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Sensory processing in Huntington's disease

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HIGHLIGHTS

- Patients with Huntington's disease (HD) have small and delayed long-latency evoked potentials (LLeps).
- When engaged in a reaction time task, HD patients have increased difficulties with perception.
- LLeps abnormalities in HD patients may be related to faulty sensorimotor integration.

ABSTRACT

Objective: An intriguing electrophysiological feature of patients with Huntington's disease (HD) is the delayed latency and decreased amplitude of somatosensory long-latency evoked potentials (LLeps). We investigated whether such dysfunction was associated with delayed conscious perception of the sensory stimulus.
Methods: Sixteen HD patients and 16 control subjects faced a computer screen showing the Libet's clock (Libet et al., 1983). In Rest trials, subjects had to memorize the position of the clock handle at perception of either electrical or thermal stimuli (AW). In React, additionally, they were asked to make a fist with their right hand, in a simple reaction time task (SRT). LLseps were recorded from Cz in both conditions.
Results: LLeps negative peak latency (N2) and SRT were abnormally delayed in patients in all conditions. AW was only abnormally prolonged in the React condition but the time difference between AW and the negative peak of the LLeps was not different in the two groups. There was a significant negative correlation between SRT and AW or LLeps amplitude in patients but not in healthy subjects.
Conclusion: Our HD patients did not show abnormalities in conscious perception of sensory stimuli but their LLeps abnormalities were more marked when they had to react. This is compatible with failure to detect stimulus salience rather than with a cognitive defect.
Significance: HD patients at early stages of the disease have preserved subjective perception of sensation but faulty sensorimotor integration.

1. Introduction

Huntington's disease (HD) is a neurodegenerative disorder, characterized by loss of medium spiny gabaergic striatal neurons (Graveland et al., 1985). Patients characteristically present with involuntary movements, mainly chorea, motor slowing, behavioral disturbances and progressive cognitive decline. A consistent but intriguing neurophysiological feature described in patients and asymptomatic gene carriers is the decrease in amplitude of the cortical somatosensory evoked potentials (Jossiasen et al., 1982; Noth and Engel, 1984; Kuwert et al., 1993; Abbruzzese and Berardelli, 2003), which mostly affects the waves evoked after 90 ms, i.e., long-latency somatosensory evoked potentials (LLeps), while peripheral nerve conduction and short-latency evoked potentials are normal (Abbruzzese and Dall'Agata, 1990). Studies of pain pathways in HD using laser stimuli have also showed delayed cor-

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tical (nociceptive) LLeps, which latency correlated with the degree of motor impairment (De Tommaso and Serpino, 2011). Importantly, HD patients showed also delayed nociceptive withdrawal reflex latency (Perrotta et al., 2012).

The striatum is known to play a role in pain modulation (Hagelberg et al., 2004; Pertovaara et al., 2005) and has a key position in motor control circuits between basal ganglia and motor cortex (Valeriani et al., 1999; Le Pera et al., 2007). Therefore, disturbances in sensorimotor integration can be expected in HD patients because of their characteristic striatal neuronal loss. Although sensory complaints are not characteristic of HD patients (Shannon, 2011), many of the abnormalities reported in these patients suggest an alteration of cortical multimodal sensory processing, which could have an impact on motor control even in early stages of the disease.

Cognitive impairment has been frequently considered responsible for the decrease in LLeps amplitude (Zopf et al., 2004; Legrain et al., 2002), but this has not been specifically tested due to the difficulty in documenting conscious perception of a stimulus in an experimental setting. The marked delay in simple reaction time (SRT) tasks in HD (Jahanshahi et al., 1993; van Vugt et al., 2004) has been considered an evidence of delayed sensory processing. However, SRT is known not to require conscious processing of the stimuli and is largely influenced by motor preparation (Henderson and Dittrich, 1998).

Conscious perception is a construct made out of sensory inputs and subjective appraisal of the sensation generated by the stimulus. This makes the use of SRT unsuitable for accurate determination of the time at which a stimulus is consciously felt. In the study reported here, we used the Libet's clock (Libet et al., 1983) to measure the time it takes for a subject to consciously perceive a sensory stimulus. With this method, the time of conscious perception can be quantified as the difference between the subjective appraisal of the sensation and the actual time at which a stimulus is issued, which we will refer to as awareness (AW). This involves fixation of information in short-term memory for it to be released at the end of the trial (Gallace et al., 2008).

