



Sensory trick efficacy in cervical dystonia is linked to processing of neck proprioception



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ABSTRACT

Background: Muscle vibration activates muscle spindles and when applied over posterior neck muscles during stance modulates global body orientation. This is characterised by a tonic forward sway response that is reportedly diminished or absent in patients with idiopathic cervical dystonia.

Objective: To investigate the impact of the sensory trick on vibration-induced postural responses.

Methods: 20 patients with idiopathic cervical dystonia and a sensory trick, 15 patients without a trick, and 16 healthy controls were recruited. Neck muscle vibration was applied bilaterally over the upper trapezius under three different conditions: 1) Quiet standing; 2) standing while performing the trick (or trick-like movement in non-responders); 3) standing while elevating the flexed arm without touching any part of the body. Centre of pressure position and whole-body orientation in the sagittal plane were analysed.

Results: Patients with a sensory trick responded similarly to healthy controls: neck muscle vibration led to an initial forward sway of the body that slowly increased during the prolonged vibration for all three conditions. This response was mainly mediated by ankle flexion. In patients without a trick, the initial sagittal sway was significantly reduced in all three conditions and the later slow increase was absent. Performance of the trick did not have an effect on any aspect of the response in either cervical dystonia group.

Conclusions: The whole-body response to neck vibration in cervical dystonia differs depending on the effectiveness of the sensory trick to alleviate the dystonic neck posture. Variable pathophysiology of proprioceptive processing may be the common factor.

1. Introduction

There are several lines of evidence suggesting that cervical dystonia (CD) is a disorder of multisensory integration and postural control [1–3]. A paradigm that has been used to investigate proprioceptive and vestibular integration in postural control involves vibration of dorsal neck muscles [4]. Vibration at 80–100 Hz applied over the muscle belly is a strong proprioceptive input which stimulates muscle spindles beneath thus simulating its lengthening. With closed eyes it creates the subjective illusion of a head-on-trunk anteflexion. This combination of an illusory lengthening of the dorsal neck muscles and of a stationary vestibular input during stance modifies the internal body representation towards a seemingly backward leaning body beneath an upright head. This unbalanced representation is subsequently corrected by a tonic

forward sway of the whole body. It has been shown that this integrated response is markedly reduced or absent in CD patients, and instead results in a more prominent head-on-trunk extension [5].

Dystonic postures can be reduced or abolished by using a so-called sensory trick (ST). This refers to episodic and specific manoeuvres mostly involving slight touch of locally confined areas at the ipsi- or contralateral face. It can alleviate dystonic posturing in a manner that seems paradoxical to the force applied in relation to the degree or direction of head rotation [6]. The benefit from performing a ST is even comparable to that from botulinum toxin injections (BTX) [7]. The underlying mechanisms are not well understood. Ramos and colleagues proposed that the ST provides an additional input to the brain that acts to normalise a pre-existing abnormal gating of sensory input to motor circuits [6]. The ability to gain benefit from a ST is variable between

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patients and may thus reflect differences in the underlying pathophysiology. For example, Kägi and co-workers found that the temporal discrimination threshold of consecutive multimodal stimuli was lower for CD patients in whom a ST produced complete alleviation of their symptoms compared with patients who experienced only partial or no effect of ST [8].

In the present study we have sought a link between the ST and the multisensory control of posture by comparing neck vibration-induced postural responses in two groups of CD patients, one with and the other without benefit of a ST. We hypothesise that 1) the pathophysiology of multisensory processing for posture control differs between these two CD groups, and 2) successful performance of a ST normalises otherwise aberrant multisensory processing.

2. Methods

The study protocol was approved by the UCL Hospitals NHS Trust ethics. All participants gave their informed consent prior to study inclusion in accordance with the declaration of Helsinki.

2.1. Subjects

36 patients with idiopathic CD with or without ST (CD + ST, CD-ST) aged between 18 and 70 years were recruited from the National Hospital of Neurology and Neurosurgery, Queen Square, London. Patients with potentially confounding health conditions such as polyneuropathy, vestibular disorders, cerebellar features or a history of stroke were not considered. CD patients with deep brain stimulation were excluded.

