

# Somatosensory Temporal Discrimination Threshold Is Increased in Patients with Cerebellar Atrophy

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**Abstract** Processing of time in the millisecond range seems to depend on cerebellar function and it can be assessed by using the somatosensory temporal discrimination threshold testing. No studies have yet investigated this temporal discrimination task in patients with cerebellar atrophy. Eleven patients with degenerative cerebellar ataxia and 11 controls underwent somatosensory temporal discrimination threshold evaluation. The degree of cerebellar dysfunction was measured by the International Cooperative Ataxia Rating Scale. Somatosensory temporal discrimination threshold was higher in patients compared to controls for each stimulated site (hand, neck, and eye). Age, disease duration, and International Cooperative Ataxia Rating Scale scores were not correlated to somatosensory temporal discrimination threshold. Somatosensory temporal discrimination threshold is abnormal in patients with cerebellar atrophy. These findings suggest that the cerebellum plays a role in modulating the somatosensory temporal discrimination threshold and confirm the role of cerebellum in the processing of time in the millisecond range.

**Keywords** STDT · Cerebellar ataxia · Electrical stimulation · Cerebellar atrophy

## Introduction

Processing of time in the millisecond range can be assessed by testing the somatosensory temporal discrimination threshold (STDT). STDT testing is a sensory discrimination task that relies on cortical and subcortical networks and assesses the ability to perceive two tactile stimuli applied to the skin as sequential in time. Several studies have demonstrated that the STDT is controlled by a number of cortical areas, including the primary sensory area (S1), pre-supplementary motor area, and anterior cingulate cortex [1–4]. The basal ganglia are also involved in the modulation of the STDT that is abnormal in patients with Parkinson's disease, multiple system atrophy (MSA), and dystonia [5–7]. The role of the cerebellum in temporal processing in the millisecond range (tens to hundreds of milliseconds) has been demonstrated in healthy subjects using temporal discrimination tasks, other than the STDT. Experiments were designed to estimate the duration of a visual stimulus or to compare the duration of two interstimulus intervals of electrical stimuli or to compare the duration of different acoustic stimuli in sub- and suprasecond interval timing [8–10].

However, no studies have demonstrated the role of cerebellum in modulating STDT. In addition, no studies have yet investigated the STDT in patients with cerebellar diseases. To this aim, we evaluated the STDT in a group of patients with degenerative cerebellar atrophy and compared these results with those obtained in healthy subjects.

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## Patients and Methods

We studied 11 patients with degenerative cerebellar ataxia (Table 1) and 11 healthy subjects of comparable age (mean age  $51.9 \pm 15.5$  years) as a control group. Magnetic resonance imaging showed cerebellar atrophy, involving only the hemispheres or both the vermis and the hemispheres. The study was approved by the local ethics committee of the Department of Neurological Sciences, University Federico II of Naples and the research was conducted in accordance with the 1964 Declaration of Helsinki.

All the subjects gave their written informed consent prior to the participation in the study. Three patients with an autosomal inheritance pattern underwent molecular analysis in order to exclude the most common spinocerebellar ataxia subtypes (SCA1, 2, 3, 6, 7, and 17) in which basal ganglia affection has been demonstrated [11]. Three patients presented with an autosomal recessive inheritance pattern and were negative for GAA expansion in FRDA gene. The remaining five patients, after excluding the acquired causes, were defined as apparently sporadic idiopathic cerebellar ataxia. All the patients underwent neurographic evaluation to rule out peripheral neuropathy. Somatosensory-evoked potentials were obtained by stimulating the left median nerve and patients with abnormal findings were not included in the study. Moreover, we excluded patients with dementia

or mild cognitive impairment and extrapyramidal clinical features. At neurological examination, five patients presented brisk deep tendon reflexes at lower limbs and six patients showed a reduced vibration sense at ankle tested by using a 128-Hz tuning fork. The International Cooperative Ataxia Rating Scale (ICARS) was used to measure the degree of cerebellar dysfunction. ICARS total score (items 1–19, maximum score 100) comprises four categories: postural and gait disorders (items 1–7, maximum score 34), limb ataxia (items 8–14, maximum score 52), speech disorders (items 15–16, maximum score 8), and oculomotor disorders (items 17–19, maximum score 6).

