Furthermore, the STN has functional connections with cortical areas involved in pain processing and with brainstem nuclei implicated in nociception and descending modulation of pain transmission. The exact processes by which these are modulated by DBS to yield an analgesic effect remain to be elucidated.

Conclusions and future directions

Psychophysical, neurophysiological and functional neuroimaging studies suggest that abnormal central processing of pain occurs in Parkinson's disease as a trait of the disease, which may contribute to pain syndromes. Central pain processing in Parkinson's disease could be affected by aberrant function in cortico-basal ganglia loops arising from nigrostriatal and/or mesocorticolimbic dopaminergic deficiency, as well as through loss of pain-modulating monoaminergic projections into the spinal cord from the brainstem, cholinergic innervation of the forebrain and changes in other neurotransmitter systems.

Psychophysical studies in Parkinson's disease patients treated with STN DBS suggest a link between STN and central pain processing, although results should be interpreted carefully due to some discrepancies determined by methodological differences. Yet, additional evidence supports such a central role of STN within the pain network: (i) the presence of connections between STN and associative and limbic cerebral cortical areas and brainstem nuclei involved in pain processing; and (ii) data from electrophysiological studies showing that STN neurons in Parkinson's disease and animal models are responsive to noxious stimuli.

We believe STN DBS may represent a meaningful tool for understanding the neurobiological basis of different subtypes of pain in Parkinson's disease and, in general, for how nociception is controlled at supraspinal level. Research in this challenging topic should deal with the inconsistency of the current classification system for pain in Parkinson's disease, which mixes clinical and anatomic-functional criteria. Indeed physiological markers of pain should be investigated in human neurophysiological studies as well as in animal models³⁸ leading to tailored therapeutic interventions for pain not only in Parkinson's disease, but also in other neurological conditions characterized by abnormal pain processing.

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Abbreviations

DBS	deep brain stimulation
STN	subthalamic nucleus

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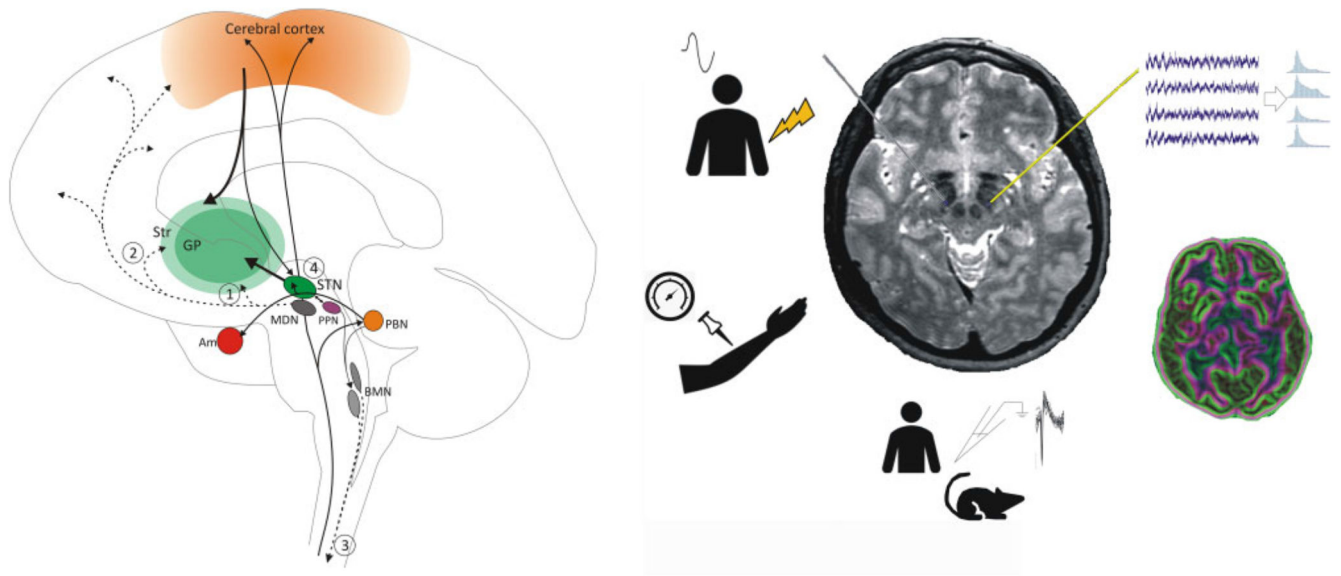


Figure 1. Schematic representation of pathways involved in Parkinson's disease pain.

