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Nociceptive inputs transmission in Huntington's disease: a study by laser evoked potentials

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Abstract

The aim of the present study was to evaluate pain perception and evoked responses by laser stimuli (LEPs) in mild not demented Huntington's Disease (HD) patients. Twenty-eight HD patients and 30 control subjects were selected . LEPs were obtained by four scalp electrodes, (Fz, Cz, referred to the nasion; T3, T4, referred to Fz), stimulating the dorsum of both hands. All patients were also evaluated by somatosensory evoked potentials (SEPs) by median nerve stimulation. Only 3 patients referred pain of arthralgic type. Laser pain perception was similar between HD patients and controls. An abnormal N2,P2 and N1 latency increase was evident in the majority of HD patients. LEPs features were similar between patients taking and not taking neuroleptics. The N2 and P2 latencies, showed a negative correlation with functional score and Mini Mental State Examination, and a positive correlation with the severity of hyperkinetic movements. A delay in nociceptive input processing emerged in HD, concurring with the main features of the disease, in absence of clinical evidence of abnormalities in pain perception. The dysfunction of pain signals transmission in HD may induce sub-clinical changes of sensory functions, which may probably interfere with sensory-motor integration and contribute to functional impairment.

Key words: Huntington's chorea; pain perception; laser evoked potentials.

Introduction

Huntington's disease (HD) is characterized by a progressive neuronal loss in the striatum that results in the alteration of central neural processing of several cortical-subcortical loops, subtending cognitive, behavioral, sensitive and motor functions (1). A dysfunction of sensory processing is reported in HD (2), concurring with changes in somatosensory evoked responses (SEPs) and impaired sensorimotor integration (3-4). The reduced amplitude of cortical SEPs has been suggested to be a useful marker of disease progression (1). Few reports are available about nociceptive pathways function in HD, though a number of neurophysiological, neuroanatomical and neuroimaging studies have shown that basal ganglia are involved in the processing of nociceptive inputs (5). In fact, multiple parallel pathways connect the basal ganglia to a number of structures involved in nociception, such as the intralaminar nuclei of the thalamus, the sensory areas of the cortex, the amygdale and the cingulate cortex (5). The neuronal loss affecting the cerebral cortex (6), may also involve the cortical areas involved in nociceptive inputs processing.

In addition, a critical role of dopamine in pain modulation has also been demonstrated. Decreased levels of dopamine may contribute to the painful symptoms that frequently occur in Parkinson's disease (7). Pain is a well recognized non motor manifestation of Parkinson disease (PD) (8), while few reports are available about pain symptoms in HD patients. Albin and Young (9) described two Huntington's disease patients with severe pain, though affective changes exhibited by both of these patients raised the question if the sensory abnormalities might be related directly to the primary disease process or may be secondary to an affective disorder. In our clinical experience, pain symptoms are rarely reported by HD patients and even in later stages of the disease there are many patients with complications, without complaining any pain.

The nociceptive pathway is accessible by laser-evoked potentials (LEPs). The study of the scalp CO_2 laser evoked potentials (LEPs) allows a non-invasive exploration of the functional status of some cerebral structures responding to nociceptive inputs. In normal subjects, CO_2 laser stimulation delivered over the hairy skin gives rise to a N2/P2 potential at vertex, peaking at a latency of about 200 and 300 ms,

respectively, and generated by inputs conveyed by Aδ fibres (10). Although the precise origin of the N2/P2 complex is still uncertain, there is evidence suggesting that several brain structures devoted to nociceptive input processing, including cingulate cortex and insula, probably contribute to N2/P2 complex generation (11). The N2/P2 complex is preceded by an earlier, far smaller negative component (N1), which is lateralized, bilateral, and probably generated by the secondary somatosensory cortex (12). The most recent theories about LEPs suggest that they are produced by a cortical network, devoted to the detecting and orienting attention toward a salient sensory event (13, 14). The aim of the study was to provide further knowledge about sensory processing in HD, by the means of laser evoked potentials. Considering that dementia modifies pain perception (15), we choose to evaluate not demented HD patients.

