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Forbes, Patrick A.; de Bruijn, Edo; Nijmeijer, SWR; Koelman, JHTM; van der Helm, Frans C T; Schouten, Alfred C.; Tijssen, MAJ; Happee, Riender

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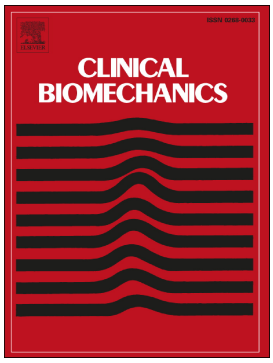

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Authors: Patrick A. Forbes[1,2], Edo de Bruijn[1], Sebastiaan W.R. Nijmeijer[4], Johannes H.T.M. Koelman[4], Frans C.T. van der Helm[1,3], Alfred C. Schouten[1,3], Marina A.J. Tijssen[4,5], Riender Happee[1]

[1]Department of Biomechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

[2]Department of Neuroscience, Erasmus University Medical Centre, Rotterdam, The Netherlands

[3]Laboratory of Biomechanical Engineering, Institute for Biomedical Technology and Technical Medicine (MIRA), University of Twente, Enschede, The Netherlands

[4]Department of Neurology and Clinical Neurophysiology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

[5]Department of Neurology, University Medical Centre Groningen (UMCG), University of Groningen, Groningen, The Netherlands

Corresponding author:
Patrick A. Forbes
P.O. Box 2040
Rotterdam, 3000CA
The Netherlands
E-mail: p.forbes@erasmusmc.nl

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ABSTRACT

Background

Effective sensorimotor integration is essential to modulate (adapt) neck stabilization strategies in response to varying tasks and disturbances. This study evaluates the hypothesis that relative to healthy controls cervical dystonia patients have an impaired ability to modulate afferent feedback for neck stabilization with changes in the frequency content of mechanical perturbations.

Methods

We applied anterior-posterior displacement perturbations (110 s) on the torso of seated subjects, while recording head-neck kinematics and muscular activity. We compared low bandwidth (0.2-1.2 Hz) and high bandwidth (0.2-8 Hz) perturbations where our previous research showed a profound modulation of stabilization strategies in healthy subjects. Cervical dystonia patients and age matched controls performed two tasks: (1) maintain head forward posture and (2) allow dystonia to dictate head posture.

Findings

Patients and controls demonstrated similar kinematic and muscular responses. Patient modulation was similar to that of healthy controls ($P > 0.05$); neck stiffness and afferent feedback decreased with high bandwidth perturbations. During the head forward task patients had an increased neck stiffness relative to controls ($P < 0.05$), due to increased afferent feedback.

Interpretation

The unaffected modulation of head-neck stabilization (both kinematic and muscular) in patients with cervical dystonia does not support the hypothesis of impaired afferent feedback modulation for neck stabilization.

Keywords: cervical dystonia; neck afferent feedback modulation; head-neck stabilization; dystonic posture; sensorimotor integration

HIGHLIGHTS

- We studied head-neck stabilization in controls and patients with cervical dystonia
- Neck reflex modulation was evaluated across torso perturbations and postural task
- Patients have elevated neck stiffness accompanied by increased neck reflexes
- Nevertheless, reflex modulation was similar in both groups across perturbations
- Cervical dystonia does not impair neck reflex modulation in head-neck stabilization