(1) Degeneration of the nigrostriatal pathways from midbrain dopaminergic nuclei (MDN) to dorsal striatum leads to the characteristic motor features of Parkinson's disease, which can give rise to pain subtypes related to motor symptoms such as dystonic, dyskinetic or musculoskeletal pain. (2) Dopamine depletion in the striatum could enhance pain perception independently of motor symptoms by affecting the way sensory stimuli are processed. (3) Loss of projections from brainstem monoaminergic nuclei (BMN) to the spinal cord could enhance the transmission of nociceptive signals to the brain. (4) The STN connects with brainstem nuclei involved in pain processing and control of descending pain modulation, including pedunculo-pontine nucleus (PPN) and parabrachial nucleus (PBN), and receives nociceptive inputs via a pathway parallel to the spino-parabrachio-amygdaloid pathway as well as from cerebral cortex. Dashed lines represent pathways that degenerate in Parkinson's disease. Am = amygdala; GP = globus pallidus; Str = striatum.

Table 1
Effect of STN DBS on Parkinson's disease reported pain

Study	n	Disease duration, years	Time from DBS surgery	Experimental condition	Type of pain	Pain measure	Effect of STN DBS
Witjas <i>et al.</i> ⁴⁹	40	12.4±4.5	12 months	ON MED/on STIM versus OFF MED/on STIM	W-OFF-P	Custom NMF questionnaire pain/sensory score	↓
Kim <i>et al.</i> ⁵⁰	29	9.9 ±4.6	3 and 24months	OFF MED post-DBS versus OFF MED pre-DBS	W-OFF-P and NFP MSK, dystonic, central, neuropathic/ radicular	NRS in seven body parts, differentiated by type of pain	New onset pain at 3 (n = 5) and 24m (n = 9) MSK or central W-OFF-P ↓, NFP ↓ Dystonic ↓, central ↓, MSK ↓ Neuropathic/radicular ↓
Gierthmuhlen <i>et al.</i> ⁵¹	12	10.5 ±4.6	6 months	Post-DBS versus pre-DBS	NS	NRS pain DETECT score	Current →, past 4 weeks ↓
Ciampi di Andrade <i>et al.</i> ⁵²	25	15.1±4.1	2.4±1.3years	Post-DBS versus pre-DBS	NS	Chronic pain prevalence	↓
Dellapina <i>et al.</i> ⁵³	8	12.4±2.6	>3 months	Post-DBS versus pre-DBS	Central pain	VAS NPSI - 'burning spontaneous' dimension	↓ → ↓
Oshima <i>et al.</i> ⁵⁴	69	11.8±7.7	2 weeks 6 months 12 months	Post-DBS versus pre-DBS	W-OFF-P, MSK, dystonic, somatic, central, neuropathic/ radicular	VAS, total and differentiated by type	MSK ↓, dystonic ↓, somatic ↓ Neuropathic/radicular ↓ Central →, total ↓
Surucu <i>et al.</i> ⁵⁵	14	6–18	3–41 months	On STIM versus OFF MED (pre-DBS)	Levodopa responsive versus Levodopa unresponsive pain	NRS	↓ in 8 (mainly levodopa responsive) → in 6 (all levodopa unresponsive)
Cury <i>et al.</i> ⁵⁶	41	15±7.6	12 months	Post-DBS versus pre-DBS	A) PD pain versus non-PD pain B) Subtypes: MSK, dystonic, neuropathic/ radicular, central, W-OFF-P	Pain prevalence (total and subtypes) VAS, BPI, MPQ, NPSI, PCS	Total ↓, MSK ↓, dystonic ↓, W-OFF-P ↓ central →, neuropathic/radicular → VAS ↓, BPI ↓, MPQ ↓ NPSI →, PCS →
Pellaprat <i>et al.</i> ⁵⁷	58	12.3±3.8	12 months	Post-DBS versus pre-DBS	NS	Short MPQ, UPDRS-II item 17 PDQ-39 bodily discomfort score	All ↓
Smith <i>et al.</i> ⁵⁸	16	12.2 ±1.0	6 and 12 months	Post-DBS versus pre-DBS	Low back pain	Global VAS and OLBPD	Both ↓

