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Somatosensory temporal discrimination in Parkinson's disease, dystonia and essential tremor: Pathophysiological and clinical implications

Antonella Conte [a,b], Gina Ferrazzano [b], Daniele Belvisi [b], Nicoletta Manzo [a], Emanuele Battista [a], Pietro Li Voti [b], Andrea Nardella [b], Giovanni Fabbrini [a,b], Alfredo Berardelli [a,b,*]

[a] Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
[b] IRCCS Neuromed, Pozzilli, IS, Italy

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HIGHLIGHTS

- To investigate whether somatosensory temporal discrimination threshold (STDT) alterations in movement disorders are related to tremor.
- STDT abnormalities in movement disorders depend on the dysfunction of primary somatosensory cortex and the basal ganglia.
- STDT testing may help clinicians to discriminate patients with upper limb postural tremor.

ABSTRACT

Objective: To investigate whether changes in the somatosensory temporal discrimination threshold (STDT) in Parkinson's disease (PD) and dystonia reflect the involvement of specific neural structures or mechanisms related to tremor, and whether the STDT can discriminate patients with PD, dystonia or essential tremor (ET).
Methods: We tested STDT in 223 patients with PD, dystonia and ET and compared STDT values in patients with PD and dystonia with tremor with those of PD and CD without tremor. Data were compared with those of age-matched healthy subjects.
Results: STDT values were high in patients with dystonia and PD but normal in ET. In PD, STDT values were similar in patients with resting or postural/action tremor and in those without tremor. In dystonia, STDT values were higher in patients with tremor than in those without tremor. The ROC curve showed that STDT discriminates tremor in dystonia from ET.
Conclusions: In PD, STDT changes likely reflect basal ganglia abnormalities and are unrelated to tremor mechanisms. In dystonia, the primary somatosensory cortex and cerebellum play an additional role.
Significance: STDT provides information on the pathophysiological mechanisms of patients with movement disorders and may be used to differentiate patients with dystonia and tremor from those with tremor due to ET.

1. Introduction

The somatosensory temporal discrimination threshold (STDT) measures a subject's ability to discriminate sensory stimuli in the temporal domain (Artieda et al., 1992; Conte et al., 2010; Tinazzi et al., 2013). Several studies have investigated the physiological mechanisms underlying the STDT in healthy subjects (Conte et al., 2012; Conte et al., 2017a; Lee et al., 2017; Leodori et al., 2017; Rocchi et al., 2016). Findings from neurophysiological studies based on transcranial magnetic stimulation suggest that the

Abbreviations: PD, Parkinson's disease; CD, cervical dystonia; ET, Essential Tremor; STDT, somatosensory temporal discrimination threshold; S1, primary somatosensory cortex; fMRI, functional magnetic resonance imaging; ISI, interstimulus interval.

* Corresponding author at: Department of Human Neurosciences, Sapienza University of Rome, IRCCS Neuromed, Pozzilli, IS, Rome, Italy.
E-mail address: alfredo.berardelli@uniroma1.it (A. Berardelli).

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STDT strongly relies on inhibitory interneurons in the primary somatosensory cortex (S1) (Antelmi et al., 2017; Conte et al., 2012; Leodori et al., 2017; Rocchi et al., 2016; Tamura et al., 2008), whereas those from functional magnetic resonance imaging (fMRI) and pharmacological studies suggest that the basal ganglia play a role in the STDT (Pastor et al., 2008; Rammsayer et al., 1992; Rammsayer, 1999). The contribution of the cerebellum to the STDT is still debated (Conte et al., 2012; Koch et al., 2009).

Further information on the physiological mechanisms underlying the STDT comes from studies on the STDT in patients with movement disorders. Abnormally increased STDT values have been reported in Parkinson's disease (PD) and dystonia (Bradley et al., 2012; Conte et al., 2013, 2016a; Di Biasio et al., 2015; Fiorio et al., 2007; Kimmich et al., 2014; Lee et al., 2010, 2016, 2017; Sadnicka et al., 2013; Scontrini et al., 2009) whereas the STDT in essential tremor (ET) is reported to be normal (Conte et al., 2015; Tinazzi et al., 2013). STDT changes in movement disorders may be caused by the involvement of specific neural structures (S1, basal ganglia and cerebellum). An alternative hypothesis is that changes in the STDT reflect specific mechanisms related to the pathophysiology of motor symptoms.

In order to gain a better understanding of the mechanisms underlying changes in the STDT, we investigated the STDT in a large sample of 223 patients affected by PD, dystonia and ET. In order to determine whether STDT alterations are related to tremor, which is a symptom shared by these three types of movement disorder, we compared STDT values in patients with PD and dystonia with tremor with those of patients with PD and dystonia without tremor. Data were also compared with those of age-matched healthy subjects. Since PD, dystonia and ET can all give rise to postural tremor, the ultimate aim of our study was to assess whether STDT abnormalities may be able to help clinicians to discriminate patients with PD, dystonia or ET with postural arm tremor. We thus analysed STDT values in patients with upper limb tremor using a ROC curve analysis to assess the accuracy of the STDT testing.

