Neurophysiologic study of central pain in patients with Parkinson disease

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ABSTRACT

Background: Patients with Parkinson disease (PD) may present with various types of pain. In some instances, no cause can be identified and pain is considered a primary disorder (primary central pain [PCP]). We hypothesized that PCP in patients with PD (PD-PCP) may be due to a dysfunction of pain pathways or the processing of pain inputs in the CNS.

Methods: We carried out a psychophysical and neurophysiologic study in 9 patients with PD-PCP, 9 patients with PD without pain (PD-NoP), and 9 healthy control subjects. We assessed the clinical characteristics of pain, performed quantitative sensory testing with thermal probes, and recorded laser-evoked potentials (LEPs) and laser-induced sudomotor skin responses (l-SSRs) in "off" and "on" conditions.

Results: In "off" condition, patients with PD-PCP had lower heat pain and laser pinprick thresholds, higher LEP amplitudes, and less habituation of the l-SSR in comparison with PD-NoP patients and control subjects. Abnormalities were more marked in the most affected side. In "on" condition, psychophysical and neurophysiologic differences disappeared or were significantly attenuated.

Conclusion: Conduction along peripheral and central pain pathways is normal in patients with Parkinson disease with or without primary central pain. However, apart from signs of hyperalgesia, our patients exhibited lack of habituation of sympathetic sudomotor responses to repetitive pain stimuli, suggesting an abnormal control of the effects of pain inputs on autonomic centers. Abnormalities were attenuated by L-dopa, suggesting that the dysfunction may occur in dopamine-dependent centers regulating both autonomic function and inhibitory modulation of pain inputs. ***Neurology*® 2007;69:2162–2169**

GLOSSARY

ADL = activities of daily living; **ANS** = autonomic nervous system; **HI** = habituation index; **l-SSRs** = laser-induced sudomotor skin responses; **LAS** = less affected side; **LEPs** = laser-evoked potentials; **MAS** = more affected side; **PAG** = periaqueductal gray matter; **PCP** = primary central pain; **PD** = Parkinson disease; **PD-NoP** = PD without pain; **UPDRS** = Unified Parkinson's Disease Rating Scale; **VAS** = visual analogue scale.

Pain is a well recognized nonmotor manifestation of Parkinson disease (PD) that affects between 40% and 75% of patients during their illness.[1-4] Apart from secondary causes of pain, such as dystonic spasms, musculoskeletal disorders, radiculo-neuritic syndromes, and akathisic discomfort, patients with PD may present with primary central pain (PCP), which is presumed to be a direct consequence of the disease itself.[5] Patients with PD with PCP (PD-PCP) usually describe bizarre and unexplained painful sensations predominating in the more affected side and in "off" condition.[1,3,6]

Central pain is most commonly associated with a lesion or dysfunction in the tracts carrying pain inputs[7] that could be seen in a variety of clinical conditions.[8-12] PCP in patients with PD has been attributed to a dysfunction of basal ganglia-thalamo-cortical circuits,[6,13] sensory circuits of the basal ganglia,[3,5] or diencephalospinal pathways.[14] With

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the introduction of laser stimuli in neurophysiology, it is now possible to assess the functional integrity of pain pathways and their cortical projections.[15-18] Laser stimuli selectively activate pain receptors in the skin, and generate an afferent volley in poorly myelinated Aδ and unmyelinated C fibers that, upon arrival to the CNS, can be recorded as the laser-evoked potentials (LEPs). Usually, LEPs are of reduced amplitude in central neuropathic pain conditions.[9,19,20] Laser stimuli can also activate structures involved in pain processing at a subcortical level[21] and cause reflex autonomic responses such as the sudomotor skin response (SSR).[18,22,23] The laser-induced SSR (l-SSR) results from a synchronized change in sympathetic outflow to sweat glands and, therefore, it may provide information on involuntary physiologic reactions to pain stimuli, such as arousal or alarm. Therefore, we considered that the analysis of l-SSRs to repeated application of laser pinprick stimuli would give a measure of the habituation of autonomic responding to nociceptive inputs.

We hypothesized that patients with PD-PCP have a disordered integration of nociceptive inputs in brainstem centers, thalamic relay nuclei, or cortical structures and that such dysfunction may be demonstrated by analyzing LEPs and l-SSRs. We also determined how the neurophysiologic responses to pain inputs correlated with motor impairment and medication state.