Study	n	Disease duration, years	Time from DBS surgery	Experimental condition	Type of pain	Pain measure	Effect of STN DBS
DiMarzio <i>et al.</i> ⁵⁹	12 STN 5 GPI	11.6±1.0	6 months	Post-DBS versus pre-DBS GPI versus STN	All types as per KPFS	KPPS and subscores MPQ LBDI	↓ ^a ↑ ↓

All studies comparing on-stimulation versus preoperative status. ↑↓ = increase/decrease; → = no change; BPI = Brief Pain Inventory; GPI = globus pallidus pars interna; KPPS = King's Parkinson's Disease Pain Scale; LBDI = Low Back Disability Index; MED = medication; MPQ = McGill Pain Questionnaire; MSK = musculoskeletal; NMF = non-motor fluctuations; NPSI = Neuropathic Pain Symptom Inventory; NFP = non-fluctuating pain; NRS = numeric rating scale; NS = not specified; OLBPD = Oswestry Low Back Pain Disability Index; PCS = Pain Catastrophizing Scale; PD = Parkinson's disease; PDQ-39 = Parkinson's Disease Questionnaire-39; STIM = stimulation; UPDRS-II = Unified Parkinson's Disease Rating Scale Part II; VAS = visual analogue scale; W-OFF-P = wearing off pain.

^aTotal score and fluctuation-related subscore only.

Table 2

Acute effect of STN DBS on pain thresholds

Study	n	Disease duration, years	Type of pain	Medication/ stimulation condition	Site tested	Modality tested	Outcome of STN DBS on thresholds
Gierthmuhlen <i>et al.</i> ⁵¹	17	10.5±4.6	12 with pre-op pain 9 'noctceptive' 4 fluctuating	OFF med ^a	Thenar eminence (MAS)	CPT HPT MPT PPT	↑ → → →
Maruo <i>et al.</i> ⁶³	17	15.5 ±5.4	Not reported	OFF med	Both hands	CPT HPT	→ →
Spielberger <i>et al.</i> ⁶⁴	15	17.3±4.8	Not reported	OFF med and ON med (versus OFF med/off stim)	MAS (site not reported)	CPT HPT	→ b
Ciampi di Andrade <i>et al.</i> ⁵²	25	15.1 ±4.1	18 (72%) with pre-op pain 9 (36%) with post-op pain	OFF med	Thenar eminence (CPT, HPT) Dorsum of hand (MPT)	CPT HPT MPT	→ → ↑
Dellapina <i>et al.</i> ⁵³	16	13.1 ±2.9 (no pain) 12.4 ±2.6 (central pain)	8 no pain 8 central pain	OFF med	Thenar eminence (MAS)	HPT	→ (no pain) ↑ (central pain)
Marques <i>et al.</i> ¹⁶	19	13.2±2.8	9 with OFF pain pre-op 1 with OFF pain post-op	OFF med	Volar arm (HPT) Digits (MPT)	HPT MPT	→ ↑
Belasen <i>et al.</i> ⁶⁵	19	Range 5–23 years	11 with chronic pain 8 with no pain	Not reported	Site with most pain Low back if no pain	MPT	↑ (60 Hz) → (high frequency)

↑ Increase; → no change; CPT = cold pain threshold; HPT = heat pain threshold; MAS = most affected side; MPT = mechanical pain threshold; PPT = pressure pain threshold.

^aIn most affected side only. Pain status characterized with painDETECT score.

^bIn OFF and ON medication conditions.