The diagnosis of CD was made by a movement disorders expert (K.P.B.). The presence of a ST was determined on clinical grounds by considering the patients' history and clinical observations. Patients with questionable benefit from ST or with forcible tricks, in nature more mechanical manoeuvres than true ST [6,9], were not considered. Furthermore, 16 healthy controls (HC) matched to age, height and weight were recruited. Disease severity was rated by the validated Toronto Westerns Spasmodic Torticollis Rating Scale and Unified Dystonia Rating Scale [10]. Study appointments were scheduled > 3 months after their last BTX injections.

2.2. Instrumentation

I.) Subjects stood erect on a force plate that recorded ground reaction forces (model 9286AA, Kistler, Winterthur, Switzerland, sampling frequency 200 Hz). Kinematic data were collected at 100 Hz using a 3D motion capture system (CODA, Charnwood Dynamics, Rothley, UK), which identified the position of infrared emitting diodes that were placed at 24 predefined body parts (see supplemental materials).

Two vibrators (2.5 g eccentric brass mass, 8 cm axis, 12 V DC motor) were fixed bilaterally over the upper part of both trapezii to deliver a proprioceptive stimulus to deep muscle receptors. Vibrators were enclosed in a 10 × 2 cm sealed cylindrical plastic tube, which was embedded inside a custom-made silicone mould with 8 cm bilateral fixation wings designed to contour around the neck. This assembly was fixed to the subject's skin using straps. Vibration frequency was set at 100 Hz.

II.) EMG activity of both trapezii was recorded in a separate experimental setting. Thus, muscle activity, which competed with the vibration as an additional proprioceptive afferent input at the muscle belly, was estimated as covariate. Two Ag/AgCl surface electrodes (distance: 2.0 cm) were placed at each site where vibration had been applied in the preceding part of the study. The trajectories of the arm while performing the ST and the control movement, respectively, were traced by a triaxial accelerometer (ACL300; Biometrics Ltd, UK). The incoming EMG signal was processed in Spike™ (Cambridge Electronic Devices, UK). EMG activity and accelerometry were recorded at

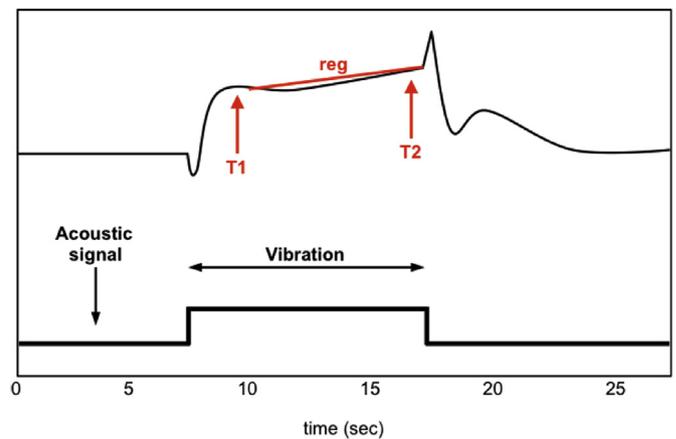


Fig. 1. Schematic CoPP curve (upper row) in relation to the output signal for neck muscle vibration (lower row). An initial ankle torque upon starting the vibration (i.e. brief negative curve excursion) is usually followed by a quick forward sway of the CoPP over 1–2 s. After this initial forward sway, there is an additional slowly progressive forward sway for the duration of the vibration. Upon cessation of the vibration, there is an abrupt backward sway followed by a short aftereffect. The study endpoints (T1, T2, reg), which were analysed in this study, are also plotted onto the CoPP curve.

2000 Hz and downsampled to 200 Hz for further analysis.

2.3. Procedure

I) Subjects stood barefooted on the force plate with their feet close together. Participants were allowed to position their forefeet 8–10 cm apart to avoid uncomfortable postures. Vibration-induced sway was recorded during three different postures: I) during quiet standing II) while performing an effective ST in CD + ST or a trick-like movement in CD-ST and HC and III) while elevating the flexed arm in front of their face, but without touching (control movement). If CD + ST had different tricks, they were instructed to use their most effective for condition II. CD-ST and HC were instructed to touch their cheek as control movement in condition II. This movement resembles the most common ST in CD [11]. Each condition was combined with and without vibration thus giving a total of six conditions. The duration of each trial was 27 s (Fig. 1). Each condition was repeated ten times. The experiment was split into blocks of six trials interrupted by short breaks to avoid fatigue. The sequence of the trials was pseudo-randomised allowing only a maximum of two identical conditions in a row. Eyes were closed during the entire trial. An acoustic tone delivered three seconds after the start of the recording signalled which movement participants were to initiate immediately and to maintain for the remainder of the recording period. Participants always performed the ST and control movement with the same hand. In the groups without an effective ST (HC, CD-ST) participants were instructed to use their dominant hand. Muscle vibration was switched on four seconds after the acoustic signal and lasted for 10 s. The recording was continued for further 10 s after switching off the vibration. Upon completion of each trial, the recordings were immediately screened for technical issues. Trials were discarded if patients made unintended movements (e.g. coughing) or if markers were not seen properly by the cameras.