Materials and methods

Subjects

This study enrolled 28 consecutive out-patients (Table 1), affected by genetically confirmed HD, attending the Ambulatory for Huntington's chorea of the Neurological Science Department of Bari University. They were recruited during their first visit. Patients taking neuroleptics continued the treatment, the other patients started the treatment after laser evoked potentials recording task. Forty age and sex matched control subjects, 23 females and 17 males, (age 40-72 mean age 54.8 ± 9.8) were also enrolled. All subjects and controls gave their informed consent prior to participation in the study. The study was approved by the local Ethics Committee of Bari Polyclinic General Hospital. The inclusion criteria in patients group were: genetically confirmed HD. Exclusion criteria were: cognitive impairment (Mini-Mental State Examination ≤ 24) 16; clinical evidence of peripheral neuropathy or of any disease potentially causing sensory impairment as diabetes mellitus, renal and hepatic failure, alcohol abuse, or any further central or peripheral nervous system disease.

Clinical examination and clinical evaluation of pain

All patients were submitted to the Mini-Mental State Examination (MMSE) (16) to evaluate cognitive impairment. In addition, patients underwent the motor section of Unified Huntington's Disease Rating Scales (UHDRS) (17) and the Total Functional Capacity Scale (18). The sensory functional status was assessed by clinical standardized evaluation to explore touch, pinprick, pressure cold, heat and vibration. Quantitative sensory testing was not performed, since it was much time consuming for our patients with limited compliance (19).

HD patients were divided in those complaining (HDCP) and not complaining of pain (HDNCP). In accordance with previous reports on PD (8) pain associated with visible dystonia was defined as dystonic pain, whereas non-dystonic pain was classified as cramping (aching pain in muscles), arthralgic (stiffness after rest and pain with motion, confined to joints), peripheral neuropathic (pain in the territory of a root or nerve), and central neuropathic pain (burning, tingling, formication, or bizarre quality). Headache and other facial pain were not analyzed (8). Quality, location and intensity of pain were assessed in all patients, using a Visual Analogic Scale from 0 (absence) to 10 (intolerable pain).

CO_2 laser stimulation and LEP recording

LEPs were recorded in the laboratory of neurophysiopathology of Pain Unit of our Department. Each subject was seated in a comfortable chair, positioned in a quiet room with an ambient temperature of 21-23°C, in an awake and relaxed state. Subjects and experimenters wore protective goggles during data acquisition. The pain stimulus was a laser pulse (wavelength 10.6 μm) generated by a CO_2 laser (Neurolas; Electronic Engineering, Florence, Italy; www.elengroup.com). The beam diameter was 2.5 mm and the stimulus duration was 25 ms. The location of the impact on the skin was slightly shifted between two successive stimuli, to avoid the sensitization of the nociceptors. The CO_2 laser stimuli were delivered at a fixed power of 7,5 Watt and 25 ms duration (19), which was perceived by all patients and controls as a painful pinprick. We took attention to settle the laser power and duration at a supra-threshold level in all cases (20), using a 10-point verbal analogue scale in which '0' corresponds to no sensation, '4' to the Pain Threshold and '10' to intolerable pain. In all patients and controls the 25 ms duration and 7,5 Watt intensity laser stimuli were judged as a painful pinprick, with a value ≥ 6 in more than 50% of 20 stimuli. We placed four electrodes at Cz, T3, T4 and Fz positions, with the reference electrode at the nasion; the T3 and T4 electrodes were referred off-line to Fz, in order to detect the N1 component (12). Another electrode was placed above the right eye to record the electro-oculogram. Signals were amplified, filtered (0.5-80 Hz) and stored on a biopotential analyzer (MICROMED System Plus, Italy). Four series of 30

laser pulses each were applied to the right and left hand in a random order, with an inter-series interval of at least 5 min. Patients and healthy controls were requested to pay attention to the stimuli. At the end of each stimulation series, all subjects were requested to rate the pain induced on average by the 30 laser stimuli, using a 0-100 visual analog pain scale (Laser-pain VAS), in which the white color corresponded to 0 (no pain) and intense red to 100 (the most severe pain imaginable). Patients and controls were requested to individuate the number which corresponded to the color expressing the intensity of the perceived laser pain.