## Stimuli and STD Procedure

Somatosensory temporal discrimination (STD) was tested by delivering paired stimuli starting at an interstimulus interval (ISI) of 0 ms (simultaneous pair), followed by progressively increasing ISIs (in 10 ms steps). The surface skin electrodes, with the anode located 2 cm distal to the cathode, were applied on the left side of the body to the hand (index finger), to the neck and near the orbit (eye). The stimulation intensity was defined for each subject by delivering series of stimuli at increasing intensities from 2 mA in steps of 1 mA. The intensity used for STD was the minimal intensity perceived by the subject in 10 of 10 consecutive

**Table 1** Clinical features of cerebellar patients

Patient	Diagnosis	Sex (m/f)	Age (years)	Disease duration (years)	Cerebellar atrophy	ICARS scores				
						Postural and gait disorders	Limb ataxia	Speech disorders	Oculomotor disorders	Total ataxia score
1	Sporadic cerebellar ataxia	m	20	10	V + H	10	11	2	1	24
2	AR cerebellar ataxia	m	54	12	H	5	3	5	0	13
3	Sporadic cerebellar ataxia	f	41	21	V + H	np	np	np	np	np
4	AD cerebellar ataxia	m	62	4	V + H	6	10	4	3	23
5	AD cerebellar ataxia	f	61	6	H	8	7	3	1	19
6	Sporadic cerebellar ataxia	m	61	41	V + H	18	12	5	4	39
7	Sporadic cerebellar ataxia	m	61	15	V + H	24	17	3	4	48
8	AD cerebellar ataxia	f	41	6	V + H	10	8	3	1	22
9	Sporadic cerebellar ataxia	m	47	20	V + H	22	17	3	3	45
10	AR cerebellar ataxia	f	41	10	V + H	2	4	3	1	10
11	AR cerebellar ataxia	m	38	14	V + H	10	7	4	1	22
		7/4	47.9 (13.3)	14.5 (10.4)		11.5 (7.4)	9.6 (4.8)	3.5 (1)	1.9 (1.4)	26.5 (13)

Under the columns, m/f ratio and mean values with standard deviations (within parentheses) are reported

f female, m male, np not performed, AR autosomal recessive, AD autosomal dominant, V vermis, H hemispheres (bilateral), ICARS International Cooperative Ataxia Rating Scale

stimuli, which was defined as the perceptual threshold (PT). Subjects had to state by voice whether they perceived a single stimulus or two temporally separate stimuli. The first of three consecutive ISIs at which the participants recognized the two stimuli as temporally separate was considered as the STD threshold (STDT). Each session comprised four separate blocks. The STDT for each stimulated body site was determined by calculating the average of the STDT values yielded by each of the four blocks and entered in the data analysis [5].

### Statistical Analysis

The *T* test for unpaired samples was used to compare the two groups for age. Mann–Whitney test was performed to evaluate any differences between patients and controls in the STDT and PT mean values for each body site.

One-way analysis of variance (ANOVA) was used to compare the STDT values recorded in the three stimulated sites in patients and healthy subjects. Correlations between the STDT values and age, disease duration, and ICARS total score and subscores were assessed by means of Spearman's rho and adjusted with Bonferroni's correction. The significance level was set at  $p < 0.05$ .

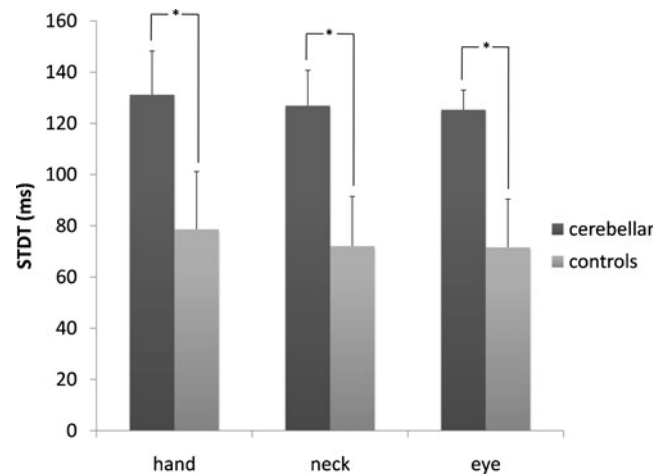
### Results

There was no difference in mean age between patients and healthy subjects. The STDT mean values (ms  $\pm$  SD) of the patients were significantly higher than those of controls for each stimulated site (hand,  $131.1 \pm 17.1$  vs  $78.6 \pm 22.5$ ,  $p = 0.0001$ ; neck,  $126.9 \pm 13.9$  vs  $72.0 \pm 19.4$ ,  $p = 0.0003$ ; eye,  $125.3 \pm 7.7$  vs  $71.6 \pm 18.8$ ,  $p = 0.0004$ ) (Fig. 1).