2. Methods

We tested the STDT in a total sample of 223 patients. One hundred and seven patients had PD, 51 had dystonia and 65 ET. Of the 107 patients with PD, 20 had rest tremor (with or without re-emergent tremor) alone, 67 also had postural and action tremor in the upper limbs and 20 did not have tremor (Postuma et al., 2015; Belvisi et al., 2018). Of the 67 PD patients with postural/action tremor, 42 had both postural and action tremor, 18 had postural tremor alone and 7 had action tremor alone. Upper limb tremor was bilateral in 52 PD patients and unilateral in 35. Of the 51 patients with dystonia, 25 had cervical dystonia (CD) with upper limb postural and action tremor, whereas 26 had CD without tremor. A group of 84 healthy age-matched subjects was used as control. Patients were recruited from the movement disorder outpatient clinic of the Department of Human Neurosciences at Sapienza University of Rome from June 2016 to June 2017. The experimental procedure was approved by the institutional review board at Sapienza University of Rome and conducted in accordance with the Declaration of Helsinki. All the participants gave their written informed consent.

The diagnosis of PD, CD and ET was based on a clinical examination, according to published criteria (Albanese et al., 2013; Berardelli et al., 2013; Jinnah et al., 2013; Postuma et al., 2015). Disease severity was rated by means of the Fahn-Tolosa-Marin rating scale for ET (Fahn et al., 1993), the Toronto Western Spasmodic Torticollis Rating Cervical Scale (Consky and Lang, 1994) for CD and the MDS-UPDRS part III for PD (Goetz et al., 2008) (Table1). PD patients were tested OFF therapy (at least 12 h after the last levodopa intake). The investigators who assessed the STDT were blinded to the clinical diagnosis. The exclusion criteria were a Mini-Mental State Examination score below 26, neuropathies, concurrent or recent exposure to drugs that may cause tremor and other neurological signs.

2.1. STDT testing

The STDT was investigated according to experimental procedures used in previous studies (Conte et al., 2010, 2012, 2016a,b, 2017b,c,d; Leodori et al., 2017; Scontrini et al., 2009). Paired tactile stimuli consisted of square-wave electrical pulses delivered with a constant current stimulator (Digitimer DS7AH) through electrodes placed on the volar surface of the index finger. The stimulation intensity used for STD testing was the minimal intensity the subject perceived in 10 out of 10 consecutive stimuli. We delivered paired stimuli at an initial interstimulus interval (ISI) of 0 ms (simultaneous pair), and progressively increased the ISI in 10-ms steps according to the ascending stepwise method. The STDT was defined as the first of three intervals at which participants recognized two stimuli as separate; the average of three STDT values was calculated and entered in the data analysis. Both hands were tested in order to evaluate any differences in tremor between the more affected and the less affected side.

3. Statistical analysis

We performed a non-parametric test (Kruskall-Wallis and Mann-Whitney *U* test) to evaluate any differences in the STDT values between the patient groups and healthy subjects as well as within the patient groups to evaluate any differences in STDT values related to the presence of tremor (CD and PD) and the type of tremor (postural/action vs. resting tremor vs. no tremor in PD). We also performed a Wilcoxon's test to evaluate any differences in the

Table 1
Demographic, clinical and neurophysiological parameters in the various subgroups of patients with Parkinson's disease (PD), in patients with cervical dystonia (CD) with and without upper limb tremor and in patients with essential tremor (ET). Values are expressed as mean ± SD.

	PD patients with rest/re-emergent tremor	PD patients with postural/action tremor	PD patients without tremor	CD patients with upper limb tremor	CD patients without upper limb tremor	ET patients
Males/females ratio	1.5	1.4	1.6	0.47	0.25	0.91
Right-handed (%)	97%	98%	96%	98%	96%	99%
Age (years)	65.5 ± 8.7	66.4 ± 9.1	67.3 ± 10.7	65.8 ± 8.3	66.2 ± 7.3	66.4 ± 10.5
Disease duration (years)	5.6 ± 3.8	5.1 ± 3.2	5.4 ± 3.9	10.8 ± 7.6	12.3 ± 8.8	11.7 ± 9.3
MDS-UPDRS part III	23.5 ± 7.6	28.1 ± 9.8	27.5 ± 9.1	–	–	–
FTM	–	–	–	6.3 ± 1.4	–	14.9 ± 9.7
TWSTRS	–	–	–	17.06 ± 10.2	16.8 ± 9.8	–
STDT values (milliseconds)	115 ± 24	111 ± 28	117 ± 22	113 ± 23	97 ± 27	79 ± 21

Abbreviations: MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; FTM, Fahn-Tolosa-Marín scale; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale; STDT, somatosensory temporal discrimination threshold.