Temporal Processing of Visuotactile and Tactile Stimuli in Writer's Cramp

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Neurophysiological studies in animals show that basal ganglia are involved not only in motor and nonmotor timing functions but also in integrating tactile and visual signals delivered in the peripersonal space. We tested temporal discrimination of cross-modal and unimodal stimuli in 13 controls and 14 patients with writer's cramp, a disorder supposedly linked to dysfunction of basal ganglia. Subjects were asked to discriminate whether pairs of visual, tactile, or visuotactile stimuli were simultaneous or sequential (temporal discrimination threshold) and which stimulus preceded the other (temporal order judgment). Patients were impaired in temporal processing of tactile and cross-modal stimuli. A significant positive correlation between temporal deficits and the severity of disability was detected for both affected and unaffected sides. Findings suggest that multimodal and not only modality-specific temporal processing is defective in focal hand dystonia. Deficits of temporal processing of stimuli delivered to the unaffected side may represent a behavioral index of the susceptibility to develop dystonia and thus have remarkable practical and theoretical implications.

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The term *dystonia* refers to a neurological syndrome supposedly linked to a dysfunction of basal ganglia and characterized by sustained muscular contractions that cause repetitive movements and abnormal postures. These prominently motor disturbances may affect many body parts (generalized) or involve a single body region (focal), mostly often the hand.[1,2] Focal hand dystonias are typically task specific and are triggered by overtrained skilled movements, such us playing instruments in musicians.[3] The so-called writer's cramp is the most common form of focal hand, task-specific dystonias.[2,4] Recent single cell recording and magnetoencephalography studies in animals[5] and in patients[6,7] with focal hand dystonia consequent on overuse or improper use of one or more digits reported neural changes in the primary somatosensory cortex representing the most trained fingers. Somatosensory abnormalities also are disclosed by recent psychophysical studies in generalized and focal hand dystonia patients who showed an impairment of somatosensory spatial[8] and temporal[9–12] discrimination. Deficits of temporal integration in focal hand dystonia have so far been tested by using only tactile stimuli under the assumption that sensory aspects of focal hand dystonia mainly affect the peripheral inputs specifically involved in the motor control of the dystonic body part. In addition to motor and nonmotor timing functions, neurophysiological studies in monkeys suggest that basal ganglia may play an important role in integrating tactile and visual stimuli delivered in close temporal and spatial register.[13,14]

This study expands current knowledge on sensory aspects of focal hand dystonia by assessing temporal discrimination not only of tactile but also of visual and visuotactile stimuli. Moreover, unlike previous studies,[10,11] temporal discrimination capabilities are assessed for stimuli delivered both on the affected and the intact side.

Subjects and Methods

We tested 14 right-handed patients affected by idiopathic focal hand dystonia. Thirteen healthy right-handed subjects matched for gender, age (range, 25–58 years), and education (range, 8–18 years) served as the control group. In six patients, dystonia was present only during writing (simple writer's cramp); in the other eight patients, dystonia was present either at rest or during more than one action (dystonic writer's cramp).[4] Duration of disease ranged from 2 to 11 years. Severity of motor impairment was evaluated by using the Burke–Fahn–Marsden movement and disability scale.[15] Eight patients were untreated; the remaining six patients had received treatment with botulinum toxin until 6 months before the study. Additional demographic and clinical information is provided in the Table.

All subjects gave their written informed consent before

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participation in the study. The work was approved by the institutional ethics committee. Tactile stimuli in a pair consisted of square wave electrical pulses delivered by means of a constant current stimulator (STM 140; HTL, Udine, Italy) through surface skin electrodes (1mm diameter) applied to the index and middle fingers of the right or the left hand. The anode was located 1.5cm distally from the cathode. The intensity of tactile stimulation was determined for each subject, by delivering series of stimuli with an increasing intensity (from 2mA in steps of 1mA). The minimal intensity at which electric stimuli were perceived in 10 of 10 stimuli was used in the experimental test. Care was taken that stimuli did not induce pain or discomfort. Mean intensity of stimulation used in writer's cramp patients (7.0mA; standard deviation, 1.2) did not differ ($p = 0.70$) from that used in control subjects (6.0mA; standard deviation, 0.6). Visual stimulation was performed by means of light-emitting diodes (LEDs) positioned on a black table (51 × 37cm) at 57cm from the subject's head and 7 degrees left or right from a central fixation point. The luminance of each LED was $140cd/m^2$, and the background luminance was approximately $15cd/m^2$. Both visual and tactile stimuli lasted 5 milliseconds. Subjects' hands were positioned near the LEDs. Subjects were asked to look at the fixation point throughout each trial (ie, each perception-verbal report cycle). The maintenance of fixation was controlled directly by the experimenter. Trials in which participants did not maintain fixation (approximately 1%) were discarded. A schematic representation of the different stimulation conditions is provided in Figure 1.