1 INTRODUCTION

Cervical dystonia (CD) is characterized by involuntary sustained muscle contractions resulting in abnormal movement or posture and impaired head movement control. Although the pathophysiology of the disorder is not fully understood, dysfunction in the basal ganglia is thought to be the primary origin (Berardelli et al.,1998;Breakefield et al.,2008;Hallett,2006). Recent studies however have described the disorder as a network problem, involving other brain regions including the cerebellum, thalamus, midbrain and cerebral cortex (Neychev et al.,2011). The involvement of abnormal sensory system features has led several researchers to suggest that CD is a sensorimotor disorder (Abbruzzese and Berardelli,2003;Breakefield et al.,2008;Kanovsky et al.,2003). For example, disturbed vestibular function in patients with CD is observed under several contexts, viz. a directional preference of the vestibular nystagmus response (Bronstein and Rudge,1986;Stell et al.,1989), delayed responses during combined vestibular and voluntary neck muscle control (Munchau et al.,2001), and altered postural responses during stance under normal conditions (Vacherot et al.,2007) and while applying neck muscle vibration (Lekhel et al.,1997). Similarly, disturbed proprioceptive integration is observed in patients with CD, viz. inaccurate knowledge and control of head posture (Anastasopoulos et al.,2014;Anastasopoulos et al.,2003), trajectory abnormalities during arm reaching tasks (Pelosin et al.,2009), and orienting abnormalities during quiet stance and dynamic stepping movements (Bove et al.,2004;Bove et al.,2007). While these studies implicate CD as a disorder of sensorimotor integration, the effects of CD on the patient's ability to modulate afferent feedback contributions during upright head-neck stabilization while exposed to torso perturbations is yet to be investigated.

Condition dependent modulation (adaptation) of afferent feedback is particularly critical for neck muscle control. This includes short and medium latency reflexes as well as longer latency responses to perturbations, originating from muscular, vestibular and visual feedback. Neck afferent feedback contributions are modulated with experimental conditions such as head inertia (Goldberg and Peterson,1986;Keshner et al.,1999;Reynolds et al.,2008), mental set (Keshner,2000) and the frequency content of torso movement (Forbes et al.,2013). However, to what degree these modulating behaviours remain functional in patients with CD is unknown. Therefore, through comparison of head-neck stabilization in CD patients to healthy controls, we may find evidence of disturbed afferent feedback modulation and provide further insight into disorder related disturbances in sensorimotor integration.

In neck muscles, patients with CD have increased facilitation of motor evoked potentials and reduced cortical silent periods (Amadio et al.,2000). These responses are thought to occur via impaired intracortical inhibition, similar to the increase in cortical excitability and decrease in intracortical inhibition during transcranial magnetic stimulation (Abbruzzese et al.,2001;Di Lazzaro et al.,2009;Ikoma et al.,1996;Kanovsky et al.,2003;Mavroudakis et al.,1995;Siggelkow et al.,2002). Therefore the sustained muscle contractions associated with CD may be related to an impaired supraspinal modulation of neck afferent feedback for head-neck stabilization. This study evaluates the stabilization responses of patients with CD during mechanical torso perturbations designed to evoke modulation of afferent feedback for the control of neck muscles. We hypothesized that CD patient's ability to modulate afferent feedback across perturbations varying in frequency content would be impaired, and therefore differ from healthy controls. Patients and matched controls were exposed to anterior-posterior torso perturbations while seated and we quantified effects on head kinematics, afferent feedback and intrinsic (co-contraction) muscle activity.

2 METHODS

2.1 Subjects

Ten cervical-dystonia (CD) patients [five men and five women, age 56 year (SD 11)] showing mainly rotational movements (twisting of the neck) and ten age and gender matched controls [age 54 years (SD 13)] participated in this study (see Table 1). The experimental protocol was in accordance with the Declaration of Helsinki and was approved by the ethics committee at the Delft University of Technology and the medical ethics committee at the Amsterdam Medical Centre. All patients were previously treated with botulinum toxin injections and the experiments were performed at least 3 months after the last injections. The dystonia severity was quantified using the clinical Tsui scale (Tsui et al.,1986) and the angle of head rotation during relaxed conditions was measured using a motion capture system (see *Data recording and processing*).