METHODS

The study was performed in patients fulfilling the current diagnostic criteria for PD[24] with predominantly unilateral signs of the disease, younger than 65 years, and with a Hoehn and Yahr stage of 2.5 or lower in "off" condition. Consecutive ambulatory patients attending our clinic were initially presented with the questionnaire Unified Parkinson's Disease Rating Scale (UPDRS), Part II, section 17, regarding painful sensory symptoms. We made a pre-selection of patients according to whether their answer was 0 (patients with no pain complaints) or different from 0 (patients with pain complaints). In patients with pain complaints we further assessed the characteristics of their pain, aiming to select those with clinical characteristics of PCP according to established criteria.[3,4] Therefore, we excluded patients whose pain could be attributable to dystonia, akathisic discomfort, musculoskeletal or radiculo-neuritic causes when these causes were well documented in the patient's files. Selected patients were further questioned on how intense their pain was in the last 60 days (pain-PAST), and how much the pain interfered with their routine activities of daily living (pain-ADL). This was done by using a visual analogue scale (VAS) for pain (www.britishpainsociety.org). We also studied healthy subjects recruited among the spouses of the patients and among colleagues to match for age and sex with those of the patients.

We excluded from the study subjects who fulfilled the following exclusion criteria: presence of symptoms suggesting depression, assessed by UPDRS questionnaire Part I, section 3, and history information; use of antidepressants, analgesics, or other drugs which could potentially affect the autonomic nervous system (ANS, i.e., beta blockers, tricyclic antidepressants, anticholinergics); presence of any known disease potentially involving the ANS (i.e., diabetes mellitus, cerebrovascular diseases); presence of chronic headache or other facial pain; and Mini-Mental State Examination score lower than 24/30.

Patients and controls underwent a conventional electrophysiologic testing of nerve conduction, performed according to standard methods,[25] and those who had abnormal electrophysiologic signs of peripheral neuropathy were excluded. Selected patients and controls were informed about the nature of the study, which was approved by the Ethical Committee of the Hospital Clinic of Barcelona in accordance with the Helsinki Declaration. Those who agreed to participate in the study were requested to sign an informed consent.

Quantitative sensory testing for warm, heat pain, and laser pinprick sensations. Thermoalgesic stimuli were applied with a Peltier type contact thermode from a Thermotest (Somedic, Sweden), with a stimulating area of 12.5 cm^2, at a ramp rate of 1°C/sec. We determined warm and heat pain thresholds using the method of limits.[26] Thresholds were defined as the mean value of five stimuli separated by interstimuli intervals of at least 60 s. Laser stimuli were applied to the dorsum of the hand using a CO_2 laser stimulator (AGM, Barcelona). This apparatus fires a laser beam of a power ranging from 0 to 15 W, a duration variable between 1 msec and 100 msec, and an area of 6.5 mm^2. Laser pinprick threshold was determined by the method of levels.[26] Stimulus intensity was calculated according to the individual's threshold, measured in mJ/mm^2 using the following formula: power × duration/area. The stimulus intensity used in the study was 1.5 times above the threshold calculated in the less affected side.

Responses induced by laser stimuli. We recorded simultaneously LEPs and l-SSRs using two independent electromyographs (a Mystro5Plus; Oxford Instruments, UK, and a Neuropack-8; Nihon-Khoden, Tokyo), triggered simultaneously from a personal computer. LEPs were recorded through pairs of 9 mm Ag/AgCl surface disc electrodes filled with conductive adhesive gel. The active electrode was placed on Cz and the reference to linked earlobes. The analysis time was 1 s. The amplifier bandpass frequency filter was 0.1 Hz to 100 Hz. In order to detect ocular artifacts due to involuntary blinks, an electrooculogram was also recorded in parallel with the LEPs acquisition. L-SSRs were recorded through surface electrodes, the active electrode attached to the palm and the reference electrode to the dorsum of the hand[27] in the side ipsilateral to the stimulus. For each subject and side, we applied a series of

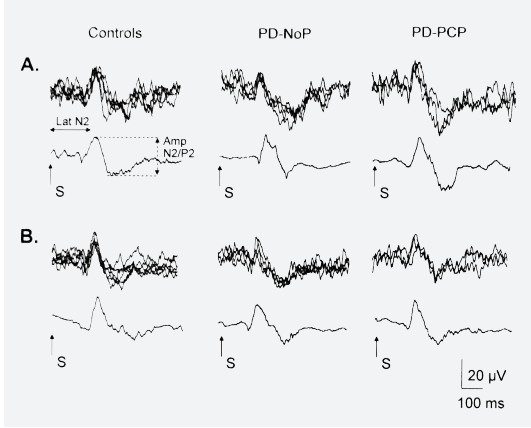
10 laser stimuli, with an interstimulus time interval of 30 s.