2) EMG recordings of both trapezii were acquired in a separate experimental setting in a subset of CD patients and HC. Participants performed the three conditions of arm movement described above while they were standing, but without simultaneously receiving the vibration. EMG recordings were repeated three times in each condition.

2.4. Data analyses

I). Recorded raw data were analysed in MATLAB R2011a

(Mathworks, Natick, US). All recordings were filtered by a Butterworth dual low-pass filter (6th order, 12-Hz cut-off frequency). The centre of pressure position (*CoPP*) in the sagittal plane, representing whole-body displacement, was analysed as the primary endpoint. The trials from each condition were averaged and the net vibration effect was calculated by subtracting the conditions without vibration from the corresponding vibration conditions. Mean amplitude between 2 and 3s (T1) and 8–10s (T2) after vibration onset were measured relative to baseline. The steepness of the *CoPP* curve was quantified by estimating the inclination of a regression line drawn through all data points within an interval lasting from the end of the initial sagittal forward sway to the end of vibration (*reg*) (Fig. 1).

Movement of body segments were analysed as secondary endpoints. These included *ankle flexion*, *head-on-trunk extension* and *head-in-space tilt* amplitudes. The amplitudes were calculated at the times T1 and T2 as for *CoPP*. Head rotation before and after initiating the ST (or trick-like movement in HC and CD-ST) was measured to quantify the response to the ST.

II) EMG activity of the trapezii was calculated as root-mean-square from the data points within each of the aforementioned time interval during vibration (T1, T2).

2.5. Statistics

Differences of discrete variables were analysed by Fisher's exact test, continuous variables by the Wilcoxon test or Mann-Whitney-U test. In order to analyse the endpoints of this study (*CoPP*, vector angles) a mixed linear model with group ($n = 3$) and condition ($n = 3$) as fixed effects was set up. EMG activity from both trapezii was entered as covariates to account for muscle activity from the trapezii as confounding factor. We stratified EMG activity according to the limb used for the different conditions. Least significant differences were used for post-hoc exploration. Correlation analyses were performed between *head-on-trunk extension*, *head-in-space tilt* and *CoPP*. This was to address whether changes of head-on-trunk position are compensatory movements to keep the head upright in space secondary to the forward sway. The level of significance was set at $p < 0.05$.

3. Results

3.1. Cohort

There were no differences between the three groups with regard to demographics. CD+ST and CD-ST were similarly affected by the dystonia with comparable disease durations and BTX doses (Table 1).

3.2. Demonstration of the ST

Prior to ST, *head rotation* to the side was more prominent in both patient groups compared to HC (group effect: $F(2,144) = 20.0$, $P < 0.001$). Comparison of the two patient groups yielded larger head rotations to the side in CD+ST than CD-ST ($p < 0.001$). *Head rotation* decreased following the initiation of the ST in CD+ST whereas it remained relatively unchanged in HC and CD-ST (group \times condition interaction: $F(2,144) = 4.59$, $P = 0.001$) (see supplementary material).

3.3. Whole-body postural response

The body swayed forward during vibration, as shown by a prolonged forward shift of the *CoPP* (Fig. 2). There was a significant main effect of group for *CoPP* amplitude at T1 ($F(2,144) = 7.17$, $P < 0.001$) and at T2 ($F(2,144) = 20.62$, $P < 0.001$). The amplitude of the sagittal *CoPP* shift at T1 and T2 was larger in both CD+ST and HC than in CD-ST ($P < 0.010$) (Table 2). There was an additional slow increase of the *CoPP* amplitude during the period of prolonged vibration (*reg*: $F(2,144) = 7.62$, $P = 0.001$). This effect was present only in HC and CD

Table 1
Demographics and disease characteristics.