2.2 Experiments

The experimental protocol and data analysis were similar to a previous study where healthy volunteers showed a profound modulation of stabilization strategies with perturbation bandwidth (Forbes et al.,2013). In short, subjects were restrained by a four-point harness to a rigid chair with a 10° inclined backrest mounted on a motion platform and exposed to

anterior-posterior perturbations (see Fig. 1). Results displayed a marked modulation (adaptation) of afferent feedback, in particular comparing the lowest (0.2-1.2 Hz) and highest bandwidth (0.2-8 Hz) perturbations. During conditions where the perturbation exceeded the oscillatory (i.e. natural) frequency of the human head-neck system, the central nervous system (CNS) is thought to decrease afferent feedback contributions (Forbes et al.,2013;Kearney et al.,1997;Mirbagheri et al.,2000;Schouten et al.,2008), likely to prevent oscillatory behaviour as a result of the time delay within afferent feedback loops. Subsequently, in this study we adopted the lowest bandwidth (0.2-1.2) and highest bandwidth (0.2-8 Hz) perturbations from Forbes et al. (2013) with minor modifications described below. Exposing both patients and controls to these two perturbations while performing head-neck stabilization tasks allowed us to examine our hypothesis of impaired afferent feedback modulation in patients.

2.2.1 Perturbations

Anterior-posterior displacement perturbations were applied through the chair. The two perturbations (low and high bandwidth) were composed of multiple sinusoids with random phase and were therefore random appearing to the subjects. Both perturbations were designed to have a flat power spectrum in velocity up to the highest frequency and are referred to further as low (LOW; 0.2-1.2 Hz) and high (HIGH; 0.2-8 Hz) bandwidth conditions. In addition, all subjects performed a no perturbation (NP) condition where no perturbation was applied throughout the trial.

Each test was 110 s long, comprised of 20 consecutive identical perturbation cycles, as well as 5 s phase-in and phase-out periods. Perturbation cycles were 5 s in length, providing a frequency resolution of 0.2 Hz. Between 0.2 and 2.0 Hz, excited frequencies were equidistantly spaced, while above 2 Hz excited frequencies were logarithmically spaced, resulting in 6 and 16 frequencies for LOW and HIGH conditions respectively. To justify using linear analysis (see *Data recording and processing*), head deviations relative to the torso were kept small within each condition (< 10 mm). In preliminary tests, patients reported the high frequency content of the HIGH perturbations to be discomforting; therefore, the amplitude of the HIGH perturbation was reduced by 40% for both patient and control groups. Although perturbation amplitude can influence head-neck system dynamics, the effect is minor relative to bandwidth changes and the head-neck system can be considered close to linear across the amplitudes applied here (Forbes et al.,2013;Keshner,2003;Keshner et al.,1995).

2.2.2 Task instruction

Patients and controls performed two tasks: (1) maintain head upright and allow the dystonia to dictate head posture (dystonic posture) with eyes closed and (2) maintain head upright and facing forward (head forward) while focusing at a stationary visual target 3 m away. The dystonic posture task represents a condition where dystonia is naturally manifest in patients, while in the head forward task we expected patients to resist the dystonia with additional muscle activity, possibly resulting in stiffening of the neck. During the dystonic posture task, healthy controls mimicked the dystonic posture of their matched patient and were asked to maintain this position (with eyes closed) as well as possible. This ensured that sensory realignment and changes in biomechanics with a different head posture would be comparable across groups. Both tasks were performed with all three perturbation conditions (LOW, HIGH and NP). All conditions were performed twice providing a total of 12 trials of 110 s.

2.3 Data recording and processing

Kinematic data of the head, trunk and platform were recorded at 200 Hz using an Oqus 6-camera motion capture system (Qualisys AB, Gothenburg, Sweden). The markers were used to define rigid bodies representing the head, trunk and platform. The x-positions (i.e. the anterior-posterior direction) of the torso (X_{T1}), head in global space (X_{GH}) and head relative to T1 (X_{RH}) were differentiated to obtain velocities. Head pitch displayed a similar behaviour as X_{RH} (Forbes et al.,2013) and is therefore not reported here. Head yaw velocity (ω_H , left-to-right rotation) was also analysed as an indicator of the twisting nature of torticollis.