ANOVA test did not detect any significant difference in STDT values among the three stimulated sites in either patients ( $F = 0.45$ ,  $p = 0.64$ ) and healthy subjects ( $F = 0.41$ ,  $p = 0.66$ ). No significant difference emerged between patients and controls in PT mean values (mA  $\pm$  SD) for each stimulated site (hand,  $5.6 \pm 1.7$  vs  $5.2 \pm 1.9$ ,  $p = 0.48$ ; neck,  $7.8 \pm 2.3$  vs  $6.3 \pm 2.3$ ,  $p = 0.14$ ; eye,  $7.3 \pm 2.3$  vs  $6.1 \pm 1.9$ ,  $p = 0.37$ ). The STDT values did not correlate with age, disease duration, or ICARS total score and subscores.

### Discussion

The novel finding of this paper is that the STDT is abnormal in all three body parts tested in ataxic patients with cerebellar atrophy. The observed abnormalities suggest that the cerebellum plays a role in modulating the STDT. Moreover, these results support those previously reported in normal subjects, suggesting that cerebellum is involved in the processing of



**Fig. 1** Somatosensory temporal discrimination threshold (STDT) tested in three body parts (hand, neck, and eye) in cerebellar patients (dark gray columns) vs control subjects (light gray columns). Each column represents mean values; the bars represent standard deviations. Asterisks represent statistical significance ( $p < 0.001$ )

time in the range of milliseconds [12]. It is important to note, however, that the role of cerebellum in processing somatosensory information is more complex and the time domain represents only one part of this process, as it has been shown in experiments with mismatch negativity study [13, 14]. In addition, in patients with degenerative cerebellar atrophy, an incorrect adapting of the cerebellum to peripheral stimulation might also impair the beginning of the somatosensory processing.

Our findings apparently contrast with those of Conte et al. [4], who found that the STDT in normal subjects was unaffected by stimulation of the left cerebellar hemisphere using the theta-burst transcranial magnetic stimulation technique (TBS). In healthy subjects, it is likely that TBS-induced cerebellar modulation is unable to induce detectable changes in STDT, whereas in the patients we studied, cerebellar atrophy leads to an imbalance of cortico-subcortical circuit underlying the STDT, therefore, uncovering the role of cerebellum in temporal processing of tactile stimuli. The role of cerebellum in temporal discrimination tasks is also supported by studies showing that patients with damage to the lateral superior hemisphere or the dentate nuclei had significant impairment in temporal processing [15, 16]. It has been, therefore, suggested that timing functions of the cerebellum are restricted to cerebellar superior and middle lobules, but also that other regions of the cerebellum may be important for temporal processing, but in different task domains.

The cerebellum is part of neural circuits in the context of an integrative model of timing and time perception [17, 18]. The shorter time intervals in the millisecond range are likely to be computed by the cerebellum, whereas the basal ganglia are involved in time intervals ranging from the millisecond-to-second range [12]. Moreover, the basal ganglia appear to be able to compensate for the errors generated by the

cerebellum through their connections with the frontal cortex [17, 18]. If we assume that this is true, the functional integrity of striatal–cortical circuits may partly compensate for STDT abnormalities in our cerebellar patients and might explain why we did not find any correlation among the STDT values and disease duration and ICARS scores. This hypothesis is supported by the findings of Lyoo and colleagues [6], who reported that the STDT values in their MSA patients were unrelated to the degree of cerebellar dysfunction, but correlated with the UPDRS motor scores. Moreover, the same authors have recently demonstrated that STDT prolongation in Parkinson's disease is significantly correlated with the degree of basal ganglia dysfunction assessed by [ $^{18}\text{F}$ ]-FPCIT positron emission tomography study [19].

## Conclusion

Our study in patients with cerebellar atrophy indicates that the cerebellum plays a role in somatosensory temporal discrimination threshold and confirms its role in the processing of time in the millisecond range.

**Conflict of Interest** The authors report no financial disclosures. No potential conflicts of interest exist.

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