EJP
European Journal of Pain

TOPICAL REVIEW

Sensory abnormalities and pain in Parkinson disease and its modulation by treatment of motor symptoms

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Funding Source
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Conflicts of interest
None declared.

Accepted for publication
16 May 2015

doi:10.1002/ejp.745

Abstract

Pain and sensory abnormalities are present in a large proportion of Parkinson disease (PD) patients and have a significant negative impact in quality of life. It remains undetermined whether pain occurs secondary to motor impairment and to which extent it can be relieved by improvement of motor symptoms. The aim of this review was to examine the current knowledge on the mechanisms behind sensory changes and pain in PD and to assess the modulatory effects of motor treatment on these sensory abnormalities. A comprehensive literature search was performed. We selected studies investigating sensory changes and pain in PD and the effects of levodopa administration and deep brain stimulation (DBS) on these symptoms. PD patients have altered sensory and pain thresholds in the off-medication state. Both levodopa and DBS improve motor symptoms (i.e.: bradykinesia, tremor) and change sensory abnormalities towards normal levels. However, there is no direct correlation between sensory/pain changes and motor improvement, suggesting that motor and non-motor symptoms do not necessarily share the same mechanisms. Whether dopamine and DBS have a real antinociceptive effect or simply a modulatory effect in pain perception remain uncertain. These data may provide useful insights into a mechanism-based approach to pain in PD, pointing out the role of the dopaminergic system in pain perception and the importance of the characterization of different pain syndromes related to PD before specific treatment can be instituted.

1. Introduction

The cardinal signs of Parkinson disease (PD) result from the decreased dopaminergic (DA) input from the *substantia nigra* to the *striatum*, leading to tremor, bradykinesia and rigidity (Samii et al., 2004). Motor abnormalities in PD are the result of alterations in the cortico-striato-thalamo-cortical circuits, which are normally modulated by dopamine among other neurotransmitters and neuropeptides (Jankovic, 2008). However, PD pathology is not restricted to nigrostriatal pathways. A large body of evidence suggests that brainstem nuclei, diencephalic and cortical areas are also affected (Braak et al., 2002) as well as extra-encephalic structures such as the spinal cord and the autonomic enteric plexus (Braak et al., 2002; Gold et al., 2013). Extranigral pathology is considered to constitute the anatomical basis for the occurrence of non-motor symptoms (NMS) in PD.

Databases

- A comprehensive literature search was performed using the PubMed, EMBASE and Google Scholar databases and included studies published before November 2014. The manuscripts identified were reviewed for relevance, and reference lists of the retrieved articles were crosschecked for additional important studies. We selected studies investigating sensory changes and pain in Parkinson disease and the effects of levodopa administration or deep brain stimulation on these symptoms.

What does this review add?

- This review summarizes the current knowledge on sensory and pain symptoms in Parkinson disease and how the motor treatment (pharmacological and neuromodulatory) affects the sensory thresholds and pain in these patients.

NMS are prevalent (Hely et al., 2005) and include autonomic dysfunction, sleep disorders, depression, anxiety, dementia, olfactory disturbances and pain (Hely et al., 2005; Chaudhuri and Schapira, 2009; Kim et al., 2009; Park and Stacy, 2009; Chaudhuri and Odin, 2010). NMS are thought to be present from the early stages of the disease and are increasingly recognized as a major cause of disability (Fasano et al., 2012). Pain has a prevalence of 40–85% in PD patients (Beiske et al., 2009; Broen et al., 2012) and is associated with significant reductions in patients' health-related quality of life compared with matched controls (Quittenbaum and Grahn, 2004). The exact mechanisms responsible for pain in PD remain largely unknown, but is has been recognized that it cannot be fully explained by the intensity of the motor symptoms fluctuations (Chudler and Dong, 1995; Spielberger et al., 2011). It is clear that the motor status (dyskinesia, rigidity, dystonia) can cause or aggravate pain in these patients (Beiske et al., 2009). Motor symptoms can be controlled by changes in medication regimen or by deep brain stimulation (DBS). However, a significant proportion of patients remain with pain despite motor improvement. There is growing evidence that brain pathology outside the DA circuits can play a role in the genesis of NMS of the disease, and pain in particular. Also, NMS may not readily respond to changes in DA treatment, and seem to be related to sensory changes caused by the disease itself. The aim of this review was to assess to which extent treatment of motor symptoms of PD (DA and neuromodulatory) influence sensory abnormalities and pain present in this disease. This characterization is of paramount importance in order to propose a pragmatic approach to treat pain in PD, which would take into account the effects of motor status and the characterization of the main pain syndromes related to PD. For example, pain syndromes that are directly related to the motor status such as dystonic pain should be managed by interventions aimed at motor control (Cury et al., 2014; Kassubek et al., 2014), such as adjustments in DA medication or DBS. On the other hand, symptoms not directly related to motor status (e.g.: central pain, peripheral neuropathic pain) are managed by different interventions such as the use of drugs acting pain and central sensitization pathways (Djaldetti et al., 2007).

