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Somatosensory temporal discrimination threshold in Parkinson's disease parallels disease severity and duration

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HIGHLIGHTS

- STDT (somatosensory temporal discrimination threshold) does not differ between PD at clinical onset and healthy subjects.
- STDT abnormalities correlate with the duration and severity of PD.
- Abnormal STDT appears when compensatory mechanisms fail to compensate altered basal ganglia activity.

ABSTRACT

Objective: To investigate whether the somatosensory temporal discrimination threshold (STDT) is already altered at the clinical onset of Parkinson's disease (PD) and whether STDT abnormalities correlate with disease progression we tested STDT values in patients with different severity of disease.
Methods: We prospectively and consecutively enrolled 63 PD patients: 26 drug-naive PD patients with symptom onset no longer than two years prior to inclusion in the study (early-phase), 37 PD patients with varying degrees of disease severity and 51 age-matched healthy subjects. The STDT was tested on the index finger of both hands, and on both sides of the face. Twelve out of 26 early phase PD patients were re-tested two years after the initial diagnosis.
Results: PD patients as a whole displayed higher STDT values than healthy subjects. STDT values did not significantly differ between early-phase PD patients and healthy subjects, whereas they were significantly higher in patients with mild/moderate and advanced PD. In early-phase PD patients STDT values at the two years-follow up assessment did not statistically differ from those obtained at baseline. Considering the whole group of PD patients STDT abnormalities significantly correlated with duration and severity of the disease.
Conclusions: STDT increases as disease progresses. In early-phase PD patients STDT values are still statistically similar to those of healthy subjects, thus implying that dopaminergic depletion alone may not be sufficient to cause STDT abnormalities.
Significance: Our study gives new insight into the sensory abnormalities in PD.

1. Introduction

The somatosensory temporal discrimination threshold (STDT) is defined as the shortest interval at which an individual recognizes a pair of stimuli as separate in time (Lacruz et al., 1991). It relies on a purely sensory process that allows the brain to "filter" the relevant sensory information from external sources (Costa et al., 2008). Previous studies on healthy subjects have suggested that the STDT depends on the integrity of a complex cortico-subcortical network in which S1 plays an encoding role and basal ganglia determine a time-related interaction between cortical and subcortical structures (Conte et al., 2012; Harrington et al., 1998a,b; Ivry, 1996).

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Some studies have demonstrated that the STDT is altered in Parkinson's disease (PD) (Abbruzzese and Berardelli, 2003; Artieda et al., 1992; Conte et al., 2010, 2013; Lyoo et al., 2012; Patel et al., 2014). Whether the STDT is already altered at the clinical onset of PD symptoms is however unknown. The results of previous studies on the relationship between STDT values and disease severity are contrasting (Conte et al., 2010; Lee et al., 2010; Lyoo et al., 2012; Rocchi et al., 2013). Studies that did find a significant association between STDT values and motor deficit scores reported that the STDT only correlated with the Unified Parkinson's Disease Rating Scale (UPDRS) subscores for axial motor deficits (Lyoo et al., 2012). A better knowledge of these issues would provide further insight into sensory disturbances in PD. In particular, if STDT abnormalities are already present at the onset of motor symptoms, the STDT may be a valuable hallmark of the disease and consequently be considered a disease trait. Alternatively, if STDT abnormalities appear during the course of the disease, STDT may be a feature which reflects disease progression in PD thus giving new insight into the pathophysiology of altered STDT. The aim of our study was to investigate whether STDT is already altered at the clinical onset of Parkinson's disease (PD) or whether STDT abnormalities develop only in the late-phase of the disease. We therefore studied STDT values in 63 PD patients in different disease stages, including patients with early-phase PD, and compared the results with those obtained from a group of 51 healthy subjects. We then investigated whether there were any correlations between the STDT values and the clinical and demographic features of the PD patients.

2. Methods

2.1. Study participants and clinical assessment

We enrolled a total of 63 PD patients (mean age 63.6 ± 8.1 years) diagnosed according to published criteria (Berardelli et al., 2013) and 51 age-matched healthy subjects recruited among caregivers and spouses of PD patients (mean age 63.1 ± 8.7 years). All participants were right-handed. Patients were consecutively and prospectively recruited from the movement disorder outpatient clinic of the Department of Neurology and Psychiatry at Sapienza University of Rome from June to December 2013. Written informed consent was obtained from all the patients and healthy subjects. The experimental procedure was approved by the institutional review board at Sapienza University of Rome and conducted in accordance with the Declaration of Helsinki.