Subjects were tested in one experimental session lasting approximately 90 to 120 minutes. The experimental test was delivered in six combinations of stimulation: two visual (left and right), two tactile (left and right), and two cross-modal (vision-touch left and vision-touch right; see Fig 1). The order of presentation of the six combinations of stimuli was counterbalanced across subjects. Each combination of stimuli was performed in four separate blocks. In the first trial of each block, pairs of simultaneous stimuli (interstimulus interval [ISI], 0 milliseconds) were delivered. In subsequent trials, ISIs were progressively increased in steps of 10 milliseconds. We considered as temporal discrimination threshold (TDT) the first of three consecutive ISIs at which subjects recognized the stimuli as asynchronous. Subjects also were asked to judge which stimulus preceded (or followed) the other. Temporal order judgment (TOJ) corresponds to the first of three consecutive ISIs at which subjects not only recognized the stimuli as separated in time but also reported correctly which stimulus in the pair preceded (or followed) the other. Although TDT provides a measure of one's capability to detect asynchrony, TOJ is likely to tap higher order abilities such as language and memory. In view of this, any differential alteration of the two indices would provide information on possibly different levels of impairment of timing functions in focal hand dystonia patients. For each index, averages of four values, one for each block, were entered in the data analysis.

Table. Demographic and Clinical Information on Writer's Cramp

Subject No.	Age/School (yr)	Diagnosis	Severity Score	Duration of Symptoms (yr)
1	29/18	WC	3	2
2	32/13	WC	6	6
3	26/18	DC	10	11
4	41/13	DC	5	8
5	46/8	WC	7	10
6	49/13	DC	7	6
7	61/11	WC	8	5
8	30/18	DC	3	10
9	55/11	DC	12	5
10	29/13	WC	4	2
11	71/11	DC	9	5
12	56/11	DC	5	2
13	23/13	WC	3	6
14	67/8	DC	6	6
Mean	43.9/12.8		6.3	6.0
SD	16.2/3.3		2.8	2.9

WC = simple writer's cramp; DC = dystonic writer's cramp; SD = standard deviation.

Results

Mean severity scores in simple (5.2) and dystonic writer's cramp (7.1) were not different according to a two-sample *t* test ($p = 0.20$). A preliminary 2 (group: simple vs dystonic cramp) X 3 (combination of stimuli: visual, tactile, and visuotactile) X 2 (side: affected vs unaffected) analysis of variance on TDT and TOJ values showed that the performance of the two dystonic subgroups was not different. In view of this, all patients were assigned to the same dystonic group.

Figure 2 shows TDTs and TOJs of writer's cramp and control subjects in the visual, tactile, and visuotactile combinations of stimuli and in the two sides of stimulation (right and left). The inspection of Figure 2 indicates three notable results. First, the two groups appear to have the same TDT and TOJ values in the visual combination. In contrast, in the tactile and visuotactile combinations writer's cramp patients appear to have higher TDT and TOJ values than controls. Second, TDT and TOJ values appear to be higher in the visuotactile than in the visual and tactile combinations. Third, TDTs and TOJs of the two groups appear to be comparable for the right (affected in writer's cramp) and left side.

These observations were confirmed by an analysis of variance for repeated measures in which the between-subjects factor was the "group" (writer's cramp and control subjects) and the within-subject factors were the "combination" of stimuli (visual, tactile, and visuotactile) and the "side" of stimulation (right and left).