2. Pain syndromes in PD

A survey evaluating the patient's perception of their most troublesome symptoms found that pain ranked high in all stages of the disease. In early-stage PD, pain was rated as the most bothersome NMS (Chaudhuri et al., 2010). Pain in PD tends to affect the side of the body that was initially or more severely affected by the motor symptoms (Perrotta et al., 2011). Pain and its relationship with the beginning of PD, as well as the presence of other pain aetiologies, were classified according to Nègre-Pagès et al. (2008) into 'PD-pain' (pain that was caused or aggravated by PD) and 'non-PD-pain' (pain related to a cause other than PD and not aggravated by PD). PD-pain should be suspected when pain is worse on the body side most affected by PD, when there is a temporal relationship between the progressive course of PD and pain aggravation and when DA drugs relieve it. In some instances, pain starts a few years before motor symptoms, frequently on the side more affected by bradykinesia, being commonly located on the shoulder or lower back (Lozano et al., 2002). Examples of PD-pain include 'wearing-off' (progressive loss of levodopa effect duration seen with disease progression, usually present in early morning or in nocturnal periods) and pain associated with motor fluctuations (e.g.: early morning dystonia, peak-dose dyskinesia). Finally, pain intensity may also fluctuate during the day, but with no correlation with the motor status, such as in the case of neuropathic (central or peripheral), visceral and muscular pain syndromes, as well as in other pain syndromes such

as restless legs syndrome (Tinazzi et al., 2006). These oscillations may be related to the fluctuations of dopamine availability in non-motor circuits and can be relieved by levodopa administration even in the absence of significant motor improvement (Tinazzi et al., 2006; Lim et al., 2008). In fact, it has been shown that patients may present non-motor 'off's', in which NMS such as anxiety and depression peak in the absence of worsening motor status (Storch et al., 2013).

Parkinson disease-pain is classically classified into the following five categories: musculoskeletal, radicular/neuropathic, dystonia-related, akathitic discomfort/pain and central pain (Ford, 1998). The most common pain syndromes are musculoskeletal and dystonic (Ford, 2009). Central pain is often described as a diffuse burning sensation and is not related to a lesion in the peripheral nervous system. This rather unusual type of pain involves different parts of the body (e.g. facial, abdominal or genital pain) and is frequently associated with autonomic symptoms, such as visceral sensations and dysphoria (Ford, 1998). While this is a clinical description that occurs in some PD cases, the current definition is not specific. Moreover, the term 'central' is unfortunate because it alludes to central neuropathic pain, which is a different clinical entity and has a different definition (Jensen et al., 2011). It is likely that most, if not all, pain syndromes directly related to PD have central mechanisms, but they do not necessarily fulfil the current criteria for central neuropathic pain (Treede et al., 2008). We prefer to use in the text the term 'central parkinsonian pain' rather than 'central pain' to avoid such confusion and misinterpretation.

3. The role of the basal ganglia in pain modulation

Two main DA pathways are well recognized. The nigrostriatal DA pathway projects from the substantia nigra to dorsal striatal structures, including the *globus pallidus*, putamen and caudate nucleus. This pathway, which is pathologically affected in patients with PD, has a well-established function in sensorimotor integration and control (Berger et al., 1991). The mesocorticolimbic DA pathway is comprised of neurons that project from the ventral tegmental area of the midbrain to subcortical structures, such as the nucleus accumbens, the thalamus and the amygdala (Le Moal and Simon, 1991; Sánchez-González et al., 2005). Distinct projections from the ventral tegmental area also innervate cortical regions, including the motor areas, prefrontal cortex and the anterior cingulated cortex (Simon et al., 1979; Schultz, 1998). As a consequence, there is a substantial overlap between the DA system and brain regions implicated in pain processing and perturbations in DA tonus in these areas could lead to motor and sensory abnormalities (Saadé et al., 1996, 1997; Chudler, 1998; Porro et al., 1999; Tashev et al., 2001; Braz et al., 2005). The DA system and the descending modulatory pathways are shown in Fig. 1. This information has clinical implications and illustrates why dopamine supplementation in PD may act specifically on the sensory system, regardless of its effects on motor pathways. The administration of levodopa ameliorates motor symptoms and changes sensory thresholds, but these effects are weekly correlated, as will be shown below.

The functional organization of basal ganglia (BG) is characterized by several interconnected anatomical structures and multiple parallel networks (Draganski et al., 2008). Multisensory afferents reach common areas in the BG (Chudler et al., 1995; Márkus et al., 2008) that serve as an important integrating point for the organization of behavioural responses to external and internal stimuli (Márkus et al., 2008). The BG receives input from cortical and sub-cortical brain regions that contribute to the BG-thalamic-cortical loops (Baev, 1995). Cortical regions involved in these feedback loops are also known to have important roles in pain processing and modulation. These areas include the frontal and parietal lobes, insular and hippocampal regions (Haber and Calzavara, 2009; Borsook et al., 2010). How this integration takes place is not well understood, but BG circuits are in a unique position to integrate cortical information to increase the speed and accuracy of data processing tasks (Leyden and Kleinig, 2008; Prodoehl et al., 2008; Borsook et al., 2010). Several lines of research proposed neuromodulatory interventions in these areas to relieve chronic pain or change pain thresholds in healthy volunteers and patients (Leone et al., 1991; Picarelli et al., 2010; Mylius et al., 2012).

While there is a considerable amount of evidence for a role of spinal dopamine in antinociception (Jensen and Smith, 1982; Jensen and Yaksh, 1984; Fleetwood-Walker et al., 1988; Liu et al., 1992), many studies have demonstrated that supraspinal dopamine networks are crucial for pain control (Ben-Sreti et al., 1983; Altier and Stewart, 1998; Magnusson and Fisher, 2000; Hagelberg et al., 2002; Pertovaara et al., 2004; Martikainen et al., 2005; Scott et al., 2006, 2007) (Fig. 1). A series of preclinical