Experimental procedure. All tests were carried out in the morning after a 14-hour discontinuation of all antiparkinsonian medications ("off" condition). We first did a clinical assessment, including UPDRS, Hoehn and Yahr scores, and a VAS determination of the intensity of ongoing pain at the moment of evaluation (pain-NOW). Psychophysical and neurophysiologic testing was carried out by an independent examiner, unaware of the results of clinical evaluation, in a warm and dimly lit room, isolated from external acoustic stimuli. Patients were then given their usual first morning equivalent dose of L-dopa (including dopaminergic agonists), plus 100 mg, and were allowed to rest for a period of at least 40 minutes. Clinical assessment, psychophysical and neurophysiologic tests were repeated when patient and physician agreed on the patient's clinical improvement, or the patient's "best on" ("on" condition). Control subjects were given 100 mg of L-dopa and tests were repeated 40 minutes later. The side to be first examined was chosen at random in both "off" and "on" conditions.

Data reduction and statistical analysis. We calculated the mean and the SD of all variables for all patients and control subjects. Data from the UPDRS part III evaluation regarding limbs motor function were used to determine the patient's more affected side (MAS) and less affected side (LAS). In patients, data were separated into MAS and LAS for "off" and "on" conditions. In control subjects, because differences between sides were not expected on SSRs[27] nor in LEPs,[28] data from both sides were pooled together. For QST, we determined the mean threshold values for warm, heat pain, and laser pinprick in each subject and calculated the grand mean and the SD for each group. Responses induced by laser stimuli were analyzed in individual recordings. For the LEPs (figure 1, upper left graph), we averaged 10 individual traces for each side to measure the mean latency of relevant peaks (N2 and P2), as the time difference between the stimulus and each of the peaks, and the mean amplitude between them (N2/P2 amplitude). For the l-SSR (figure 2, upper left graph), we measured the amplitude of the first response in each series. Also, we averaged 10 individual traces for each side to measure the mean onset latency and the mean amplitude. In order to assess the habituation of autonomic responses to pain stimuli, we defined the habituation index of l-SSR (l-SSR-HI). This was calculated as the number of recordings out of the 10 stimuli in which the amplitude of the SSR was lower than 50% of the amplitude of the response to the first stimulus in the same series. Therefore, reduced habituation was expressed by low HI values.

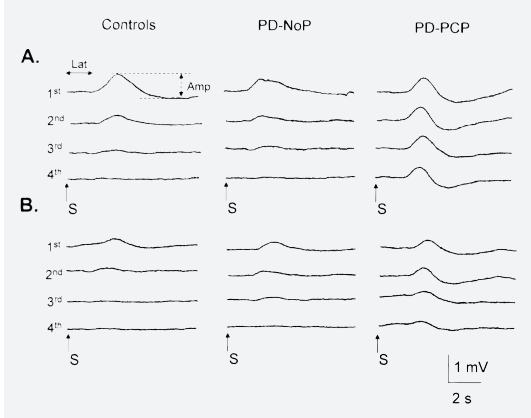
We focused our statistical analyses on three types of comparisons: among groups of subjects, between MAS and LAS, and before and after L-dopa intake. We used one-factor repeated measures analysis of variance (ANOVA) for group comparisons. A post hoc analysis using the Bonferroni test was carried out on variables where significant differences were found. Paired Student t test was used for the analysis of possible differences between sides of patients and effects of medication in both patients and controls. Categorical variables were analyzed using a χ^2 test. Correlation analyses were done using the Pearson test for comparison of amplitude of LEP and l-SSR with clinical characteristics, such as age, pain-PAST, pain-ADL, pain-NOW, UPDRS scores, and duration of disease. A value of $p < 0.05$ was considered to define statistical significance.

Figure 1 Laser-evoked potentials (LEPs) for a representative control subject, a patient with Parkinson disease (PD) without pain (PD-NoP), and a patient with PD with primary central pain (PD-PCP), before (A) and after L-dopa (B)



The upper graph of each pair shows the superimposition of consecutive responses and the lower graph shows their averaging. As shown schematically in the upper left graph, latencies of N2 and P2 were measured from the stimulus (S) to the peak of the response (marked only for N2). Amplitude was measured between N2 and P2 peaks. Note the enhanced N2/P2 amplitude in the PD-PCP group, and its decrement after L-dopa intake.

Figure 2 Four consecutive laser-induced sudomotor skin responses (l-SSRs) recorded from control subjects, patients with Parkinson disease (PD) without pain (PD-NoP), and patients with PD with primary central pain (PD-PCP), before (A) and after L-dopa (B), marked as ordinal numbers in the left of each line



As shown schematically in the upper left graph, latency of the response was measured from the stimulus (S) to the onset of the negative deflection. Amplitude of the response was measured as the largest negative to positive peak difference. Note that the l-SSRs from the control subject and the patient with PD-NoP are reduced or even absent in the third to fourth stimulus. In contrast, no habituation was present in the patient with PD-PCP.