	CD+ST	CD-ST	HC	p-values
Age	54.4 \pm 8.5	60.7 \pm 8.3	58.7 \pm 10.0	0.111
Sex (males/total)	6/20	6/15	5/16	0.806
Height	168.7 \pm 9.8	167.3 \pm 10.5	168.9 \pm 18.8	0.598
Weight	71.9 \pm 11.7	73.8 \pm 13.8	73.8 \pm 18.8	0.907
BMI	25.3 \pm 3.5	26.4 \pm 4.5	25.6 \pm 5.1	0.759
Disease duration	15.3 \pm 12.4	16.5 \pm 12.7	n.a.	0.842
Family history	7/20	3/15	n.a.	0.458
Dystonic head tremor	8/20	7/15	n.a.	0.741
Patients receiving BTX	18/20	14/15	n.a.	0.727
Patients receiving BTX to the trapezius	9/20	4/15	n.a.	0.267
BTX dose (trapezius) ^a	41.3 \pm 60.9	39.3 \pm 73.6	n.a.	0.961
BTX dose (total) ^a	481.3 \pm 138.3	558.7 \pm 221.1	n.a.	0.136
TWSTRS I	17.6 \pm 5.1	17.7 \pm 3.8	n.a.	0.967
TWSTRS II	9.9 \pm 3.8	7.1 \pm 6.0	n.a.	0.106
TWSTRS III	8.7 \pm 9.5	6.3 \pm 3.7	n.a.	0.364
UDRS	13.2 \pm 7.9	11.7 \pm 5.8	n.a.	0.551

Abbreviations: BMI – body mass index, BTX – Abobotulinum toxin, CD – patients with idiopathic cervical dystonia, HC – healthy controls, n.a. – not applicable, ST – sensory trick, TWSTRS – Toronto Westerns Spasmodic Torticollis Rating Scale, UDRS – Unified Dystonia Rating Scale.

^a BTX dose is provided as units.

+ST but not in CD-ST ($p < 0.020$).

3.4. Correlation of EMG activity with *CoPP*

EMG recordings from a subset of 18 CD+ST, 10 CD-ST and 11 HC were available. EMG activity from the trapezius ipsilateral to the limb used for the ST and control movements correlated with the forward shift of *CoPP* at T1 ($F(1,106) = 6.97$, $P = 0.010$) and less strongly at T2 ($F(1,106) = 4.25$, $P = 0.042$). The EMG activity from the contralateral trapezius correlated with the *CoPP* at T1 ($F(1,106) = 5.76$, $P = 0.018$). When EMG activity was entered as a covariate into the model, there was still a main effect of group for *CoPP* at T2 ($F(2,106) = 8.46$, $P < 0.001$) in this subset of participants, similar to that seen in the whole cohort (see 3.3).

3.5. Body-segment postural responses

The vibration-evoked forward body sway was largely produced by *ankle flexion* (group effect: T1: $F(2,144) = 9.53$, $P < 0.001$; T2: $F(2,144) = 11.11$, $P < 0.001$), which was more prominent in both HC and CD+ST than in CD-ST ($P \leq 0.001$). Vibration also gave rise to a *head-on-trunk extension* in all three groups. It was larger in CD+ST than in CD-ST. This difference was only seen at the later time point (group effect: T2: $F(2,144) = 4.19$; $P = 0.017$; post-hoc analysis: $P = 0.021$). Likewise, *head-in-space backwards tilt* was larger in CD+ST than in CD-ST at the later time point (T2: $F(2,144) = 5.32$, $P = 0.006$; post-hoc: $P = 0.003$). There was no group \times condition interaction for any of these tilt angles, which would be required to show a ST-specific effect in CD+ST. A strong correlation between the amplitude changes of *head-in-space tilt* and *head-on-trunk extension* was seen in all three groups for each condition, but there was not a significant correlation between *head-in-space tilt* and *CoPP* nor *head-on-trunk extension* and *CoPP* (see supplementary material).