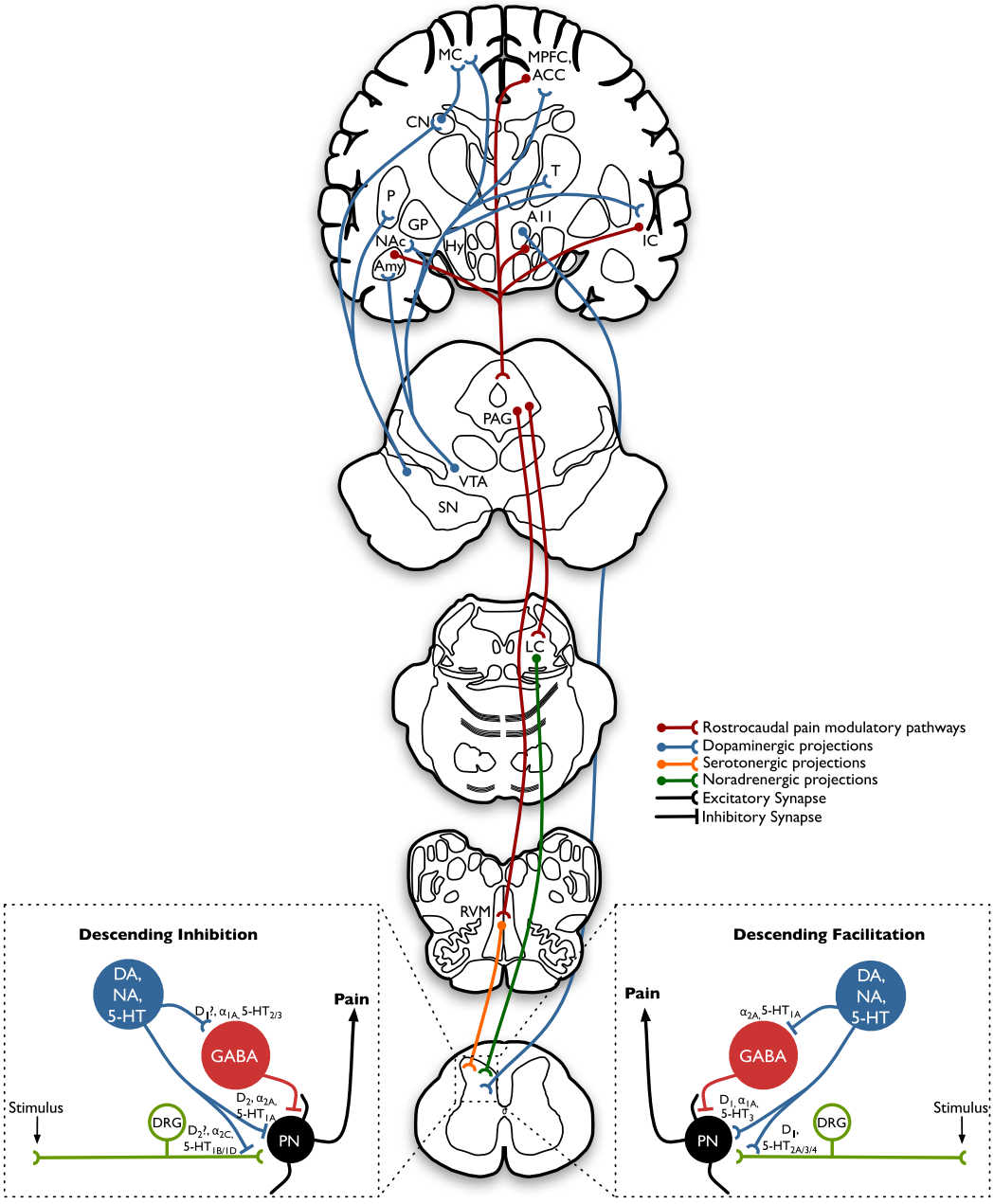

Figure 1 Basal ganglia basic circuitry, pain descending modulatory system and neurotransmitter projections to cortical, subcortical and spinal cord structures. Dopaminergic pathways (blue), including nigrostriatal DA system projects from the substantia nigra pars compacta to dorsal striatal structures, globus pallidus, putamen and caudate nucleus; and the mesocorticolimbic DA pathway, which is comprised of neurons that project from the ventral tegmental area of the midbrain to subcortical structures, such as the nucleus accumbens, thalamus, amygdala and cortical structures, such as the motor, prefrontal and the anterior cingulated cortices. The hypothalamic A11 nucleus provides dopamine-mediated inhibitory projections to nociceptive transmission in the spinal cord. Rostrocaudal pain-modulatory pathways (red, green and orange) include cortical and subcortical projections to the brainstem (red) (PAG, locus coeruleus and rostral ventromedial medulla), noradrenergic (green) and serotoninergic (orange) projections to the spinal cord. There is a substantial overlap between dopaminergic brain regions and those that are most commonly implicated in pain processing. Abbreviations: mc, motor cortex; mpfc, medial prefrontal cortex; acc, anterior cingulated cortex; t, thalamus; gp, globus pallidus; sn, substantia nigra; amy, amygdala; vta, ventral tegmental area; hy, hypothalamic nuclei; cn, caudate nucleus; p, putamen; ic, insula cortex; nac, nucleus accumbens; A11, hypothalamic nuclei; pag, periaqueductal grey; lc, locus coeruleus; rvm, rostral ventromedial medulla; DA, dopamine, NA, noradrenaline, 5-HT, serotonin, DRG, dorsal root ganglia, PN, projection neuron.

studies showed that dopamine produces pain-relieving effects under tonic stimuli, suggesting that these supraspinal mediated antihyperalgesic effects depend on the brain reward system. Using the formalin test, it was shown that dopamine agonists, as well as local infusions of morphine and DiMe-C7 (substance P analogue) in the dopamine-rich ventral tegmental area, all produce antihyperalgesic effects (Altier and Stewart, 1998). Microinjections of dopamine agonists in the rostral agranular insular cortex and the anterior cingulate cortex also triggered antihyperalgesic effects in a neuropathic pain model (López-Avila et al., 2004; Coffeen et al., 2008). Exogenous opioids (Di Chiara and Imperato, 1988; Spanagel et al., 1992) and opioid agonists (Spanagel et al., 1992) promote dopamine release within 10–30 min of their administration in rats, with peak effects observed after approximately 60 min. This time course suggests that the dopamine and opioid systems may work together in pain processing, with the opioid system responding rapidly to noxious stimuli and subsequently promoting dopamine release as part of the action of the descending pain-modulatory system. Taken together, these pharmacological trials provide indirect evidence for interactions between dopamine and nociceptive systems.