LEP analysis

An investigator blind to the clinical condition analyzed the LEPs for 1 s, with a 100 ms pre-stimulus time, at a sampling rate of 512 Hz. All runs containing transient activities that exceeded 65 μV at each recording channel were excluded from the average by an automatic artifact rejection algorithm. In addition, further artifacts were visually inspected and an average of at least 15 artifact-free responses was obtained off-line. For each stimulation site, an average across the two series of stimuli was obtained for right and left hands. LEPs were identified based on their latency and distribution, and three responses were labelled according to Valeriani *et al*. (21). The N2a (namely N2) and P2 components were detected at the vertex (Cz), as a positive-negative complex in the time range 220-340, while the N1 component was checked at T3-Fz, for right-hand stimulation and T4-Fz, for left-hand stimulation, as a smaller negative wave in the latency range 150-180 msec (21, 22). Absolute latencies of the scalp potentials were measured at the highest peak of each response component, and the amplitude of each wave was measured from the baseline. We examined the amplitude of the N1 wave and N2/P2 complex. The mean values of laser-VAS and LEPs latencies and amplitudes were computed across the two sides for patients and normal subjects, in order to perform comparison between patients taking or not taking neuroleptics, and correlation between LEPs and clinical features. The asymmetry of LEPs amplitudes and latencies (23) was computed considering the absolute inter-side difference in patients and controls, in order to emphasize the presence of unilateral dysfunction of nociceptive inputs conduction.

Statistical analysis

After the Kolmogorov-Smirnov statistic, with a Lilliefors significance level, was applied for testing normal distribution of data, the Student's t test for unpaired data was used to compare LEPs features, laser-VAS values and asymmetry indexes between patients and controls and between patients referring and not referring pain, and taking or not taking neuroleptics. The Spearman test was employed to verify the correlations between LEPs and demographic and clinical features. All the analyses were performed using SPSS version 11.

Results

Clinical features in HD patients

Among the 28 patients, only three referred pain of arthralgic type (Table 1). The mean VAS values for spontaneous pain was 4.5 ± 1.2. No patient presented sensory deficits.

Laser pain and evoked responses

The laser VAS was similar between groups (Table 2). The N2, P2 and N1 waves latencies were significantly prolonged in patients compared with controls (Fig. 1, Table 2). The N1 and N2/P2 amplitudes were slightly, though not considerably, reduced in HD patients. In 22 patients, the LEPs latency exceed the normal limits for at least one wave (6 patients presented with a prolongation of N1, N2 and P2 latencies, 10 with a latency increase of N2 and P2 waves, in 6 patients the P2 latency was beyond normal limits). In 4 further patients the N2 and P2 latency increase concurred with a vertex complex amplitude reduction. All the LEPs latency inter-side asymmetries were slightly and not significantly increased in HD patients compared to controls, and also the N1 and N2/P2 amplitudes asymmetries were similar between the two groups.

Relationships between LEP features and clinical data

Patients taking neuroleptics did not show different LEP patterns, compared with drug-free patients (Fig. 2). No difference in laser pain VAS was detected between the two groups (patients taking neuroleptics: 44.23 ± 20.61; drug-free patients: 43.93 ± 19.9 Student's t test 0.24; p value n.s.). The comparison of LEP features between patients complaining and not complaining of pain, was not performed for the small number of HDCP patients. The N2 and P2 latencies, showed a negative correlation with the functional capacities, and a positive correlation with the severity of hyperkinetic movements (Table 3). In addition, a negative correlation was

Table 1

Clinical features of Huntington's disease patients The Total Motor Score of Unified Huntington's Disease Rating Scales (UHDRSM), and the Chorea, Total Functional Capacity Scale (TFC) and Mini Mental State Examination (MMSE) scores are reported. The neuroleptic treatments were: olanzapine (olan), clotiapine (clot), xaneazine (xenaz), prometazine (prom)

CASES	AGE	SEX	DURATION	CAG	UHDRSM	CHOREA	TFC	MMSE	TREATMENT	PAIN SYMPTOMS
1	45	F	5	45	53	12	6	24	–	ARTHRALGIC
2	51	F	3	44	24	15	13	25	–	ABSENT
3	68	F	5	41	25	7	5	25	OLAN	ABSENT
4	47	M	2	45	55	15	13	26	–	ABSENT
5	54	M	2	43	11	6	13	25	–	ABSENT
6	61	M	5	42	45	15	7	25	–	ABSENT
7	56	M	5	42	39	17	13	24	CLOT.	ABSENT
8	50	M	5	44	37	10	11	25	CLOT	ABSENT
9	55	M	1	42	32	17	6	25	PROM.	ARTHRALGIC
10	41	M	5	46	6	2	13	30	–	ABSENT
11	66	F	5	42	28	5	8	26	PERF.	ABSENT
12	55	F	3	41	20	8	13	30	–	ABSENT
13	54	M	1	43	15	12	12	28	–	ARTHRALGIC
14	40	M	2	46	11	1	6	24	–	ABSENT
15	62	F	4	42	47	13	7	30	XENAZ.	ABSENT
16	35	M	3	48	7	6	13	30	–	ABSENT
17	40	F	5	47	17	2	9	28	–	ABSENT
18	57	F	5	43	42	8	7	25	CLOT.	ABSENT
19	66	F	3	40	4	3	11	26	-	ABSENT
20	64	F	3	42	39	20	7	24	-	ABSENT
21	33	F	3	56	21	11	4	26	-	ABSENT
22	55	M	1	41	1	1	13	28	-	ABSENT
23	34	F	5	54	54	19	1	24	-	ABSENT
24	43	F	2	43	38	15	2	25	-	ABSENT
25	43	M	1	45	17	3	12	30	-	ABSENT
26	50	M	5	44	37	4	4	24	-	ABSENT
27	49	F	3	44	8	4	13	28	-	ABSENT
28	35	M	1	44	2	1	13	30	-	ABSENT