The significance of the main effect group (TDT, $F_{(1,25)} = 12.3$, $p = 0.002$; TOJ, $F_{(1,25)} = 13$, $p = 0.001$) is because of the better performance of controls (TDT, 68.2 milliseconds; TOJ, 73.5 milliseconds) than writer's cramp (TDT, 154.6 milliseconds; TOJ, 163.8 milliseconds). The significant effect of combina-

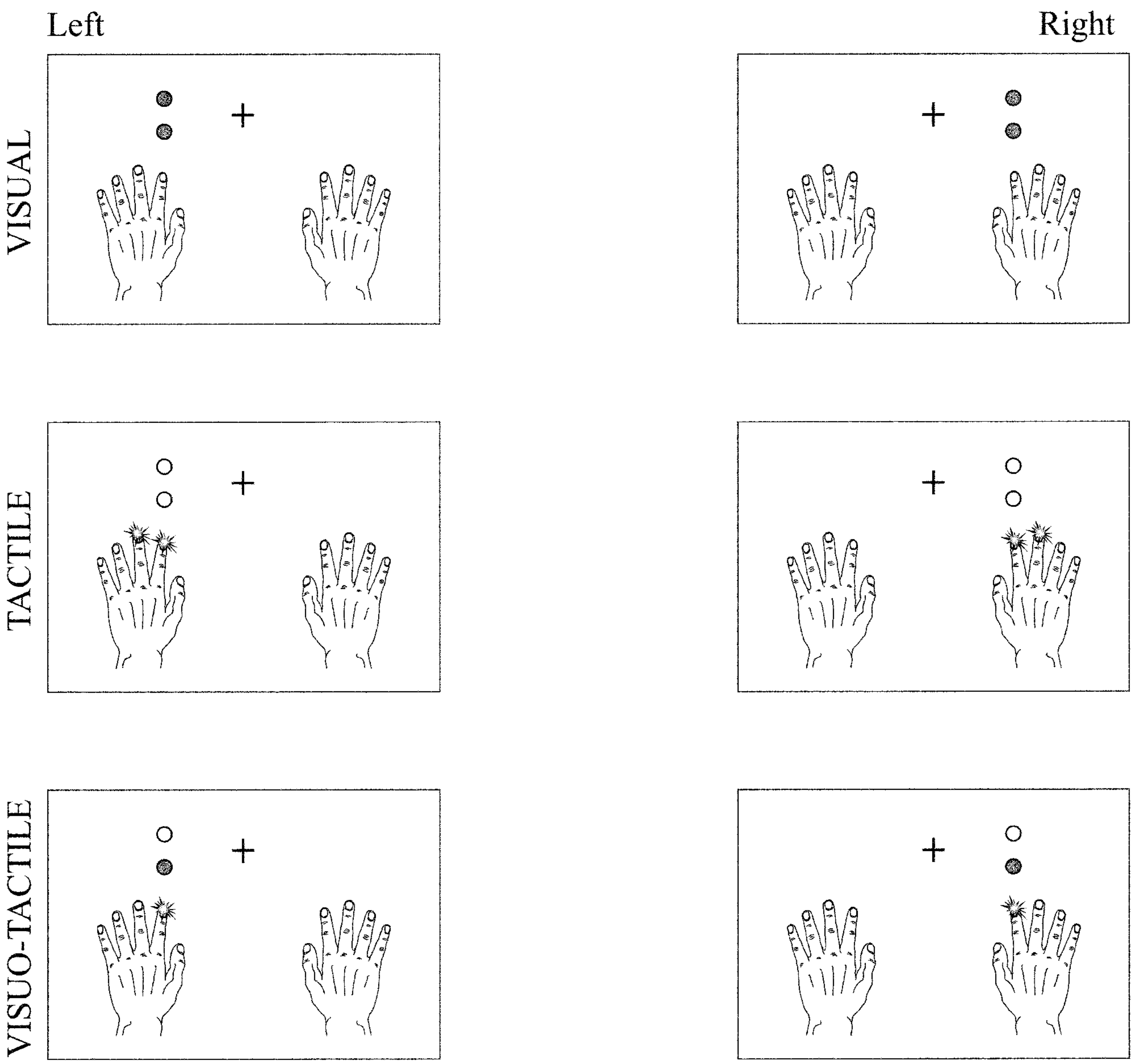

Fig 1. Schematic representation of the experimental conditions. In the visual combination two flashes (gray circles) *were delivered through light-emitting diodes positioned to the right or to the left visual field. In the tactile combinations, two electrical stimuli were positioned on the volar surface of the distal phalanx of the index and middle fingers of both hands. In the visuotactile combination, one electric stimulus and one flash* (gray circle) *were delivered within the same personal and peripersonal hemispace (either the right or the left).*