Positron emission tomography (PET) studies in healthy subjects (Hagelberg et al., 2002; Pertovaara et al., 2004; Martikainen et al., 2005; Scott et al., 2006, 2007) suggested an increase in the release of the dopamine after thermal and chemical induced painful stimulation. The studies with PET published so far demonstrate that increased dopamine activity is associated with less subjective pain (and conversely, that reduced dopamine activity is linked to greater subjective pain). These results are consistent with the hypothesis of supraspinal antinociceptive effects of dopamine. Interestingly, Becker et al. showed that effects on the motivation to endure or to avoid nociceptive stimulation would be more consistent with dopamine's well-established role in the motivation to obtain reward. Thus, dopamine might either inhibit or facilitate the perception of nociceptive stimuli to bias an organism towards endurance or avoidance depending on the relative importance of the nociceptive input. This is an important point to be considered and raises the issue of the actual role of dopamine in painful perception. While the involvement of dopamine in modulation of pain experiences seems indisputable, its involvement in nociception (the transmission of nociceptive input from the periphery to the brain, and the initial steps of cortical processing) is subject to active debate (Becker et al., 2013).

4. Central and peripheral processing of pain in PD

It has originally been postulated that pain in PD would be 'musculogenic' mainly related to prolonged contractions sustained by abnormally rigid muscles and/or postural abnormalities found in PD (Snider et al., 1976; Goetz et al., 1986). However, this model is simplistic and fails to account for the occurrence of all of the different pain syndromes seen in PD. First, there are patients with severe rigidity who do not have pain. Goetz and colleagues (Goetz et al., 1986) found that the severity of PD symptoms did not differ between those with and without pain. Second, pain can begin before motor symptoms in a significant proportion of patients (Lozano et al., 2002). Third, it has been reported that long-term improvement in rigidity following unilateral pallidotomy did not change painful symptoms present bilaterally before surgery despite motor improvement (Honey et al., 1999). Thus, pain in PD cannot be fully explained by the intensity of motor symptoms such as rigidity, tremor and dystonia (Chudler and Dong, 1995; Ford, 2010). Quantitative measurements of pain sensation and neuroimaging studies have reported reduced pain thresholds and abnormal cortical activation in PD (Djaldetti et al., 2004; Gerdelat-Mas et al., 2007; Mylius et al., 2009). When compared with healthy subjects, the nociceptive flexion reflex, electrical pain threshold, cold pain threshold (CPT) and heat pain threshold (HPT) were lower in PD patients (Spanagel et al., 1992; Chudler, 1998; Mylius et al., 2009), suggesting disruptive central functioning of pain integration pathways in PD. Dopamine and DBS change pain perception by increasing pain detection thresholds, and dopamine withdrawal results in widespread activation of the sensory cortex in response to painful stimuli and in alterations in the processing of sensory inputs in PD (Battista and Wolff, 1973; Gerdelat-Mas et al., 2007). An original model has been recently proposed to explain primary central parkinsonian pain in PD (Juri et al., 2010). It proposes that dopamine depletion leads to an intrastriatal amplification of sensory inputs from cortico-striatal projections. Consistent with this model, the amplitude of the laser-evoked potentials (LEPs) were greater in PD patients with primary central parkinsonian pain than in PD patients without pain or in controls (Schestatsky et al., 2007). This difference was observed during the off condition, while the LEP amplitude returned to normal values during the 'on' period. The abnormalities were more marked in the

most affected side. Possible explanations for LEP amplitude increase are sensitization of primary afferent pathways, a defect in descending nociceptive inhibitory control or higher attention towards the stimulated limb (Garcia-Larrea et al., 2002). The decrement of LEP amplitude caused by levodopa intake in PD patients with pain is not a definitive proof for the involvement of dopamine in pain perception, as suggested by previous studies (Chudler and Dong, 1995; Scott et al., 2007), because similar effects have been described for analgesic drugs, or even placebo (Wager et al., 2006).

'Neural noise' has been put forward to explain the sensory deficits in PD. Receptive fields of tactile and proprioceptive inputs to BG are relatively small. However, DA denervation of the striatum is accompanied by expansion of sensory receptive fields, to the extent that they can be activated from both sides of the body. It has been speculated that this process may introduce 'noise' into sensory perception, resulting in increased thresholds and reduced discriminative capacities for different sensory modalities (Conte et al., 2013). This might be the reason why functional imaging studies found reduced activation of the sensorimotor cortex during perceptual discrimination tasks in PD patients (Cao et al., 2011). Increased noise would reduce the overall increase in activation that would be expected when sensory information reaches BG of PD patients. It has been hypothesized that levodopa treatment and DBS would reduce 'noise' in this system, leading to better discrimination of signals (thresholds). Also, PD is marked by excessive synchronous activity in the beta (8–35 Hz) band throughout the cortico-BG network. Put in a simple way, beta-range cortical oscillations would 'contaminate' the BG oscillatory activity and prevent its desynchronization, which is necessary for voluntary movement to occur. The current view that beta hypersynchrony is a pathophysiological marker of PD motor signs is supported by correlations between improved mobility and attenuated beta hypersynchrony after therapeutic doses of medication (dopamine) or DBS (Kühn et al., 2004, 2006; Ray et al., 2008). STN-DBS is also related to spatially specific suppression of beta synchrony in the motor cortex (Whitmer et al., 2012). It is still not fully known how these effects could explain the sensory changes in PD patients, but it is believed that the dopamine administration and DBS would override the altered (hypersynchronic) electrical activity of the STN and allow information to flow due to a decrease in intrastriatal 'noise'.