Information regarding the demographic characteristics, family history and disease course were collected during a face-to-face interview. Parkinsonian motor symptoms were assessed using the Hoehn and Yahr Scale (H&Y) and the UPDRS part III (Table 1). All the patients underwent the Mini-Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Montreal Cognitive Assessment (MOCA) and Hamilton Rating Scale for Depression (HMRD).

Since the temporal sensory processing data yielded by STDT testing are only reliable if cognitive functions are normal, patients with a MMSE score lower than 26, a FAB score lower than 15 or a MOCA score lower than 24 were excluded. We also excluded patients with a HMRD score higher than 10. All participants were screened for peripheral sensory neuropathy by medical history and bed-side clinical examination. Any patients or healthy subjects who had a clinically-diagnosed peripheral sensory neuropathy or which presented major risk factor for neuropathy (e.g. diabetes, chronic metabolic diseases, autoimmune diseases, etc.) were not included in the study. No patient had a history of central nervous system disease different from PD, neither was taking drugs with actions on the central nervous system other than dopaminergic treatment. Healthy subjects had no history of any neuropsychiatric disorders and were not taking drugs with actions on the central nervous system at the time of the experiments.

We included patients in different stages of disease: 26 early-phase drug-naïve PD patients with onset of symptoms no longer than two years prior to inclusion in the study (early phase: H&Y = 1–2.5), 37 PD patients with a disease duration longer than two years and varying degrees of disease severity (28 mild/moderate: H&Y = 1–3; 9 advanced: H&Y = 4–5) who were on chronic dopaminergic treatment. PD patients on chronic dopaminergic treatment were tested OFF dopaminergic therapy (12 h after the last dose of dopaminergic medication). A subgroup of 12 of the 26 drug-naive PD patients who started dopaminergic therapy after the first assessment were tested again two years later in the OFF therapy condition.

2.2. STD procedure

The STD was investigated by delivering paired stimuli starting with an interstimulus interval (ISI) of 0 ms (simultaneous pair), and progressively increasing the ISI in 10 ms steps, according to the experimental procedures used in previous studies (Conte et al., 2012; Scontrini et al., 2009). Paired tactile stimuli consisted of 100-μs square-wave electrical pulses delivered with a constant current stimulator (Digitimer DS7AH) through surface skin electrodes with the anode located 0.5 cm distally to the cathode, which was applied to the volar surface of the index finger of the left and right hands, and to the left and right sides of the face. The stimulation intensity was defined for each subject by delivering a series of stimuli at an increasing intensity starting from 2 mA in 0.5 mA steps; the intensity used for the STD was the minimal intensity perceived by the subject in 10 out of 10 consecutive stimuli. The first of three consecutive ISIs at which participants recognized the stimuli as temporally separate was considered the STDT value. To keep the subjects' attention level constant during the test and minimize possible perseverative responses, we included "catch" trials consisting of a single stimulus delivered randomly. Paired stimuli were delivered at intervals of between 3 and 5 s. Patients were asked to report, as soon as possible, whether they perceived a single stimulus or two temporally separated stimuli by saying "one" or "two" after each stimulation in the interval preceding the next paired stimuli. Each session comprised four separate

Table 1
Clinical and demographic features of patients.

	Subjects	Age (years)	Disease duration (months)	Hoehn & Yahr	UPDRS III	MMSE	MOCA	FAB	Hamilton
Early-phase PD	26	64.4 ± 8.6	13.23 ± 7.9	1.5 ± 0.6	13.3 ± 5.5	28.7 ± 1	26.8 ± 2	17.2 ± 1	5.1 ± 2
Mild/Moderate PD	28	64.6 ± 8.7	108.9 ± 66.9	2.2 ± 1.1	25.9 ± 11.7	28.6 ± 1	26.6 ± 2	16.9 ± 1	5.0 ± 3
Advanced PD	9	61.4 ± 6.1	164.0 ± 31.2	4.1 ± 1.1	39.7 ± 10.1	27.9 ± 1	27.8 ± 1	16.0 ± 1	6.0 ± 3
Kruskal–Wallis' test *p*	–	0.62	<0.000001	<0.000001	<0.000001	0.5	0.2	0.13	0.4

UPDRS III: Unified Parkinson's Disease Rating Scale (UPDRS) part III. PD: Parkinson's disease. Data are expressed as mean ± SD.