tion (TDT, $F_{(2,50)} = 63.7$, $p < 0.001$; TOJ, $F_{(2,50)} = 57.8$, $p < 0.001$) is because cross-modal tasks (TDT, 109.9 milliseconds; TOJ, 118.0 milliseconds) were more difficult than tactile (TDT, 66.4 milliseconds; TOJ, 80.5 milliseconds) and visual (TDT, 54.9 milliseconds; TOJ, 57.7 milliseconds) tasks. The interaction group X combination (TDT, $F_{(2,50)} = 16.7$, $p < 0.001$; TOJ, $F_{(2,50)} = 16.1$, $p < 0.001$) was significant. Post hoc comparisons (performed by using *t* tests and Bonferroni correction) showed that patients were significantly more impaired than controls in cross-modal than visual and tactile tasks. Indeed, differences between performance in the cross-modal and visual combinations (Cr-V) and between performance in the cross-modal and tactile combinations (Cr-T) were higher in writer's cramp (Cr-V: TDT, 83.7 milliseconds; TOJ, 92.4 milliseconds; Cr-T: TDT, 64.4 milliseconds; TOJ, 52.4 milliseconds) than in control subjects (Cr-V: TDT, 26.3 milliseconds; TOJ, 28.2 milliseconds; Cr-T: TDT, 22.4 milliseconds; TOJ, 22.4 milliseconds; $p < 0.036$ in all cases). In a similar vein, differences in performance between patients and

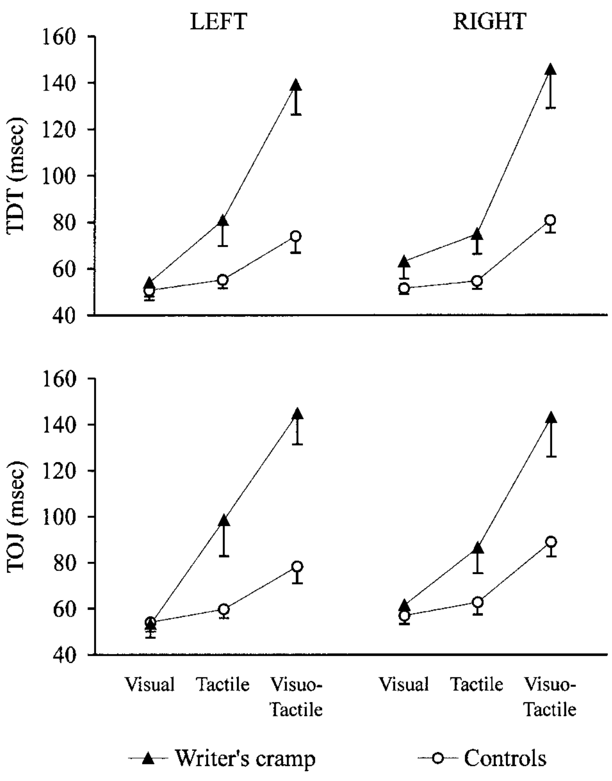

Fig 2. Mean values and standard errors (over four blocks) of temporal discrimination threshold (TDT) and temporal order judgment (TOJ) in writer's cramp and control subjects in the visual, tactile, and visuotactile combinations of stimuli.

controls were significantly higher for cross-modal (TDT, 59.0 milliseconds; TOJ, 73.2 milliseconds) than tactile (TDT, 23.7 milliseconds; TOJ, 39.7 milliseconds) and visual (TDT, 6.2 milliseconds; TOJ, 2.8 milliseconds) combinations ($p < 0.038$ in all cases). No other effects or interactions were significant. In particular, the insignificance of the triple interaction Group X combination X side implies that performance was comparable on the left and right side not only in controls but also in focal hand dystonia patients.