Muscle activity (EMG) was recorded using surface electrodes (2 mm diameter electrode pickup, 2 cm between electrodes, Porti, TMSi, Twente, NL) bilaterally from sternocleidomastoid (SCM), semispinalis capitis (SEMI) and splenius capitis muscles (SPL). These muscles contribute to head-neck stabilization in the anterior-posterior direction (Keshner,2003). EMG was recorded at 2000 Hz and high-pass filtered (20 Hz second-order zero phase Butterworth) to remove motion artefacts, rectified and normalized to average muscle activity obtained from isometric maximum voluntary force experiments performed in addition to the perturbation trials (de Bruijn et al.,2015). Briefly, subjects were seated and restrained with their head fixed in an isometric device. Subjects applied maximal transversal forces in flexion (SCM) and extension (SPL/SEMI) for 8 s (2 repetitions) while visual feedback of the generated force was provided.

Normalized EMG was used to derive two separate EMG signals representing 1) baseline muscle activity (e_b) counteracting gravity and including co-contraction, and 2) afferent feedback resulting in time varying activity in response to perturbations (Forbes et al.,2013). Baseline muscle activity (e_b), was calculated by low-pass filtering separate EMG signals (20 Hz 2nd order Butterworth), averaging left and right muscles, and then taking the mode over the entire test duration. The mode is the most common value where values are rounded to the nearest thousandth generating a bin size of 0.001. Afferent feedback was represented by the "weighted neck muscle EMG signal" $e_w(t) = w_1e_1(t) + w_2e_2(t) + w_3e_3(t) + w_4e_4(t) + w_5e_5(t) + w_6e_6(t)$ combining activity of the six flexor and extensor muscles as a single signal similar to our previous study (Forbes et al.,2013).

Kinematic ($\dot{X}_{T1}$ and $\dot{X}_{RH}$) and weighted feedback EMG (e_w) signals were used to estimate frequency response functions (FRFs). FRFs describe the dynamic behaviour of a system as a function of frequency using magnitude and phase, where magnitude indicates the amplitude of the output relative to the input and phase indicates the timing of the output relative to the input. The power spectra (auto and cross) used to estimate the FRFs were calculated and averaged in the frequency domain over the 40 five second segments. The kinematic FRF (kFRF) was calculated between input torso motion ($\dot{X}_{T1}$) and output relative head motion ($\dot{X}_{RH}$) and describes the dynamic behaviour of the system, including effects of associated feedback pathways (see block diagram in Fig. 2). The EMG FRF (eFRF) was calculated between the measured head motion ($\dot{X}_{RH}$) and weighted EMG (e_w), and provides an inferred open-loop estimate (Fitzpatrick et al.,1996;van der Kooij et al.,2005) of afferent feedback caused by head motion. Thus, variation of eFRFs with condition directly reflects modulation of afferent feedback gains. Variation of kFRFs can reflect modulation of feedback and/or modulation of co-contraction (see block diagram in Fig. 2). Coherence between input and output signals was used to assess the quality of correlation between these two signals. In general, coherence ranged from 0.55-0.95 for kFRFs and from 0.25-0.65 for eFRFs in both patients and controls, exceeding the 95% confidence threshold (0.074) for all frequency points (Halliday et al.,1995).

2.4 Statistical analysis

The effects of bandwidth (LOW and HIGH), task (dystonic posture and head forward) and group (patients and controls) on the root-mean-square (RMS) kinematic responses were

evaluated using a 2×2×2 repeated measures ANOVA. Because NP conditions did not elicit afferent feedback caused by perturbations, a separate 2×2 rm-ANOVA was performed on the NP data. To evaluate whether controls reproduced the posture of the matched patients, the difference in head yaw posture between patients and controls was assessed using 3×2 repeated measures ANOVAs [perturbation (LOW, HIGH and NP) and group] separately for the dystonic posture and head forward tasks.