Besides abnormalities in pain processing at the central level, it is also possible that pain in PD depends on peripheral nervous system injury such as nociceptor neurodegeneration (Reichling and Levine, 2011). Histological evaluation of skin biopsies in patients with PD has revealed a significant reduction in epidermal nerve fibres and Meissner corpuscles (Nolano et al., 2008) and in unmyelinated nerve fibre density (Kanda et al., 1996). Nolano et al. (2008) suggested, after analysing skin biopsies in patients with PD and observing reduced free and encapsulated nerve endings, that peripheral deafferentation in PD could at least partly account for the impairment in sensory function. Although PD is associated with degeneration of some peripheral cutaneous receptors, and can affect DA projections to the cortex, the fact that many sensory changes occur early in the course of the disease, when the extent of pathology is limited, supports a primary role for the BG in mediating these changes.

5. Effects of dopamine replacement on sensory thresholds and pain in PD

A series of studies using quantitative sensory testing (QST) evaluated the changes in sensory thresholds in PD patients under levodopa therapy or DBS (on-medication and on-stimulation, respectively) and after several hours of treatment withdrawal (off-medication).

It has been reported that PD with pain would present lower HPT compared to pain-free patients (Djaldetti et al., 2004). The administration of levodopa significantly raised pain threshold in PD patients but has no effects on healthy subjects (Brefel-Courbon et al., 2005). CPT were significantly lower in PD patients in the off-medication condition compared with healthy controls. The administration of levodopa significantly increased CPT (Brefel-Courbon et al., 2005), mechanical pain and tolerance thresholds (Marques et al., 2013) as well HPT and heat pain tolerance in PD (Slaoui et al., 2007). The RIII threshold was significantly lower in PD patients than in healthy subjects in the off-medication condition (Gerdelat-Mas et al., 2007), which was significantly increased after administration of levodopa. Studies on the effects of dopamine replacement therapy on sensory symptoms in PD patients and their main results are listed in Table 1. Care must be taken when interpreting QST results in PD patients. There is an overall problem in the literature when differentiating a genuine change in sensory/pain thresholds from a global change in the cognitive ability (and

Table 1 Effects of dopamine therapy on sensory thresholds in Parkinson disease.

	N	Study design	Sensory assessment	Main findings
Djaldetti et al. (2004)	36	Group 1: 36 PD patients without fluctuations Group 2: 15 PD patients with fluctuations Control group: 28 healthy subjects Evaluation: Off-medication condition. Group 2: On/off-medication conditions	Tactile thresholds with von Frey filaments WS; HPT	Tactile and WS thresholds did not differ between patients groups and control subjects. HPT was lower in patients with PD who experienced pain compared with those who did not.
Brefel-Courbon et al. (2005)	09	Group: 09 PD patients without pain Control group: 09 healthy subjects Evaluation: On/off-medication conditions	Thermal stimulation on cold water PET-scan	In off condition, pain threshold in nine PD patients was significantly lower than in nine controls. Administration of levodopa significantly raised pain threshold in PD patients but not in controls. During off condition, there was a significant increase in pain-induced activation in right insula and prefrontal and left anterior cingulate cortices in PD compared to control group. Levodopa significantly reduced pain-induced activation in these areas in PD.
Slaoui et al. (2007)	20	Group: 20 PD patients Control group: None Evaluation: On/off-medication conditions	Heat pain tolerance threshold HPT; CPT	Levodopa increased HPT and CPT and heat pain tolerance threshold in PD patients.
Gerdelat-Mas et al. (2007)	13	Group: 13 PD patients without pain Control group: 10 healthy subjects Evaluation: On/off-medication conditions	Nociceptive flexion reflex (RIII)	RIII threshold was significantly lower in PD patients than in healthy subjects in the off condition. Levodopa significantly increased the RIII threshold of PD patients.
Lim et al. (2008)	50	Group 1: 12 PD patients without fluctuation or dyskinesia Group 2: 15 PD patients with fluctuation Group 3: 23 PD patients with dyskinesia Control group: 20 healthy subjects	CPT and cold pain tolerance threshold	CPT and tolerance were higher in control group. After levodopa administration, dyskinetic patients exhibited a large increase in CPT and tolerance that was absent in Group 1. There was no significant difference in pain sensitivity change scores between the fluctuation patients and the group 1 or 3, suggesting that dyskinesia and pain may share common pathophysiological mechanisms in PD.
Nolano et al. (2008)	18	Group: 18 PD patients without pain Control group: 30 healthy subjects Evaluation: On-medication condition	Tactile threshold Mechanical pain perception WDT; CDT; HPT; CPT	PD patients showed a significant increase in tactile and thermal thresholds and a significant reduction in mechanical pain perception.
Dellapina et al. (2011)	25	Group 1: 13 PD patients without pain Group 2: 12 PD patients with pain. Control group: None Evaluation: On-medication condition (after apomorphine) Placebo controlled	Nociceptive flexion reflex (RIII) HPT PET-scan	Apomorphine did not significantly modify pain thresholds compared with placebo as well as it did not influence pain cerebral activation pattern.
Nandhagopal et al. (2010)		Group: 12 PD patients without pain Control group: 13 healthy subjects Evaluation: On/Off-medication conditions	VAS; HPT	There was no difference in VAS and HPT between PD patients (on- vs off-conditions) and control group.

WS, warm sensation; WDT, warm detection threshold; CDT, cold detection threshold; HPT, heat pain threshold; CPT, cold pain threshold; VAS, Visual analogue scale.

motivational drive) during the tests that analyse such symptoms. The patients tend to be more attentive and compliant when their clinical status is improved (on-medication and on-stimulation). Moreover, the motor symptoms such as rigidity, akinesia and tremor induce continuous sensory input, which may render difficult for the patient to concentrate on superimposed sensory stimuli such as a thermal probe or a mechanical liminal stimulus. In addition, the use of the method of limits to determine thermal thresholds is influenced by the patient's reaction time. PD patients have asymmetric bradykinesia, which can influence the results in an unpredictable manner. This approach has been used in some reports (Gierthmühlen et al., 2010; Marques et al., 2013). One technical solution is to use the forced choice method, in which different temperatures are presented to the patients, who are required to say whether they perceived it. This method is not influenced by the motor status and may provide more coherent results (Ciampi de Andrade et al., 2012).