Table 1 Demographic and clinical data from healthy control subjects (n = 9), patients with Parkinson disease without pain (PD-NoP; n = 9), and patients with primary central pain (PD-PCP; n = 9)

Characteristics	Controls	PD-NoP	PD-PCP*
Age, y	58.9 ± 5.4	59.0 ± 8.6	61.2 ± 6.6
Men/women	5/4	5/4	6/3
Weight	70.1 ± 2.3	69.1 ± 2.6	68.2 ± 9.6
Height	1.68 ± 2.4	1.70 ± 1.1	1.72.0 ± 1.0
L-dopa dose, mg	100.0†	302.0 ± 78.5	306.0 ± 63.9
Disease duration, y	—	5.4 ± 3.6	6.0 ± 4.1
H & Y = 0	9 (100%)	—	—
H & Y = 1	—	2 (22.2%)	3 (33.3%)
H & Y = 2	—	4 (44.4%)	4 (44.4%)
H & Y = 2.5	—	3 (33.3%)	2 (22.2%)
H & Y = 3 to 5	—	—	—
UPDRS, LAS	—	1.2 ± 1.8	3.6 ± 4.6
UPDRS, MAS	—	8.0 ± 2.7	10.8 ± 4.2
UPDRS, total	—	17.1 ± 3.7	19.1 ± 2.3

*No significant differences were noted between patients with PD-NoP and PD-PCP (all comparisons were made using one factor analysis of variance, with exception of sex and H & Y scores, in which a χ^2 test was used).
†L-dopa given 40 min before tests.
H & Y = Hoehn and Yahr score; UPDRS = Unified Parkinson's Disease Rating Scale; LAS = less affected side; MAS = more affected side.

RESULTS Initially a total of 24 patients with PD were selected for the study. However, six patients had to be excluded during the first session: one because of concomitance of pain and dystonia in "off" condition that was not evident in the selection phase, one because additional anticholinergic medication had been added since the time of the selection, and four because of recording artifacts that precluded analysis of LEPs, l-SSRs, or both. Finally, 18 patients were evaluated, 9 in the PD-PCP group and 9 in the PD-NoP group. Nine healthy control subjects were also selected. There were no differences between patients of both groups and controls with regard to sex (χ^2; $p > 0.05$), age, weight, and height (ANOVA; $p > 0.05$ for all comparisons). Hoehn and Yahr and UPDRS were not different between PD-NoP and PD-PCP patients (Bonferroni post-test; $p = 0.2$). There was no correlation between pain-PAST or pain-ADL and data on demographic and clinical characteristics of our patients ($r < 0.1$; $p > 0.05$ for all correlations). Table 1 displays data on demographic and clinical characteristics of the patients.

In agreement with our selection criteria, neither control subjects nor patients with PD-NoP made any mark other than 0 on pain-PAST or pain-ADL. PD-PCP patients marked pain-PAST at a mean of 5.3 (SD = 1.9; range 4.0 to 8.0) and pain-ADL at 5.0 (SD = 0.8; range 4.0 to 6.0). Pain-NOW in "off" (mean of 5.1 and SD of 1.3) was not different from pain-PAST (*t* test; $p = 0.1$). The most frequent descriptors used by PD-PCP patients to refer to their symptoms were burning, itching, and tearing sensations. None of them reported pain before the diagnosis of the disease. The pain was usually spontaneous, with periods of exacerbation, poorly localized and usually more intense in MAS than in LAS. It involved the whole hemibody in six patients and only the arm in three.

Warm, heat pain, and laser pinprick thresholds. Thresholds for warm sensation were similar between control subjects and patients [$F(2,24) = 0.03$; $p = 0.9$] or between MAS and LAS within the same group of patients (*t* test; $p > 0.05$ for patients of two groups). Heat pain and laser pinprick thresholds were different between groups [$F(2,24) = 32.02$; $p = 0.02$ for heat pain and $F(2,24) = 12.8$; $p = 0.01$ for laser pinprick]. Post hoc analysis showed that differences were due to lower thresholds for both types of stimulus in PD-PCP patients than in PD-NoP patients and control subjects, with no significant differences between PD-NoP patients and control subjects. Heat pain and laser pinprick thresholds were lower in MAS than in LAS in PD-PCP patients (*t* test; $p < 0.001$ for both), but not in PD-NoP patients (*t* test; $p > 0.05$ for both). Table 2 shows data regarding QST, LEP, and l-SSR in all groups.