4. Discussion

Previous studies have consistently found reduced postural responses to dorsal neck vibration, a strong proprioceptive stimulus, during stance

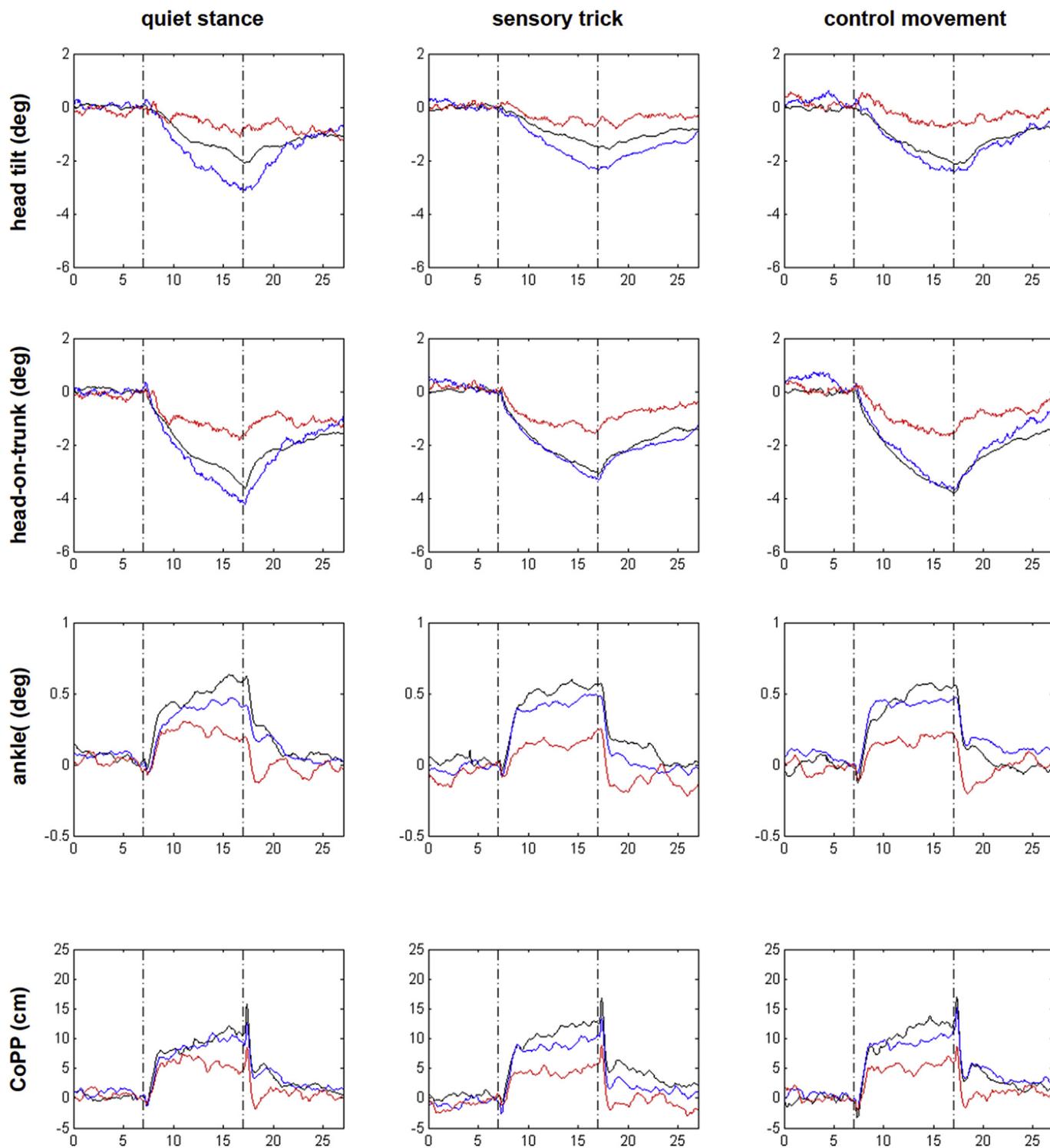


Fig. 2. The results of the CoPP and kinematic analysis of the ankle and different neck angles are shown. The x-axis represents the time course of the experiment (sec), the y-axis the amplitude of the response in relation to baseline, which was set to 0. The dashed lines indicate the start and the end of the vibration. The responses from healthy control persons are the curves in black, those from CD+ST in blue and those from CD-ST in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

in CD cohorts [5,12,13]. However, neither the efficacy of a ST nor performance of a ST was investigated in these studies. Our current results therefore enrich the picture with the new finding that the postural response to dorsal neck vibration was smaller than control responses only in the CD group unable to use a ST to alleviate their symptoms (CD-ST). Those who gained benefit from a ST (CD+ST) showed larger responses than CD-ST and were not different to healthy control

participants. These contrasting responses in the two CD groups support our first hypothesis that there are differences in the pathophysiology of CD patients with and without an effective ST, and that one such difference relates to proprioceptive processing for posture control. However, we did not observe any effect that was specifically linked to the performance of an effective ST itself.