The role of pain modulation by dopamine is also supported by data from functional imaging studies. In the off condition, there was a significant increase in pain-induced activation in the right insula and prefrontal and left anterior cingulate cortices in neuroimaging studies in PD patients compared to the control group. Levodopa significantly reduced pain-induced activation in these areas in PD (Brefel-Courbon et al., 2005).

Laser-evoked potentials recordings revealed significantly reduced N_2P_2 amplitudes bilaterally in treated patients with hemiparkinsonism compared with controls (Tinazzi et al., 2008). Acute levodopa administration to pain-free PD patients did not change the N_2P_2 amplitudes. However, PD Patients with central pain parkinsonism showed higher LEP amplitudes when compared to pain-free patients and healthy controls, suggesting that the presence of pain may disturb the central pain processing mechanisms and its relationship with autonomic responses (Schestatsky et al., 2007).

Very few studies assessed the effects of DA drugs other than levodopa on sensory thresholds. Apomorphine did not significantly modify subjective and objective pain thresholds in PD patients compared with placebo (Dellapina et al., 2011). Moreover, subjective and objective pain thresholds were not significantly different after treatment with apomorphine and placebo, thereby raising the possibility that monoamine systems other than DA systems are involved in pain modulation. Interestingly, acute pain evoked in rats by thermal stimulation and tonic pain evoked by formalin injection were decreased by intraventricular or striatal microinjection of the DA agonist apomorphine, whereas microinjection of the DA antagonist haloperidol lead to an increase in nociceptive responses (Magnusson and Fisher, 2000). The same pattern of attenuated nociceptive response is produced with striatal microinjection of the D2-like DA receptor agonist quinpirole, and exacerbated nociception with the antagonist eticlopride, but not with D1-like DA-receptor-selective agonists or antagonists (Lin et al., 1981; Magnusson and Fisher, 2000). These observations suggest that stimulation of D2-like DA receptors in the striatum inhibits nociception behaviours in response to acute and tonic pain.

Studies on the effects of DA medication on proprioception have yielded controversial results. Some investigators found that increased detection thresholds for arm position sense, arm motion sense or weight perception were not improved by levodopa (Jobst et al., 1997; Maschke et al., 2003), while others showed that DA therapy improved haptic and kinaesthetic function in patients with mild to moderate PD (Li et al., 2010). Additional studies showed that the worsening of proprioception and sensory aspects of postural instability in patients PD was more evident in patients in the DA treatment 'on' state than in the 'off' state (Mongeon et al., 2009).

Taken together, these studies suggest that PD patients have abnormal sensory detection and pain thresholds, and these sensory changes are modulated after the administration of dopamine irrespective of motor improvement. Whether the dopamine has a real antinociceptive effect or only a pain modulation effect remains uncertain. The dopamine influences in proprioception is still unknown.

6. Effects of DBS on sensory thresholds and pain syndromes in PD patients

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective treatment for the motor symptoms of PD (Lin et al., 1981; Krack et al., 2003). Its effects on NMS have become more widely acknowledged in recent years. It has been shown that STN-DBS could produce significant pain relief in more than 80% of PD patients, particularly during off periods (Tolosa et al., 2007; Kim et al., 2008). However, a direct correlation between pain improvement and motor control after DBS has not been reported (Wolz et al., 2012; Marques et al., 2013). On the other hand, surgery (DBS) has a clear effect in sensory thresholds.

Several studies have evaluated the effect of STN-DBS on sensory perception in PD patients using QST. DBS significantly increased subjective HPT and reduced pain-induced cerebral activity in the somatosensory cortex in PD patients with pain, while it had no effect in pain-free patients (Dellapina et al., 2012). It has been shown that STN-DBS modulates preferentially small fibre-dependent sensory thresholds and has no effect on vibration detection threshold (Ciampi de Andrade et al., 2012) while may significantly increase mechanical pain and tolerance thresholds (Marques et al., 2013). Table 2 summarizes the main studies regarding DBS and pain.

There is evidence suggesting that DBS may provide different analgesic effects depending on the type of PD-pain syndromes. Kim et al. (2008) showed that dystonic pain was the most responsive (100%) to STN-DBS, followed by central (54%), musculoskeletal (27%) and neuropathic radicular pain (17%). Longitudinal studies on the long-term effects of DBS on pain in PD patients are scarce. One study showed that no new pain developed in 14 PD patients who were followed up for 12 months after DBS (Loher et al., 2002). Another group showed new pain in 5 PD patients during a 6-month follow-up of 16 PD patients after surgery (Oshima et al., 2012). The pain occurring de novo was mainly musculoskeletal in nature.