Responses to laser stimuli. Regarding LEPs, no differences between groups were found for latencies of N2 [$F(2,24) = 0.13$; $p = 0.9$] or P2 [$F(2,24) = 0.23$; $p = 0.8$]. However, differences were found for N2/P2 amplitude [$F(2,24) = 14.5$; $p = 0.001$]. PD-PCP patients showed higher LEP amplitudes than PD-NoP patients or control subjects (Bonferroni post-test; $p < 0.01$ for both comparisons), with no differences found between MAS and LAS in any group of patients (*t* test; $p > 0.05$ for both groups). Figure 1 shows representative traces of LEPs for each group of subjects in "off" and "on" conditions.

Regarding l-SSRs, no differences between groups were found for mean latency [$F(2,24) = 0.77$; $p = 0.4$] or amplitude of the first l-SSR [$F(2,24) = 0.63$; $p = 0.5$]. However, differences were found for l-SSR-HI [$F(2,24) = 58.8$; $p < 0.001$] and mean l-SSR amplitude [$F(2,24) = 19.2$; $p < 0.001$]. Post hoc analyses revealed that differences were due to a lower l-SSR-HI and a higher mean l-SSR amplitude in PD-PCP patients than in PD-NoP patients and control subjects (Bonferroni

Table 2 Neurophysiologic data from healthy control subjects (n = 9), patients with Parkinson disease without pain (PD-NoP; n = 9), and patients with primary central pain (PD-PCP; n = 9) in "off" condition for more affected side

Tests	Variables	Controls	PD-NoP	PD-PCP	p*
QST	Warm (°C)	35.5 ± 0.6	35.3 ± 1.0	35.9 ± 1.8	NS
	Heat pain (°C)	44.9 ± 1.0	43.7 ± 1.7	41.7 ± 0.5	0.02
	Laser pinprick	12.3 ± 0.9	13.1 ± 0.5	9.02 ± 1.0	0.01
LEP	N2 (ms)	210 ± 17	202 ± 41	208 ± 40	NS
	P2 (ms)	315 ± 25	310 ± 15	338 ± 41	NS
	N2/P2 amplitude (μV)	41.8 ± 4.9	40.6 ± 6.4	48.5 ± 5.7	0.01
l-SSR	Mean latency (ms)	1.8 ± 0.4	1.8 ± 0.6	1.9 ± 0.2	NS
	Mean amplitude (μV)	0.9 ± 0.4	0.8 ± 0.2	1.6 ± 0.2	<0.001
	Amplitude 1st (μV)	3.0 ± 1.1	2.7 ± 0.6	2.9 ± 0.5	NS
	Habituation index	7.5 ± 1.2	7.1 ± 0.6	3.1 ± 0.9	<0.001

*One factor analysis of variance.
QST = quantitative sensory testing; LEP = laser-evoked potential; l-SSR = laser-induced sudomotor skin responses; NS = not significant.

post-test; $p < 0.001$ for both). No significant differences were found in any l-SSR variables between PD-NoP patients and controls. There was no correlation between mean l-SSR amplitude and pain scores ($r < 0.1$; $p > 0.05$ for both pain scores). Figure 2 shows representative recordings of l-SSR obtained from the first four consecutive laser stimuli in all groups before and after the administration of L-dopa. Regarding inter-side differences, in PD-PCP patients, the l-SSR-HI was lower and the mean amplitude of l-SSR was higher in MAS than in LAS (*t* test; $p < 0.05$ for both).

Effects of medication. After L-dopa intake ("on" condition) PD-PCP patients reported lower pain-NOW scores (mean of 3.6; SD of 1.1) than in "off" condition (paired *t* test; $p < 0.05$) and had a higher l-SSR-HI and lower l-SSR mean amplitude than in "off" condition (*t* test; $p < 0.05$ for both). However, the values were still significantly different from those found in PD-NoP patients and control subjects (Bonferroni post-test; $p < 0.01$ for both). Regarding the other variables measured with QST and neurophysiologic tests, differences among groups were no longer present after L-dopa intake.