found between the MMSE scores and the N2 and P2 latencies.

Discussion

This is the first study dealing with nociceptive pathways function in Huntington's disease. A general interest concerning pain features has inspired many researchers in basal ganglia disorders, specially Parkinson's Disease (8). A case-control study showed that the overall frequency of pain was significantly greater in PD patients than in controls (8), confirming that basal ganglia dysfunction may cause alteration of pain processing (5). In our HD group, only three patients referred pain of arthralgic type, probably not linked with the disease itself. These data need to be confirmed by studies including a control population and patients in different stages of the disease. Though the occurrence of dementia may compromise the assessment of pain symptoms in the later stages of the disease (24), these evaluations may clarify if a low frequency of pain symptoms in HD may be supported by a dysfunction of nociceptive pathways.

In fact, we found an altered LEP pattern in HD, for an evident latency increase of all the examined

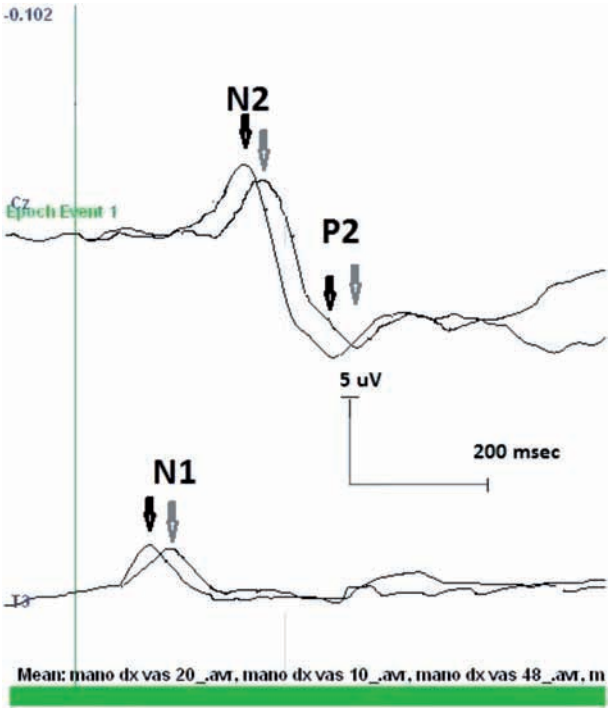

FIG. 1. — Grand average of laser evoked potentials by right hand stimulation computed across controls subjects (n° 40) and Huntington's disease patients (dotted line) (n° 28). The black and the grey arrows indicate the main LEPs respectively in normal subjects and HD patients.

LEP waves. Few studies described latency increase of somatosensory evoked responses in patients with HD (25-27), while the most of the studies reported an amplitude reduction of cortical SEPs (1, 28-30). The occurrence of abnormalities in nociceptive stimuli conduction, may firstly suggest an impairment of impulse transmission at the central level, along the spino-thalamic pathway at subcortical or cortical level, considering that in our patients there was no clinical evidence of peripheral neuropathy. An alternative explanation for the LEPs abnormalities may be linked with a sub-clinical cognitive impairment and attentional loss affecting HD patients in a mild stage of the disease. The latency increase involved also the N1 temporal wave, which is less influenced by attention changes: moreover, attention modulates vertex LEP amplitude without latency modification (32). In addition, the cognitive P3 is generally easily discernible and hardly confounded with LEP waves (12), which represent the most consistent neurophysiological pattern in nociceptive pathways examination (33). According to Iannetti and Mouraux (13, 14), vertex potentials reflect brain processing in response to multimodal salient stimuli, and do not reflect nociceptive-specific brain activities. In our patients, we observed a significant correlation between LEPs latency increase and test evaluating cognitive decline. Despite the MMSE scores were compatible with normal or slightly compromised cognitive functions, a deficit in orienting attention toward salient stimuli, may be an early sign of cognitive deterioration, supporting the abnormalities of the later LEPs. Moreover, in our patients, the slowing in sensory processing was further expressed by the latency increase of the early N1, which is