The Spearman correlation coefficient was used for assessing in writer's cramp the possible relationships between the severity score[15] and the performance in unimodal and cross-modal combinations, for both the left and the right sides of stimulation. A high positive correlation for tactile (Spearman correlation: TDT, $p = 0.036$; TOJ, $p = 0.011$) and visuotactile (TDT, $p = 0.036$; TOJ, $p = 0.004$) stimuli delivered on the affected side was found. Moreover, the severity of dystonic symptoms correlated also with the performance in the unaffected side both for tactile (TDT, $p = 0.001$; TOJ, $p = 0.016$) and visuotactile stimuli (TDT, $p = 0.008$; TOJ, $p = 0.008$). Scatter plots are shown in Figure 3.

No correlation between duration of illness and performance in the temporal discrimination tasks (performed by means of the product-moment Pearson correlation) was found ($r^2 < 0.50$; $p > 0.173$).

Discussion

This study assessed temporal integration of visual, tactile, and visuotactile stimuli delivered both on the intact and the dystonic side of writer's cramp patients. Previous studies on temporal discrimination in dystonia recorded the ability to perceive as separate two sequential stimuli (TDT). In addition to TDT, we re-

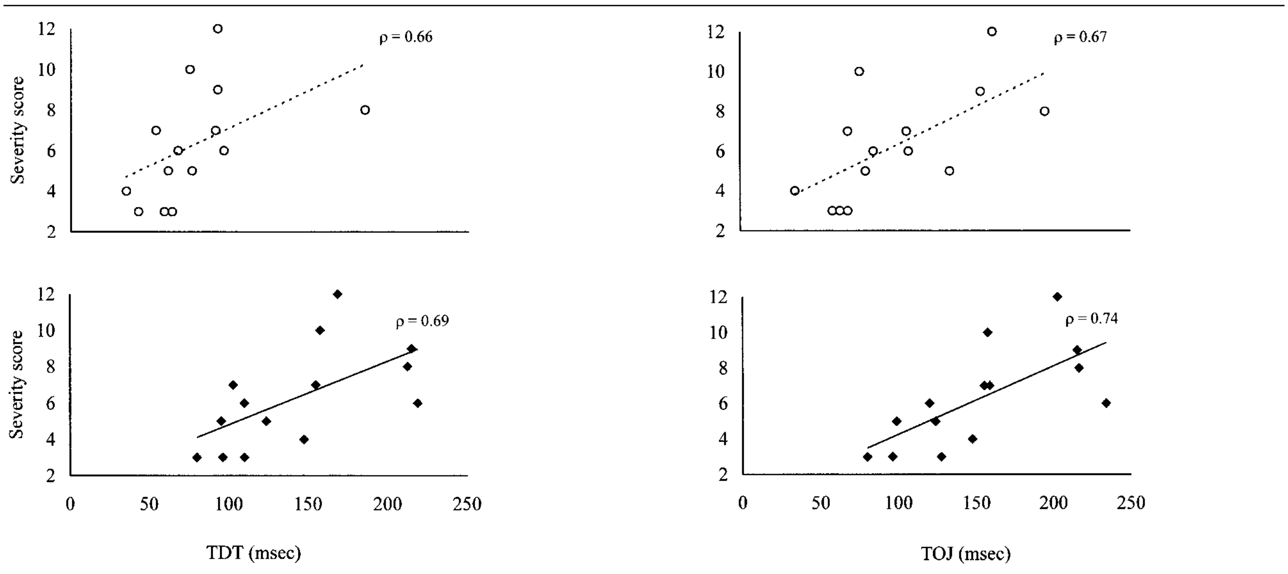

Fig 3. Scatterplots show the Spearman correlation between the severity scores and performance in the tactile (circles, dashed line) *and the visuotactile* (diamonds, solid line) *combinations. ρ indicates the Spearman correlation coefficient. TDT = temporal discrimination threshold; TOJ = temporal order judgment.*

corded TOJs, that is, the attribution of the correct stimulus priority, an ability that appears based on a multistep process requiring the integrity of specific sensory systems (somatosensory, visual, auditory) and of more complex cognitive functions.[9]