DISCUSSION The first relevant finding of our study is that conduction of volleys generated by pain stimuli is preserved in PD-PCP patients, which implies normal function in peripheral nerve small fibers and tracts mediating nociceptive inputs between the receptor and the brain. Nevertheless, several other results suggest that our patients had abnormalities in the integration of pain inputs in CNS circuits: 1) Patients with PD-PCP had higher LEP amplitudes and lower thermal and laser pinprick thresholds than PD-NoP patients and control subjects, suggesting enhanced responsiveness to pain stimuli. 2) The LEP and QST abnormalities predominated in the side more affected by the motor signs of the disease, and were more marked in "off" than "on" condition, suggesting a relationship between hyperalgesia and dopaminergic activity. 3) Habituation of l-SSR to successive stimuli was reduced in PD-PCP patients in comparison to PD-NoP patients and control subjects, suggesting an abnormal effect of pain inputs on autonomic centers. Patients of the two groups did not differ on age, duration of disease, and UPDRS scores, which indicates the absence of clinical clues for PCP. We did not find a significant correlation between pain and demographic data. This is in contrast to a previous report,[4] in which a significant correlation was found between pain and disease duration and UPDRS scores. However, only 1% of the patients from this study[4] had clinical characteristics compatible with PCP. Our patients reported that the ongoing pain was more frequent and more intense in the side of predominant motor impairment. This is in accordance with a previous study,[6] although the opposite association (i.e., pain predominating contralateral to the body side with motor signs) has also been described.[1,2] We did not find interside asymmetries with regard to thermal thresholds in PD-NoP patients, probably because our patients had a better general condition than those reported in previous studies.[6,13]

LEPs obtained in patients with central neuro-

pathic pain are usually of lower amplitude, even in the case of hyperalgesia.[19,20] In contrast, although the symptoms of our patients were compatible with central neuropathic pain,[29,30] the LEPs were not reduced but enhanced. Possible explanations for LEP amplitude enhancement are sensitization of primary afferent pathways, a defect in descending nociceptive inhibitory control, or higher attention toward the stimulated limb.[16,20] All of them could contribute to central pain in patients with PD in the context of enhanced LEPs, although higher attention toward the stimulated limb usually leads to asymmetric LEPS, which seems not to be the case of our patients.[20] The decrement of LEP amplitude caused by L-dopa intake in our PD-PCP patients is not a definitive proof for the involvement of dopamine in pain perception, as suggested by previous studies,[5,31] because similar effects have been described for analgesic drugs,[32,33] or even placebo.[34] However, our patients showed higher pain thresholds and lower subjective perception of ongoing pain in "on" condition. This is in accordance with previous reports addressing L-dopa effects on thermal thresholds[13,35] and suggests an influence of dopamine on pain perception. Indeed, analgesic properties of dopamine have been described in painful conditions, such as diabetic neuropathy,[36] postherpetic neuralgia,[37] and metastatic bone pain.[38] Nevertheless, L-dopa is known not to fully alleviate pain in PD,[1,39] an observation supported by our own findings. This suggests that neurotransmitters other than dopamine, such as noradrenaline, serotonin, acetylcholine, and peptidergic neurons, may participate in the processing of pain in PD.[40]

The hyperalgesia to pain stimuli found in our PD-PCP patients is in line with the results obtained from previous QST studies done in patients with PD using various stimulus modalities.[6,13,35,41] This finding is in contrast with the observation of elevated warm and heat pain thresholds observed in stroke[8,9] or patients with MS [11] with central pain, where a structural damage of spino-thalamo-cortical tract may lead to both elevated thresholds and chronic deafferentation pain.[30] Our patients had no lesions in pain pathways, which could explain the absence of high thermal thresholds. Such clinical discrepancy in pain thresholds in different central pain conditions illustrates the complexity of neuropathic pain symptomatology, where one mechanism may be responsible for many different symptoms and the same symptom may be caused by different mechanisms.[42]

The activation of the sympathetic fibers by pain inputs is a physiologic reaction of autonomic centers.[21-23] This response was normal in our patients (normal mean latency and normal amplitude of the first l-SSR potential), indicating the integrity of the somato-sympathetic circuit in patients with mild PD. In contrast, the l-SSR-HI was significantly lower in PD-PCP patients than in other groups and such reduction was more prominent in MAS and in "off" condition. It might be argued that reduced habituation could be simply a consequence of ongoing hyperalgesia. However, the subjective perception of pain was not correlated with l-SSR amplitudes. Thus, our findings suggest that PD-PCP patients have an autonomic hyper-reactivity to pain inputs generated in MAS. Such dysfunction seems not to be strictly related to dopamine deficiency, since neither the l-SSR-HI nor the mean amplitude of l-SSRs normalized after L-dopa intake.