We included EMG activity of the trapezius as confounding factor in

Table 2
Study endpoints (CoPP, ankle flexion, head orientation).

		CD+ST	CD-ST	HC
CoPP (cm)				
T1	quiet standing	7.4 ± 5.0	6.2 ± 6.3	7.8 ± 4.3
	sensory trick	8.1 ± 5.1	4.3 ± 3.5	9.5 ± 6.3
	control movement	9.1 ± 4.6	4.9 ± 3.8	8.8 ± 5.0
T2	quiet standing	10.0 ± 4.2	5.0 ± 4.5	11.3 ± 6.0
	sensory trick	10.0 ± 5.2	5.2 ± 5.0	12.6 ± 5.8
	control movement	10.4 ± 6.4	6.0 ± 3.9	12.5 ± 5.1
Reg	quiet standing	0.5 ± 0.6	-0.1 ± 0.6	0.6 ± 0.6
	sensory trick	0.3 ± 0.7	0.1 ± 0.5	0.5 ± 0.6
	control movement	0.4 ± 0.7	0.2 ± 0.5	0.6 ± 0.9
ankle flexion (deg)				
T1	quiet standing	-0.3 ± 0.3	-0.1 ± 0.8	-0.4 ± 0.3
	sensory trick	-0.3 ± 0.3	0.0 ± 0.6	-0.5 ± 0.4
	control movement	-0.4 ± 0.3	0.0 ± 0.9	-0.4 ± 0.3
T2	quiet standing	-0.4 ± 0.3	0.0 ± 1.0	-0.5 ± 0.3
	sensory trick	-0.4 ± 0.3	0.1 ± 0.9	-0.5 ± 0.3
	control movement	-0.4 ± 0.4	0.1 ± 1.1	-0.5 ± 0.3
head-on-trunk extension (deg)				
T1	quiet standing	1.9 ± 3.5	1.1 ± 1.2	1.6 ± 1.8
	sensory trick	1.8 ± 1.5	0.9 ± 1.1	1.6 ± 1.2
	control movement	1.6 ± 3.1	1.2 ± 1.3	1.9 ± 1.7
T2	quiet standing	3.9 ± 4.8	1.7 ± 2.2	3.2 ± 2.3
	sensory trick	3.1 ± 2.0	1.5 ± 2.0	2.9 ± 1.8
	control movement	3.3 ± 4.2	2.0 ± 2.4	3.6 ± 2.5
head tilt (deg)				
T1	quiet standing	-1.2 ± 3.2	-0.4 ± 1.2	-0.7 ± 1.9
	sensory trick	-0.9 ± 1.7	-0.3 ± 1.4	-0.6 ± 1.3
	control movement	-0.9 ± 2.8	-0.0 ± 1.4	-0.9 ± 1.7
T2	quiet standing	-2.9 ± 4.5	-0.9 ± 1.9	-1.8 ± 2.5
	sensory trick	-2.2 ± 2.1	-0.6 ± 1.8	-1.4 ± 2.0
	control movement	-2.3 ± 4.6	-0.7 ± 2.2	-1.9 ± 2.5

Abbreviation: CD – patients with idiopathic cervical dystonia, CoPP – Centre of Pressure Position, HC –healthy control, ST – sensory trick.

our statistical model. This EMG activity arose from muscle activity due to the dystonia and/or the performed task. Theoretically, the muscle activity may have activated sensory endings and competed with vibration-evoked end-organ activation, or else it may have altered mechanical transmission of the vibration within the muscle [4]. Because there was still a strong group effect after correcting for EMG activity, we conclude that there is a genuine difference in proprioceptive processing between the two patient groups that is associated with the ST itself. The lack of recordings from other neck muscles, however, limits the estimation of concurrent muscle activity as confounding factor. Furthermore, measuring muscle spindle activity by microelectrode recording of sensory afferents would have been a more precise method to assess the impact of confounding muscle activity on spindle activity, but this approach would technically not have been feasible in our paradigm.