Results demonstrate a clear alteration of temporal processing of visuotactile and tactile stimuli in patients with idiopathic writer's cramp. Note that, unlike previous studies in parkinsonian patients (who presented with alterations of temporal discrimination of tactile, visual, and auditory stimuli),[16] our focal hand dystonia patients were not impaired in temporal discrimination of pairs of visual stimuli. The tactile and visuotactile temporal deficits found in our study were comparable for TDT and TOJ, thus indicating that no amplification of the deficits at the different neural levels supposedly involved in the tasks occurred. That temporal processing of tactile stimuli is impaired in our patients is in keeping with studies in patients with different disorders of the basal ganglia, including generalized[9,12] and focal hand dystonia.[10,11] TDT and TOJ values were significantly higher for visuotactile than for tactile and visual stimuli in both controls and patients. This effect can be because under these conditions both temporal processing and multisensory integration is required. Relevant to the purposes of this study, however, is the fact that differences between cross-modal and unimodal values were higher in patients than in controls. Thus, the disproportionate impairment of the ability of writer's cramp patients to perceive as temporally separated pairs of visuotactile stimuli is an entirely novel result of this study. This alteration may be particularly informative in light of the relationships between focal hand dystonia and dysfunctions of a neural network involving basal ganglia, a set of structures implicated both in temporal processing[16–18] and in the integration of visuotactile stimuli in the peripersonal space.[14] Temporal processing of tactile and visuotactile stimuli resulted impaired on both the dystonic and nondystonic hand. Interestingly, radiological and electrophysiological findings in idiopathic dystonia show that basal ganglia may be affected bilaterally despite unilateral clinical manifestations.[19–21]

The presence of a significant correlation between temporal discrimination of somesthetic stimuli and the severity of disease found in our patients may suggest that local somesthetic factors explain, at least in part, sensory deficits in focal hand dystonia. However, a high positive correlation between temporal processing and severity of disease was found also for visuotactile stimuli. Remarkably, a high positive correlation was found also when tactile and visuotactile stimuli were delivered to the unaffected side. These findings would suggest that abnormalities in timing tactile and visuotactile events occurring in the unaffected (personal or peripersonal) space may represent a susceptibility to develop focal hand dystonia in the clinically normal hand. It is known, indeed, that some writer's cramp patients who learn to write with the opposite hand, may develop over time a similar focal dystonia in the non dominant hand.[4] Unfortunately, the capability of focal hand dystonia patients to label as simultaneous or sequential pairs of tactile stimuli has been tested hitherto only on the affected hand.[10,11] Deficits of performance with tactile and visuotactile stimuli on the affected and unaffected side and their correlation with severity of illness are very much in keeping with a recent magnetoencephalography study in unilateral task-specific dystonia.[22] The study showed a clear disorganization of the somatic representation of the dystonic and nondystonic hand which correlated with the severity of clinical impairment.[22] According to the authors, sensory abnormalities of the nondystonic hand are to be considered as endophenotypic traits of dystonia. The presence of neural network alterations in asymptomatic patients is also suggested by a positron emission tomography study of DYT1 dystonia carriers in which a similar pattern of metabolic activation emerged both in patients with abnormal movements and in those who did not manifest any symptom.[23] That alterations of temporal tactile and visuotactile processing are comparable on the intact and the dystonic side suggests that temporal sensory deficits reported in this study are not a mere consequence of abnormal movements and postures, but they may be independent and even pre-exist overt manifestations of dystonia. Note also that the alterations on the nondystonic side found in our study may represent a possible behavioral index of susceptibility to develop dystonia. Future studies with our simple psychophysical paradigm in nondystonic twins, siblings, or relatives of dystonic patients may turn out to be of major importance for correlating genotypic and phenotypic variables underlying idiopathic dystonia.

In conclusion, although no casual relationship between the alterations found in our study and writer's cramp can be drawn, the results are in keeping with neuroimaging and neurophysiological studies showing that the frontal lobe-basal ganglia circuit plays a fundamental role in complex timing functions[17,24–26] and in cross-modal integration of visuotactile inputs.[14]

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