STN-DBS is thought to modulate BG circuitry and cortical regions related to sensory integration. This could explain the high rate of improvement of central parkinsonian pain in PD patients (Trost et al., 2006; Kim et al., 2008). PET study showed that STN-DBS significantly reduced pain-induced activation in the right somatosensory cortex in PD patients with central parkinsonian pain. Conversely, in pain-free PD patients, STN-DBS did not induce any significant modification (Dellapina et al., 2012). STN-DBS could restore defective functioning of the BG motor circuitry by inhibiting pathological excitatory glutamatergic outputs of the STN (Benazzouz and Hallett, 2000). Neuropeptides are also involved in the modulation of DA nigrostriatal input. Substance P is present in the direct striato-pallidal pathway, while enkephalin acts in the indirect striato-pallidal pathway (Loher et al., 2002; Dellapina et al., 2012; Kim et al., 2012). An imbalance in substance P and enkephalin input in patients with pain could in part explain the different sensory modulation of the BG under DBS in pain and pain-free PD patients. Although, the target of STN-DBS is downstream, the enkephalin-GABAergic projections and axon collaterals of the excitatory STN-Globus pallidus internal connection could feed back to the globus pallidus external, which is itself under GABAergic/enkephalergic inhibitory control. It is unknown whether such collaterals could have any influence on the enkephalin containing striatopallidal nerve endings. The physiological mechanisms by which STN-DBS improves thermal thresholds in PD remain unclear; however, several hypotheses have been put forward. STN stimulation may indirectly lead to the activation of the somatosensory cortex and thereby improve sensory discrimination. A study with FDG-PET was conducted to determine the impact of STN-DBS on the regional cerebral metabolic rate of glucose in eight patients with advanced PD before surgery as well as in the DBS on- and off-conditions. In the on-condition, clusters of significantly increased regional cerebral metabolic rate of glucose were found in lower thalamic nuclei reaching down to the midbrain area and remote from the stimulation site in the right frontal cortex, temporal cortex and parietal cortex (Hilker et al., 2004). This finding is compatible with other studies showing similar parietal changes with STN stimulation (Altier and Stewart, 1999; Le Jeune et al., 2010). Thus, STN-DBS may influence not only the frontal but also the parietal cortex, and a contribution of STN to sensory function, as well as to its roles in associative, limbic and BG circuits, has been confirmed (Hilker et al., 2004). This metabolic change may result in an altered temperature sensation that is associated with parietal and BG circuits.

In addition to its effects in the sensitive-discriminative aspects of pain, DBS could have a positive effect on the affective-motivational dimension of chronic pain. Through the limbic component of the STN, DBS could influence the activity of the nucleus accumbens, which is involved in the modulation of emotional and motivational-affective behaviour, and which takes part in robust pain-modulatory systems. Thus, STN-DBS could modify pain perception in PD by enhancing tolerance of the patients through modifying the emotional aspects of pain (Le Jeune et al., 2010).

The effects of stimulation to other targets such as the globus pallidus and thalamus on sensory symptoms have been much less frequently investigated. Unilateral DBS has been reported to improve contralateral off-period dystonia (100% reduction), pain (74%), cramps (88%) and dysesthesias (100%) 1 year after surgery (Loher et al., 2002). There was also a less pronounced amelioration of ipsilateral off-period dystonia and sensory symptoms. With bilateral pallidal DBS, scores for dystonia were improved by 86%, for pain by 90%, for

Table 2 Effects of deep brain stimulation on pain in Parkinson disease.

	N	Assesment time points	Control group	Sensory assessment	Correlation with motor symptoms	Correlation with other non-motor symptoms	Main findings
Zibetti et al. (2007)	36	Baseline, 12, 24 months	No	Sensory item of UPDRS	No	No	Pain improved after 12 and 24 months
Witjas et al. (2007)	40	Baseline, 12 months	No	Sensory symptoms of NMS scale	No	No	Pain improved after 12 months
Kim et al. (2008)	29	Baseline, 3 months	No	VAS	No	No	Pain improved after 3 months
Gierthmühlen et al. (2010)	17	6 months, NP	No	MDT; VDT; CDT; CPT; WDT; HPT; MPT	No	No	Thermal detection threshold improved on on-stim condition. No difference in pain thresholds in both conditions (on-stim vs. off-stim conditions)
Ciampi de Andrade et al. (2012)	30	12 months, NP	Yes	VDT; MDT; MPT; WDT; CDT; HPT; CPT	Yes	No	Thermal detection threshold improved, mechanical and thermal pain thresholds increased in on-stim condition
Oshima et al. (2012)	69	Baseline, 2, 6, 12 months	Yes	VAS	No	No	Pain improved after 2, 6 and 12 months
Kim et al. (2012)	21	Baseline, 3, 24 months	No	VAS	No	No	Pain improved after 3 and 24 months
Maruo et al. (2011)	17	NR, NP	Yes	WDT; CDT; HPT; CPT	No	No	There was no difference in thermal detection threshold between on-stim and control group, but it was lower in on-stim compared with off-stim. There were no differences in pain thresholds.
Spielberger et al. (2011)	15	36 months, NP	No	WDT; CDT; HPT; CPT	Yes	No	There were no changes in thresholds between on-stim and off-stim conditions.
Wolz et al. (2012)	34	13 months, NP	No	Sensory symptoms of NMS scale	Yes	No	There were no changes in pain between on-stim and off-stim conditions. Improvement on pain intensity has not been correlated with motor improvement after surgery
Sürücü et al. (2013)	14	Ranged from 3 to 41 months, NP	No	VAS	No	No	Eight patients who had improvement of pain with levodopa challenge before surgery showed even greater improvement after DBS, showing that stimulation has an effect on pain addition of dopa.
Dellapina et al. (2012)	16	12 months, NP	Yes, pain-free PD patients	HPT Pet-Scan	No	No	DBS significantly increased HPT and reduced pain-induced cerebral activity in the somatosensory cortex in patients with pain, whereas it had no effect in pain-free patients

Table 2 (*Continued*)

	N	Assesment time points	Control group	Sensory assessment	Correlation with motor symptoms	Correlation with other non-motor symptoms	Main findings
Marques et al. (2013)	19	36 months (mean), NP	No	HPT; HPTo; MPT; MPTo	Yes	No	MPT/MPTo increased after DBS and levodopa administration compared with off state. There were no differences in HPT or HPTo. Improvement on pain intensity has not been correlated with motor improvement after surgery
Pellaprat et al. (2014)	58	Baseline, 12 months	No	MPQ; item 17 UPDRS part II	Yes	Yes - Depressive symptoms	DBS decreased the prevalence of pain from 89.7% to 81% and the McGill score was decreased in patients who remained with pain. This improvement was not correlated with motor improvement, depression scores or levodopa reduction.
Cury et al. (2014)	41	Baseline, 12 months	No	MPQ; BPI; VAS; NPSI; PCS	Yes	Yes – NMSS	DBS decreased pain after surgery, but the motor and nonmotor symptom improvements after DBS did not correlate with pain relief. The improvement in quality of life was correlated with pain relief.