There is growing evidence favoring a relationship between ANS and pain.[21,43,44] A support for such connection is the existence of several autonomic nuclei at brainstem level that generate stimulus-specific patterns of autonomic responses and control of nociceptive inputs.[44-46] The activation of these nuclei by noxious stimuli probably contributes to activation of analgesic descending pathways, as a rapid response to pain.[47] It is known that the neural degeneration in PD follows an ascending course starting from lower medulla to the cortex level,[48] and could affect several nuclei responsible for autonomic control and pain modulation at the brainstem. A dysfunction in the region of periaqueductal gray matter (PAG) would provide an explanation for the relationship between pain and autonomic function in our patients because of the anatomic proximity of PAG to the substantia nigra, and the dopaminergic activity in some of its neurons.[49] The possibility exists that PD-PCP patients have a regional vulnerability for degeneration of mesencephalic neurons involving the PAG.[50] In fact, there is now evidence that polymorphisms in the gene for catechol-*O*-methyltransferase (COMT), an enzyme that delays the breakdown of dopamine, can predispose patients to increased pain sensitivity.[51]

Our study has some limitations. First, major depression may alter the expression of pain[52] and electrodermal activity.[53] We did not specifically assess symptoms of depression. However, our patients were not in psychiatric treatment or using psychotropic drugs. Although this does not exclude the possibility of the existence of a subclinical mood disorder, we believe that major

depression was not likely to play a significant role in pain evaluation and l-SSRs of our patients. Second, the L-dopa effects on thermal thresholds and LEP amplitudes were not placebo-controlled and, therefore, our results cannot be conclusive. Despite these limitations, though, we can conclude that PD-PCP patients show clinical and neurophysiologic signs of hyperalgesia, affecting predominantly MAS, that respond partially to dopamine. Pain in these patients does not seem to be related to a lesion in the pain pathways, but to central sensitization or defective inhibitory control over afferent inputs. The decreased habituation of the l-SSR to repeated stimuli indicates reduced CNS control over pain inputs, which could also be related to dysfunction of neuronal centers responsible for both autonomic function and inhibitory modulation of pain inputs.

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REFERENCES

1. Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. Neurology 1976;26:423–429.
2. Koller WC. Sensory symptoms in Parkinson's disease. Neurology 1984;34:957–959.
3. Ford B. Pain in Parkinson's disease. Clin Neurosci 1998;5:63–72.
4. Tinazzi M, Del Vesco C, Fincati E, et al. Pain and motor complications in Parkinson's disease. J Neurol Neurosurg Psychiatry 2006;77:822–825.
5. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain 1995;60:3–38.
6. Djaldetti R, Shifrin A, Rogowski Z, Sprecher E, Melamed E, Yarnitsky D. Quantitative measurement of pain sensation in patients with Parkinson disease. Neurology 2004;62:2171–2175.
7. Merskey H, Bogduk N, eds. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Seattle : IASP Press; 1994:209–212.
8. Bogousslavsky J, Regli F, Uske A. Thalamic infarcts: clinical syndromes, etiology, and prognosis. Neurology 1988;38:837–848.
9. Rousseaux M, Cassim F, Bayle B, Laureau E. Analysis of the perception of and reactivity to pain and heat in patients with Wallenberg syndrome and severe spinothalamic tract dysfunction. Stroke 1999;10:2223–2229.
10. Defrin R, Ohry A, Blumen N, Urca G. Characterization of chronic pain and somatosensory function in spinal cord injury subjects. Pain 2001;89:253–263.
11. Svendsen KB, Jensen TS, Hansen HJ, Bach FW. Sensory function and quality of life in patients with multiple sclerosis and pain. Pain 2005;114:473–481.
12. Ducreux D, Attal N, Parker F, Bouhassira D. Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia. Brain 2006;129:963–976.
13. Brefel-Courbon C, Payoux P, Thalamas C, et al. Effect of L-dopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. Mov Disord 2005;20:1557–1563.
14. Lindvall O, Bjorklund A, Skagerberg G. Dopamine-containing neurons in the spinal cord: anatomy and some functional aspects. Ann Neurol 1983;14:255–260.
15. Bromm B, Treede RD. Human cerebral potentials evoked by CO2 laser stimuli causing pain. Exp Brain Res 1987;67:153–162.
16. Treede RD, Lorenz J, Baumgartner U. Clinical usefulness of laser-evoked potentials. Neurophysiol Clin 2003;33:303–314.
17. Cruccu G, Anand P, Attal N, et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004;11:153–162.
18. Veciana M, Valls-Solé J, Schestatsky P, Montero J, Casado V. Abnormal sudomotor skin responses to temperature and pain stimuli in syringomyelia. J Neurol 2007;254:638-645.
19. Casey KL, Beydoun A, Boivie J, et al. Laser-evoked cerebral potentials and sensory function in patients with central pain. Pain 1996;64:485–491.
20. Garcia-Larrea L, Convers P, Magnin M, et al. Laser-evoked potential abnormalities in central pain patients: the influence of spontaneous and provoked pain. Brain 2002;125:2766–2781.
21. Bingel U, Quante M, Knab R, Bromm B, Weiller C, Buchel C. Subcortical structures involved in pain processing: evidence from single-trial fMRI. Pain 2002;99:313–321.
22. Cervera A, Veciana M, Valls-Solé J. Sympathetic sudomotor skin responses induced by laser stimuli in normal human subjects. Neurosci Lett 2002;334:115–118.
23. Rossi P, Truini A, Serrao M, et al. Sympathetic skin response evoked by laser skin stimulation. Funct Neurol 2002;17:129–132.
24. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184.
25. Johnsen B, Fuglsang-Frederiksen A. Electrodiagnosis of polyneuropathy. Neurophysiol Clin 2000;30:339–351.
26. Chong PS, Cros DP. Technology literature review: quantitative sensory testing. Muscle Nerve 2004;29:734–747.
27. Claus D, Schondorf R. Sympathetic skin response. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 1999;52:277–282.
28. Truini A, Galeotti F, Romaniello A, Virtuoso M, Iannetti GD, Cruccu G. Laser-evoked potentials: normative values. Clin Neurophysiol 2005;116:821–826.
29. Boivie J. Central pain and the role of quantitative sensory testing (QST) in research and diagnosis. Eur J Pain 2003;7:339–343.
30. Boivie J, Leijon G, Johansson I. Central post-stroke pain: a study of the mechanisms through analyses of the sensory abnormalities. Pain 1989;37:173–185.
31. Scott DJ, Heitzeg MM, Koeppe RA, Stohler CS, Zubieta JK. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J Neurosci 2006;26:10789–10795.
32. de Tommaso M, Losito L, Libro G, et al. Effects of symptomatic treatments on cutaneous hyperalgesia