We hypothesize that, if HD patients had a disordered conscious perception of sensory stimuli, AW would be delayed beyond the expected delay of the LLeps. Additionally, we included in the study quantitative sensory testing (QST) methods, in order to determine sensory thresholds, and SRT tasks to the same type of sensory stimuli, in order to evaluate early sensory-motor processing.

2. Patients and methods

The local Ethics Committee approved our study following guidelines of human research. All studies were performed in a single session and room, by the same examiner, using an electromyograph Dantec KeypointNet for all recordings. The device was equipped with the appropriate accessories for receiving a sweep-trigger-in signal and sending time-controlled trigger-out 5 V signals.

2.1. Study population

We studied 16 genetically confirmed HD patients and 16 healthy control subjects, matched for age and gender. Patients were assessed using the shortened version of the Unified Huntington's disease rating scale (UHDRS). We selected patients with no relevant cognitive and functional deficits according to the Attention section of the Mattis Dementia Rating Scale (MDRS) (Lucas et al., 1998) and the Total Functional Capacity Scale (TFC) (Huntington Study Group, 1996). Additional criteria for exclusion were: relevant facial/neck chorea (more than 1 in the facial chorea score), *clinical or electrophysiological* signs of peripheral nerve damage or symptoms of cognitive decline (Lemiere et al., 2004). Relevant demographic, clinical and laboratory data *of patients finally included in the study* are reported in Table 1. No patient was under treatment with dopamine antagonists.

2.2. Quantitative sensory testing

We examined perception and pain thresholds to heat and cold stimuli, using a thermode from Thermotest (SenseLab, Sweeden) applied to the distal third of the ventral right forearm. Subjects had to press a switch when they perceived the first sensation of temperature for perception thresholds to heat and cold, or pain for pain threshold to heat, from a baseline temperature of 32 °C. We averaged 4 trials for perception and 2 trials for pain thresholds.

2.3. General procedure

Subjects were sitting in a quiet room with an ambient temperature of 24 °C. The experiment consisted in two test conditions: "Rest", where subjects were required to just pay attention to the somatosensory stimulus and report on the position of the Libet's clock handle at the end of the trial, and "React", where in addition to this, they were requested to make a fist with their right hand as fast as possible after perception of the stimulus. A few training trials were executed until subjects felt confident with the procedure.

2.3.1. Electrical and thermoalgesic stimuli

Two stimulus modalities (electrical and thermal) were tested in each condition and were pseudorandomly combined with Rest and React conditions in four consecutive blocks. Electrical stimuli were applied with a bar electrode (inter-electrode separation of 2.5 cm) to the skin of the ventral distal third of the right forearm. Sensory perception threshold was calculated individually by progressively increasing stimulus intensity in steps of 0.2 mA. The electrical shocks used during the experiment were of an intensity of 2 times the sensory perception threshold, considered non-painful by all subjects. Thermoalgesic noxious stimuli were applied with a thermofoil thermode from a Pathway contact heat stimulator (Medoc, Ramat Yishai, Israel), which was set to reach a peak temperature of 53 °C at the speed of 70 °C/s. Habituation to thermalgesic stimuli was avoided by moving the thermode to a new place around the distal third of the ventral forearm after each stimulus. The stimulus intensity was above pain threshold for all our subjects.

2.3.2. Recording evoked potentials and reaction time

Gold chloride cup recording electrodes were attached to the scalp at Cz and the reference at the bridge of the nose. Impedances were maintained below 5 kΩ. Amplifier band pass frequency filters were 0.1–50 Hz. EEG epochs of 5 s were collected time-locked to the stimuli. Additional electrodes were placed over the orbicularis oculi muscle of the right side to notice eventual eye movement artefacts and reject the trial if they interfered with the recording. In the React condition, task execution onset latency was recorded with a movement transducer, a piezoelectric accelerometer model 348720 (Bionic Ibérica S.A., Barcelona, Spain), attached to the 3rd finger. For each stimulus type and condition, we collected ten artifact-free trials.

2.3.3. Determination of AW with the Libet's clock

A computer screen was placed 1 meter in front of the subjects, at eye level. It showed the image of a two-dimensional clock, with a single 1.3 cm long needle that rotated the whole circumference in clockwise direction every 2560 ms. The clock had conventional 5-min markings, to make it easy for the subject to identify the position of the handle at any of the 60' spaces that we usually identify