Table 2

Mean values and standard deviations (SD) of Laser evoked potentials (LEPs) latencies and amplitudes and VAS values in Huntington's Disease (HD) patients (HD) and normal controls (N). The results of the Student's t test for unpaired data are shown

RIGHT							LEFT			
variable	cases	n°	Mean	SD	t test	p	Mean	SD	t test	p
N2 latency (msec)	N	40	229.50	25.40	-2.21	0.03	219.17	25.09	-2.65	0.01
	HD	28	251.77	49.21			263.38	65.08		
P2 latency (msec)	N	40	313.83	18.98	-3.21	0.002	309.33	20.90	-2.65	0.01
	HD	28	353.86	65.29			359.21	74.62		
N2P2 amplitude (uV)	N	40	11.87	10.43	1.00	0.32	12.55	5.80	1.32	0.19
	HD	28	9.58	6.27			10.41	6.23		
N1 latency (msec)	N	40	163.00	41.79	-2.04	0.045	138.17	35.93	-3.21	0.002
	HD	28	188.18	38.12			195.90	65.81		
N1 amplitude (uV)	N	40	3.90	1.67	1.06	0.29	4.55	2.43	0.41	0.68
	HD	28	3.22	2.65			4.15	3.59		
VAS	N	40	42.95	29.90	0.11	0.92	46.88	29.17	1.62	0.11
	HD	28	43.37	21.86			46.02	23.69		

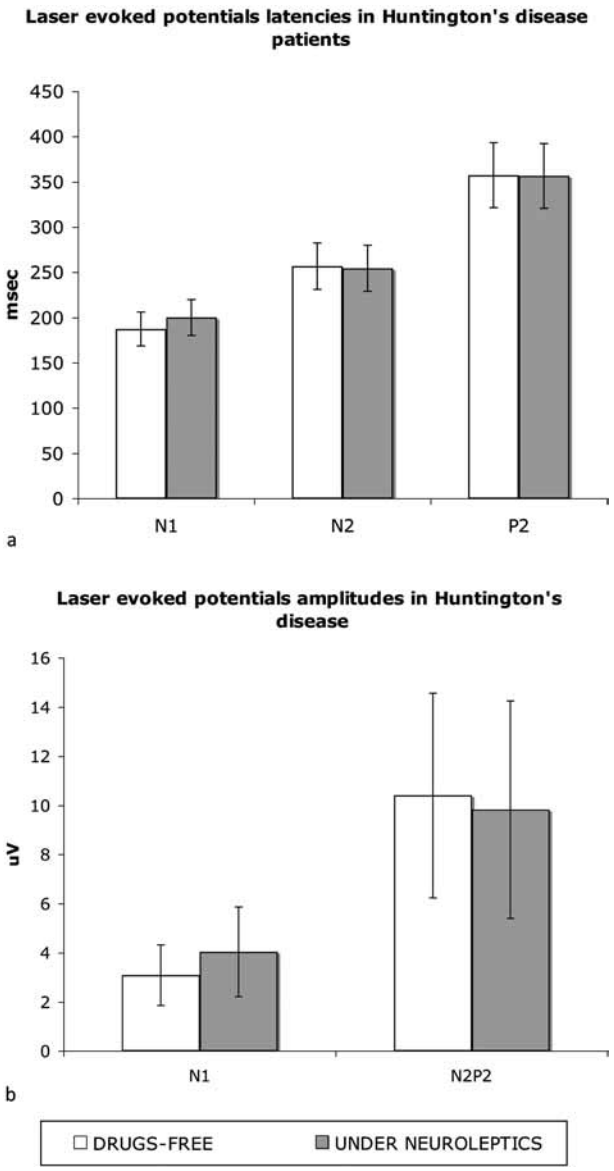

FIG. 2. — Mean values ± SD of laser evoked potentials latencies (a) and amplitudes (b) in the 21 Huntington's disease not submitted vs the 7 patients submitted to neuroleptic treatment. The results of Student's t test were not significant.

considered to be more specific for pain elaboration than the later vertex complex (14), and which showed no significant correlation with the cognitive impairment. We can suppose that the earlier and later phases of cortical processing of nociceptive inputs, including the activation of cortical areas devoted to the discriminative aspects of pain and alertness preceding further cognitive or motor reaction correlated to relevant sensory imput, may be altered in HD patients, before they manifested conclamated dementia. The LEP amplitudes were slightly and not significantly reduced in our HD patients, but the hypothesis that in the course of the disease LEP attenuation may occur for an increasing dispersion along the pain pathways and a progression of cortical atrophy, should be tested in a more advanced state of the disease. Considering that a linear relationship is generally described between N2/P2 amplitude and subjective pain rating (12), the absence of LEP amplitude abnormalities may concur with the normal laser pain perception in our early HD patients.