Similar statistical analyses on the baseline EMG (e_b) used a 3×2×2 repeated measures ANOVA to examine effects of perturbation (NP, LOW and HIGH) and task (head forward and dystonic posture) across both groups (patients and controls). For analysis of the kFRFs and eFRFs we used 2×2×2×6 MANOVAs (bandwidth×task×group×frequency points). Here we evaluated magnitude and phase at the lowest six frequency points (i.e. 0.2-1.2 Hz) present in both bandwidth conditions. A significance of 0.05 was used for all analyses.

3 RESULTS

3.1 Head posture

In three patients clear tremor or jerking movements were observed during no-perturbation (NP) trials. Patients 2 and 8 showed pronounced movement tremor, identified as clear peaks in the autospectra of head yaw (twist) velocity at 4.5 and 4.0 Hz respectively. Patient 7 showed jerking head movement and an overall increase in the autospectra of head yaw velocity across a wide bandwidth (0.2-8 Hz) in comparison to all controls and non-tremulous patients. To exclude the influence of tremor or jerking movements on the stabilization behaviour, these patients were removed from further analyses. Because we used age and gender matched controls who mimicked patient specific head orientations during the dystonic posture task, the three matched controls were also removed, resulting in 7 patients [five men and two women, mean age 54 years (SD 12)] and 7 controls [mean age 51 years (SD 15)].

Patients remarked that the head forward task was more strenuous than the dystonic posture task, particularly during perturbations. During both tasks, mean absolute head yaw (twist) of patients and controls was not significantly different across perturbations [$P = 0.184$, $F_{1,12} = 2.0$, head yaw relative to NP: dystonic posture = 4.8° (SD 4.8) and head forward = 2.6° (SD 2.1); across both groups; n = 28]. This indicates that subjects maintained a similar posture during trials with and without perturbations. During the head forward task, patient mean absolute head yaw was not significantly different from controls [patients = 6.9° (SD 5.6) vs.

controls = 2.3° (SD 2.3); P = 0.056, $F_{1,12}$ = 4.5; across all perturbations n = 21 per group], indicating that patients succeeded in countering the dystonic posturing effects of CD when trying to keep their head forward. During no-perturbation trials, patient mean head yaw varied from 2-66°, see Table 1 and Fig. 1B. As instructed, healthy controls matched the patient head yaw throughout all dystonic posturing conditions, however they did not match the patient yaw precisely, resulting in patient vs. control differences of 13.2° (SD 10.6) across all dystonic posturing conditions (NP, LOW and HIGH; n = 21).

3.2 Head kinematics and muscle co-contraction

Between patients and controls, no significant difference was found for the majority of RMS kinematic measures across all conditions (i.e. both with and without perturbation, see Fig. 3). An exception was head yaw velocity ω_H . Even after removal of the 3 tremulous patients as described above, the RMS head yaw velocity was 1.3-2 times larger in patients relative to controls (P = 0.026, $F_{1,12}$ > 6.4) with perturbation (i.e. LOW and HIGH, see Fig. 3). An increase in patient baseline EMG (e_b) was found for all muscles – in some conditions 1.5-2 times larger – both with and without perturbations; however, these differences were not significant, likely because of the large variability within the patient group (see Fig. 4; SCM: P = 0.355, $F_{1,12}$ = 1.0; SPL: P = 0.355, $F_{1,12}$ = 0.9; SEMI: P = 0.374, $F_{1,12}$ = 0.9). To ensure that trends in baseline EMG were not confounded by differences in muscle strength across patients and controls (as used for scaling), we compared forces generated during maximum voluntary contraction (MVC) tasks and found no significant difference between patients and controls (flexion: patients = 92 N (SD 29), controls = 76 N (SD 40) , t_{18} = 1.1, P = 0.294; extension: patients = 162 N (SD 42), controls = 153 N (SD 79), t_{18} = 0.3, P = 0.765; independent samples t-test).