and laser evoked potentials during migraine attack. Cephalalgia 2005;25:359–368.
33. Cruccu G, Leandri M, Iannetti GD, et al. Small-fiber dysfunction in trigeminal neuralgia: carbamazepine effect on laser-evoked potentials. Neurology 2001;56:1722–1726.
34. Wager TD, Matre D, Casey KL. Placebo effects in laser-evoked potentials. Brain Behav Immun 2006;20:219–230.
35. Slaoui T, Mas-Gerdelat A, Ory-Magne F, Rascol O, Brefel-Courbon C. Levodopa modifies pain thresholds in Parkinson's disease patients. Rev Neurol 2007;163:66–71.
36. Ertas M, Sagduyu A, Arac N, Uludag B, Ertekin C. Use of L-dopa to relieve pain from painful symmetrical diabetic polyneuropathy. Pain 1998;75:257–259.
37. Kernbaum S, Hauchecorne J. Administration of L-dopa for relief of herpes zoster pain. JAMA 1981;246:132–134.
38. Nixon DW. Use of L-dopa to relieve pain from bone metastases. N Engl J Med 1975;292:647.
39. Lee MA, Walker RW, Hildreth TJ, Prentice WM. A survey of pain in idiopathic Parkinson's disease. J Pain Symptom Manage 2006;32:462–469.
40. Buzas B, Max M. Pain in Parkinson's disease. Neurology 2004;62:2156–2157.
41. Urakami K, Takahashi K, Matsushima E, Sano K, Nishikawa S, Takao T. The threshold of pain and neurotransmitter's change on pain in Parkinson's disease. Jpn J Psychiatry Neurol 1990;44:589–593.
42. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–1964.
43. Petrovic P, Petersson KM, Hansson P, Ingvar M. Brainstem involvement in the initial response to pain. Neuroimage 2004;22:995–1000.
44. Benarroch EE. Pain-autonomic interactions. Neurol Sci 2006;27:S130–S133.
45. Rainville P, Bao QV, Chretien P. Pain-related emotions modulate experimental pain perception and autonomic responses. Pain 2005;118:306–318.
46. Zambreanu L, Wise RG, Brooks JC, Iannetti GD, Tracey I. A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. Pain 2005;114:397–407.
47. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 1997;14:2–31.
48. Braak H, Del Tredici K, Rüb U, de Vos RAI, Steur E, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
49. Flores JA, El Banousa F, Galán-Rodriguez B, Ferndandez-Espejo E. Opiate anti-nociception following lesion of large dopamine neurons of the periaqueductal grey: critical role for D1 (not D2) dopamine receptors. Pain 2004;110:205–204.
50. Lu L, Neff F, Fischer DA, et al. Regional vulnerability of mesencephalic dopaminergic neurons prone to degenerate in Parkinson's disease: a post-mortem study in human control subjects. Neurobiol Dis 2006;23:409–421.
51. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain 2006;125:216–224.
52. Klossika I, Flor H, Kamping S, et al. Emotional modulation of pain: a clinical perspective. Pain 2006;124:264–268.
53. Guinjoan SM, Bernabo JL, Cardinali DP. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J Neurol Neurosurg Psychiatry 1995;59:299–302.