The nociceptive system is largely influenced by the functional state of basal ganglia (5). In PD patients, changes in LEP amplitude without latency increment has been reported , which implies normal function in tracts mediating nociceptive inputs to the cortex with an abnormal integration of pain inputs in CNS circuits (34). Moreover, complex interactions exist between motor and nociceptive cortex. In normal subjects, voluntary movement reduces laser evoked potentials (LEPs) (35), suggesting that a physiological activation of the motor cortex inhibits cortical pain processing. In our HD patients, we found a correlation between the gravity of chorea and the degree of LEPs vertex latency increase, so we can suppose that the involuntary movement may interfere with nociceptive inputs transmission. In addition, poor functional abilities corresponded to longer LEPs latencies, suggesting that the involvement of pain-related circuits may influence the gravity of disease expression. In our HD series, no significant sensory deficit was found, despite LEPs abnormalities affected the most of patients. Sensory deficit are not a frequent symptom in HD (36), but the frequently reported SEPs abnormalities (1, 25-30) suggest a subclinical disturbance of proprioceptive regulation, which may interfere with sensory-motor integration (2). On the basis of previous reports (1) and the present results, we can suppose that the processing of somatosensory nociceptive and not nociceptive inputs is altered in the mild stage of HD. In a future development of the present study, the comparison with middle latency SEPs would also give an aid in confirming that the deficit in orienting attention toward salient stimuli involves other forms of sensory processing, other than the nociceptive one.

The correlation between LEPs impairment and motor and functional deterioration, may not necessary be an expression of a direct influence of pain pathways dysfunction on motor performances and functional abilities, but it may outline that degenerative process affects different pathways including those for pain processing, as also suggested by PET studies (2). We couldn't evaluate if the LEP pattern was more expressed in patients suffering from

Table 3

Correlations between laser evoked potentials latencies and clinical and neuropsychological features in Huntington's disease patients

SPEARMAN RHO								
		AGE	UHDRSM	DURATION	CAG	TFC	CHOREA	MMSE
N2	Correlation Coefficient	0.185	0.236	0.051	0.348	-0.488	0.314	-0.498
	Sig. (2-tailed)	n.s.	n.s	n.s.	n.s.	**0.01**	n.s	**0.007**
P2	Correlation Coefficient	0.035	0.271	0.008	-0.365	-0.492	0.378	-0.571
	Sig. (2-tailed)	n.s	n.s.	n.s.	n.s	**0.008**	**0.047**	**0.006**
N1	Correlation Coefficient	0.04	0.117	-0.226	-0.143	-0.028	0.123	-0,345
	Sig. (2-tailed)	n.s	n.s.	n.s.	n.s.	n.s.	n.s.	n.s
	N	28	28	28	28	28	28	28

painful symptoms, for the small series. Moreover, no patient reported symptoms of primary central pain, which should subtend LEP modifications. The enlargement of HD population, may also contribute to clarify if the slowing in nociceptive input processing may subtend the rarity of pain symptoms in HD for a subclinical deficit in pain perception, probably progressing in the course of the disease. The few patients under neuroleptic treatment, had an analogous LEP pattern as the drugs free HD sufferers, as functional changes of nociceptive pathways are not reversed by reduction in dopamine neurotransmission.

Our data support for the first time evidence for functional changes of pain pathways function in mild-stage HD patients, concurring with motor deterioration, cognitive decline and functional impairment. A slowing in the attentional mechanisms subtending sensory processing, evident in the present study for the nociceptive inputs, may concur with early cognitive decline, and possibly cooperate to the worsening of functional capacities. Pain is a marginal argument in HD, but these data may explain the clinical experience that in later stages of the disease there are many patients with complications, without complaints of pain, for a possible progression of pain processing dysfunction. These data are far to be conclusive about the relevance of nociceptive pathways examination in HD assessment, but they suggest the need of further studies in larger populations to clarify if the relationships between LEPs abnormalities and clinical correlates in pain perception may provide further markers of disease progression in view of improving clinical approach.

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