Across tasks there was a slight increase in RMS global head velocity during the dystonic posture task relative to the head forward task (see Fig. 3 $\dot{X}_{GH}$: P < 0.001, $F_{1,12}$ = 25.7) but no significant change of relative head velocity or head yaw velocity (see Fig. 3, $\dot{X}_{RH}$: P = 0.833, $F_{1,12}$ = 0.1; ω_H : P = 0.202, $F_{1,12}$ = 1.8) for both patients and controls. This was accompanied with an increase in baseline EMG of SPL and SCM during the dystonic posture task relative to the head forward task for patients and controls (SPL: P = 0.039, $F_{1,12}$ = 5.4, SCM: P = 0.045; $F_{1,12}$ = 4.8). However, separate ANOVAs performed on the two groups indicated this to be significant only for the control group (SCM: P = 0.016, $F_{1,6}$ = 11.0; SPL: P = 0.023, $F_{1,6}$ = 9.3; SEMI: P = 0.030, $F_{1,6}$ = 8.1).

Increasing bandwidth (HIGH vs. LOW) had a significant effect on all RMS head velocities (see Fig. 3); across all subjects (patients and controls) it decreased global head velocity by ~2 times ($\dot{X}_{GH}$: $P < 0.001$, $F_{1,12} = 2584.1$), increased relative head velocity by ~1.5 times ($\dot{X}_{RH}$: $P < 0.001$, $F_{1,12} = 78.3$) and increased head yaw velocity ~2-3 times ($\dot{\alpha}_H$: $P < 0.001$, $F_{1,12} = 50.6$). These results match our previous study (Forbes et al. 2013) and indicate for both patients and controls that: (1) during LOW perturbations, the head is more stationary relative to the torso and (2) during HIGH perturbations, the head is more stationary in space. The effect on yaw velocity was not previously reported and illustrates a cross-coupling between the applied anterior-posterior perturbation and head twist, which was present in both patients and controls, but significantly stronger in patients ($P = 0.026$, $F_{1,12} > 6.4$). These responses were not associated with changes in baseline EMG for any muscle (see Fig. 4), indicating muscle co-contraction to be invariant across perturbation conditions (i.e. NP, LOW and HIGH) for both patients and controls.

3.3 Head-neck stabilization and afferent feedback

We first examined the response of healthy controls during the head forward task to highlight key features of typical stabilization and afferent feedback for subsequent comparison to patient data. Stabilization dynamics are depicted by kFRFs (Fig. 5A) representing kinematics, and eFRFs (Fig. 5B) representing afferent feedback. At low frequencies (0.2-0.8 Hz) the kFRFs show relative head movements of approximately 10-20% (i.e. a kFRF magnitude of 0.1), thus indicating that the head moves with T1. Above 2 Hz a kFRF magnitude around one and a phase approaching -180° indicate that the head is nearly stationary in space. Afferent feedback depicted by eFRFs (see Fig. 5B) indicates a magnitude that increases above 1 Hz, which functions to dampen system dynamics at high frequencies (Keshner et al.,1995;Peng et al.,1996).

Modulation with perturbation bandwidth in healthy controls was apparent in kFRFs and eFRFs (Fig. 5). A significant main effect of bandwidth on kFRFs was found ($P < 0.001$, $F_{2,11} = 60.0$), where relative head motion magnitude increased by ~2-3 times from LOW to HIGH bandwidth perturbations. This was associated with a decrease in the eFRF magnitude by ~1-4 times (main effect: $P < 0.001$, $F_{2,11} = 13.3$). Modulation of kFRF and eFRF magnitudes with perturbation bandwidth was consistent across all control subjects. Because baseline EMG (i.e. co-contraction) did not vary across these two conditions we interpret the decrease in neck

stiffness during HIGH bandwidth conditions as the central nervous system modulating (decreasing) afferent feedback gains (i.e. eFRF magnitude).