One difference between our data and previous reports concerns the focal neck extension response to vibration. Lekhel and colleagues reported exaggerated neck extension responses to the vibration in their CD patients, even though the group as a whole showed diminished postural sway responses [5]. We did not observe a significantly greater head-on-trunk extension in either of our CD groups. The reason for these different observations remains unclear, although it should be noted that the period of vibration was shorter in our study [5]. Nonetheless, it seems that in our CD-ST cohort, the reduced global whole-body postural response was not instead replaced by an enlarged focal body-segment neck-extension response. One might conceive of such a reciprocal arrangement between the global and focal responses if the proprioceptive input remained normal but could not be integrated with vestibular signals to drive a whole-body response. The proprioceptive input might then be interpreted solely as a simple muscle stretch to be counteracted by a muscle shortening causing an enhanced focal neck-on-trunk extension. However, the fact that both global and local

responses were attenuated in the CD-ST group suggests that proprioceptive input was attenuated before it engaged motor processes.

Because vibration predominantly stimulates muscle spindles [4], a spindle afferent deficit in CD-ST may be considered as one possible origin of this group difference. Muscle spindles are innervated through β - and γ -motoneurons, which elicit contractions of intrafusal muscle fibres [14]. Intrafusal contraction avoids a slackening of the spindles during muscle shortening and adjusts muscle spindle sensitivity to stretch [14–17]. A different γ -drive to the neck muscle spindles in the two clinical groups is therefore a possible explanation for our results. Indeed, in one study an overactive γ -drive to specific forearm muscles at rest was considered likely to be present in patients with writer's cramp since vibration-evoked dystonia was abolished by lidocaine [18], which preferentially blocks small diameter γ -motoneurons. In our case we would have to postulate an abnormally reduced, rather than overactive, γ -drive in the CD-ST group to account for their reduced postural responses. BTX injections may theoretically have influenced muscle spindle sensitivity since they lead to a transient denervation of muscle spindles [14,19–21]. In our study, however, an equal proportion of participants were injected in the trapezius with similar doses of BTX in both patient groups. Furthermore patient visits were scheduled when their treatment effect was expected to have worn off.

A spindle afferent gain deficit could be another explanation for our results, since in dystonia patients abnormalities in proprioception were found at the spinal and brainstem levels, as well as the cortex [22]. Neuronal activity within some of these network nodes can be modulated by ST [23]. The neural integrator for head control in the brainstem, arguably located in the interstitial nucleus of Cajal, has been proposed as a central network node in CD and receives direct projections from Ia afferents [24]. Plasticity of cerebello-thalamo-cortical motor loops is presumably modulated at this site by proprioceptive input from the neck, although there are substantial differences between patients with CD and healthy persons in how neuronal plasticity is controlled within these loops [25]. Alternatively, reduced central transmission of spindle afferent information could have arisen at the spinal level by increased presynaptic Ia afferent inhibition. Descending projections from the interstitial nucleus of Cajal terminate at motor neurons which supply the neck muscles [26]. They also project to sections of the spinal cord where terminals of Ia afferent fibres are located [26,27].

Because there was no ST-specific effect on processing of proprioceptive information in either CD group, a proprioceptive deficit alone probably does not explain the ST effectiveness. However it seems unlikely that CD+ST and CD-ST can be regarded as distinct phenotypes since CD+ST may lose their trick over time [28]. Nonetheless, our findings are interesting as they indicate that preserved proprioception could be a prerequisite for experiencing alleviation by a ST. Presumably a preserved gain for proprioceptive information may also apply to the upper limb performing the trick. This input could allow higher-level networks to better integrate this spatial information into the body schema, possibly acting as a surrogate reference frame for head control.

In summary, we have shown a difference in one pathophysiological aspect of multisensory processing for control of posture between patients with and without an effective ST. In a next step it would be interesting to know what happens to information from other sensory systems such as visual and vestibular information during the performance of the trick. Also the role of proprioceptive inputs from the arm warrants further study.

Authors' roles

- 1) Research project: A. Conception, B. Organization, C. Execution;
- 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Florian Brugger: 1A-C, 2A-B, 3A
 Amy Peters: 1B-C
 Dejan Georgiev: 1B-C, 2C, 3B
 Georg Kägi: 1A, 2C, 3B
 Bettina Balint: 1B-C, 3B
 Kailash P. Bhatia: 1A-C, 3B
 Brian L. Day: 1A-C, 2A, 2C, 3B

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2018.11.029>.

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