UPDRS-III, Unified Parkinson's Disease Rating Score; WS, warm sensation; VDT, vibration detection threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPTo, mechanical pain tolerance; WDT, warm detection threshold; CDT, cold detection threshold; HPT, heat pain threshold; HPTo, heat pain tolerance; CPT, cold pain threshold; VAS, visual analogue scale; NMS, Non-motor symptoms; MQP, McGill Pain Questionnaire; BPI, Brief Pain Inventory; NPSI, Neuropathic Pain Symptom Inventory; PCS, Pain Catastrophizing Scale; NMSS, Non-Motor Symptoms Scale; NR, not reported; NP, not prospective.

cramps by 90% and for dysesthesia by 88%. Ablative procedures are still frequently used surgical procedures used in PD to control motor symptoms. Laitinen and colleagues reported that 63% of their patients had some degree of 'dystonia/pain' before pallidotomy and only 32% had some pain after surgery (Laitinen et al., 1992). Also, 'pain and discomfort scores' were improved in 10 of 12 patients at 6 months after pallidotomy (Baron et al., 1996). A prospective analysis of the long-term effect of ablative surgery in 21 PD patients who had PD-related pain showed a significant reduction in overall pain scores at 6 weeks and 1 year following the procedure (Honey et al., 1999).

7. Conclusions and future directions

Pain is a common NMS in patients with PD and is associated with poor quality of life.

Several lines of evidence indicate that patients with PD exhibit deficits in perception of tactile, painful and thermal inputs. The sensory abnormalities may be seen early in the course of disease and were, therefore, originally thought to result from DA deficit in the BG. Sensory disturbances present in PD are modulated by motor treatment, but these effects do not directly correlate with motor improvement itself, probably reflecting a direct effect of levodopa/DBS in somatosensory loops (Chudler and Dong, 1995; Spielberger et al., 2011) and/or a better performance secondary to an improvement in cognitive drive and motivation during 'on' state (Becker et al., 2013). In this line, DBS has a strong modulator effect on sensory thresholds and pain relief in PD, which is a major determinant of improvement in quality of life after the procedure (Cury et al., 2014). However, since pain relief did not correlate with motor improvement after DBS, it suggests that not all PD-related pain syndromes are due to motor slowness and increase in tonus, being probably related to effects of motor treatment interventions on non-motor pathways. Therefore, it is crucial to well characterize the pain syndromes that respond to motor treatment adjustment and which do not, in order to

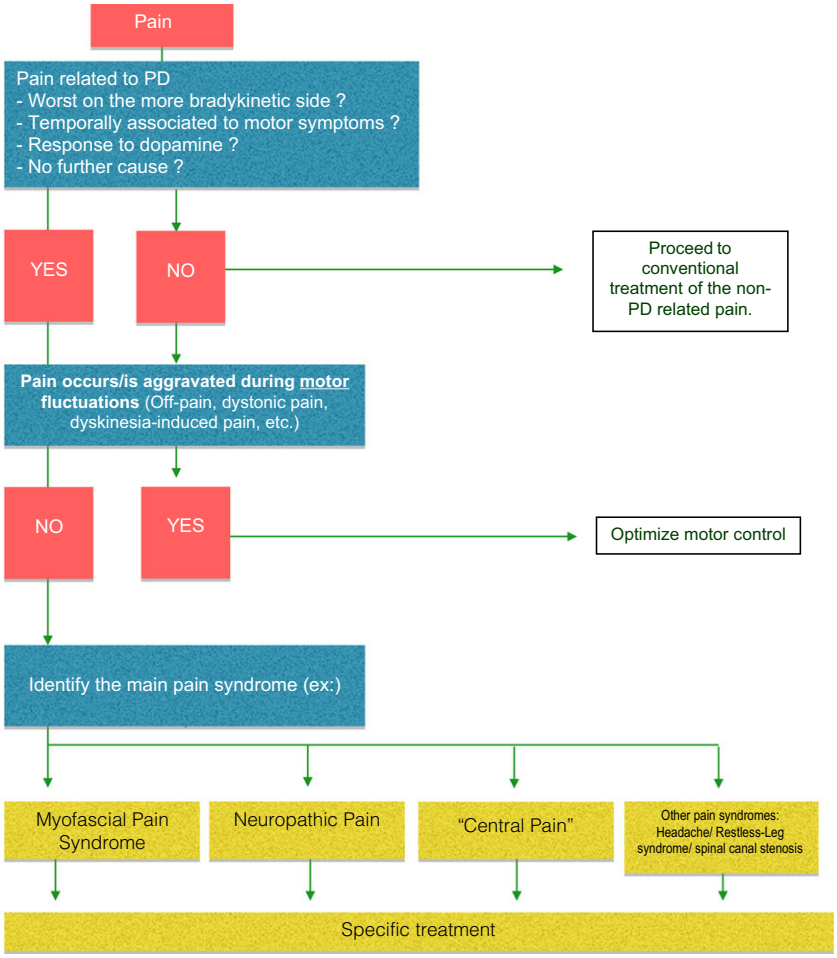

Figure 2 Proposal for clinical approach to patients with Parkinson disease and pain.

propose a pragmatic and linear management of these patients (Fig. 2).

Finally, different pain syndromes are associated with PD and their pathophysiology remains only partially known. Specific questionnaires designed for pain assessment in PD could help distinguish between its different pain syndromes and thus be employed to screen for pain in PD, guide its assessment and monitor its mechanism-based treatment.

Acknowledgments

We thank Ryan Patel for technical assistance in designing Fig. 1.

Author contributions

R.G., M.G.S.G., S.P.L., E.T.F., E.R.B. and M.J.T.: Organization of the research project, review and critique of manuscript. R.G.C. and D.C.A.: Conception, design and execution of the project.

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