Fig. 6 shows FRF magnitudes for all conditions. Since the variations in kinematics and afferent feedback were limited primarily to changes in magnitude, we present only the magnitude of kFRFs and eFRFs. Comparison between patients and controls revealed no significant main effect of group for both kFRFs ($P = 0.447$, $F_{2,11} = 0.8$) and eFRFs ($P = 0.135$, $F_{2,11} = 2.4$), suggesting that patients maintained head-neck stabilization dynamics similar to healthy controls. Across perturbation bandwidths, patient modulation resembled that of healthy controls (compare Fig 6 left and right columns): during the HIGH bandwidth perturbation, head relative motion increased by 2-3 times and afferent feedback decreased by 2-4 times relative to the LOW bandwidth perturbation, indicating a decrease in neck stiffness. These effects of bandwidth were found in kFRFs and eFRFs of all patients.

The effect of task was significant for both the kFRFs ($P < 0.001$, $F_{2,11} = 37.5$) and eFRFs ($P = 0.005$, $F_{2,11} = 8.8$). Within the healthy control group, the dystonic posture task decreased kFRF magnitude (i.e. increased neck stiffness) by ~1-2 times and increased eFRF magnitude (i.e. increased afferent feedback) by ~2-3 times relative to the head forward task. This was consistent during both LOW and HIGH bandwidth perturbations and across all control subjects. Because muscle co-contraction (i.e. baseline EMG) also increased during the dystonic posture task, the increase in neck stiffness was attributed to both increasing intrinsic stiffness and afferent feedback. Although we found no main effect of group (patients vs. controls), a significant interaction effect of task and group was found for eFRFs ($P=0.012$; $F_{2,11}=6.8$) and just exceeded significance for kFRFs ($P = 0.056$; $F_{2,11} = 3.1$). Comparison of the two subject groups within each task revealed significant differences during the head forward task (kFRF: $P = 0.038$; eFRF: $P = 0.021$) but not during the dystonic posture task (kFRF: $P = 0.557$; eFRF: $P = 0.807$). During the head forward task, patients had and increased neck stiffness relative to controls (i.e., increased kFRF magnitude) for both perturbations (LOW and HIGH), attributed to increased afferent feedback (i.e. eFRF magnitude) which was 2-3 times higher for patients (see Fig. 6). In contrast, during the dystonic posture task, patient kFRFs and eFRFs were similar to controls for both the LOW and HIGH bandwidth perturbations.

4 DISCUSSION

This study compared dynamic head-neck stabilization and associated neck afferent feedback during anterior-posterior torso perturbations of a group of patients with cervical dystonia with a group of age and gender matched healthy controls. Both groups performed head-neck postural tasks – natural forward facing (HF) or dystonic posturing (DP) – during torso perturbations with varying frequency content that were designed to elicit bandwidth dependent neck afferent feedback modulation. Patients and controls demonstrated similar kinematic and muscular responses to stabilize the head and neck. This emerged both from the RMS head global and relative motion, and from the frequency response functions capturing kinematics (kFRF) and afferent feedback (eFRF) in the tested frequency range of 0.2-8 Hz. Coherences in patients were similar to controls for both kinematics and EMG and were always significant, supporting the use of frequency domain analysis, and indicating motion and muscular activity being highly related to applied torso perturbations.

Across the two perturbation bandwidths, patient stabilization dynamics and afferent feedback modulation matched that of healthy controls; neck stiffness and afferent feedback decreased during high bandwidth perturbations. This indicates a shift from minimizing head-on-trunk translation with low bandwidth to minimizing head-in-space translation with high bandwidth perturbations. Thus the main results of this study indicate ‘normal’ afferent feedback in CD patients, which is accompanied with ‘normal’ modulation to changes in perturbation bandwidth. No evidence was found for deviating afferent feedback and/or supraspinal control of sensorimotor integration in CD patients. Although our study is limited in the number of patients and controls tested, based on our current results any effect that may arise from a larger population would likely be small. However limited differences were observed between patients and controls, and these are discussed below.

Patients displayed a larger RMS head yaw (twist) velocity in all conditions, which remained significant after removal of three tremulous patients. Head yaw increased with perturbation being highest with high bandwidth. This suggests a cross-coupling between applied anterior-posterior torso perturbation and head yaw velocity. The head yaw velocity did not vary with posture (dystonic posture vs head forward task), which suggests that this cross-coupling is not simply related to posture. It shall, however, be noted that this potential cross-coupling is weaker but still clearly present in healthy controls. Patients also displayed a 1.5-2 times larger baseline EMG suggesting elevated co-contraction. However, this was not significant due to

large variability, which may be associated with between subject differences, electrode placement and the limited set of muscles studied.

All patients reported that the head forward task required increased effort. However, baseline EMG was higher (although not significant) in the dystonic posture task. This contradicted our expectation that patients would increase muscle contraction during the head forward task to counter the effects of CD. We considered the possibility that patient baseline EMG was confounded by dystonic activity in muscles used to assess baseline EMG (see Table 1). To account for this we reassessed baseline EMG using only assumed non-dystonic muscles (based on clinical and polymyography data). However, again, no significant difference was found between head forward and dystonic posture tasks. One potential explanation is that deeper axial muscles associated with intervertebral control and spinal stabilization (Bexander et al.,2005;Lee et al.,2005;Moseley et al.,2002), and not measured in this experiment, contributed to countering the dystonic posture to maintain a stable head forward posture.

During the head forward task patients had an increased neck stiffness relative to controls, which was attributed to increased afferent feedback. Nevertheless, this did not impede their ability to modulate afferent activity across perturbation bandwidths, which qualitatively matched healthy controls as discussed above. The modulation of afferent feedback observed across tasks for both patients and controls may also be affected by the change in head posture. Across the two tasks, spindles maintain a different set point and the vestibular organ reorients with the head, while the underlying biomechanics of the head and neck and the set-point of the muscles change. However, because of variability in posture across subjects, separation of sensory and biomechanical contributions is not possible. Vision may have also contributed to the changes in both stabilization and afferent feedback dynamics across tasks, particularly at low frequencies. In healthy controls, the presence of vision was previously shown to decrease head motion, likely due to the necessity to visually fixate on a stationary target (Forbes et al.,2013). However in the current study, head motion increased for healthy controls with the eyes open during the head forward task (i.e. increased kFRF magnitude), which suggests that posture was the more dominant effect across tasks. The visual feedback during the head forward task may also have had specific effects in patients. Functioning as a sensory trick, vision may have allowed subjects to better define their head orientation in space and minimize the disruptive effects of dystonia. Although sensory tricks are traditionally associated with cutaneous input by touching the cheek (Deuschl et al.,1992;Kaegi et al.,2013;Martino et al.,2010;Muller et al.,2001), recent studies have shown that vision can also act as a sensory

trick (Lee et al.,2012). If we assume the visual task functioned as a sensory trick, this may explain reduced baseline EMG during the head forward task since sensory tricks are associated with a reduction or cessation of muscle activity (Deuschl et al.,1992). However, we reiterate that the reduction in baseline EMG across tasks was not significant for patients.

5 CONCLUSIONS

The results of the current experiment show that afferent feedback contributes to dynamic anterior-posterior stabilization of the head-neck system in cervical dystonia patients in a similar way as in healthy controls. Furthermore patients modulate neck afferent control in response to variation of perturbation bandwidth in a 'normal' manner. This does not support our hypothesis of impaired afferent feedback modulation for neck stabilization.

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8 TABLES

Table 1 Clinical characteristics of 10 patients with cervical dystonia. Head yaw orientation and direction were measured as the mean head yaw rotation during trials without perturbation (i.e. no perturbation trials).

Patients	Age	Sex	Disorder duration (years)	Tsui score	Head yaw orientation (direction)		Tremor or jerk[a]	Muscles treated with botulinum toxin
1	38	M	4.5	7	15°	(R)	0	l-SCM/r-SPL
2	63	F	4.0	11	13°	(R)	1	l-SCM/l-SPL/r-SPL
3	56	F	4.0	9	66°	(R)	0	l-SCM/r-SPL
4	46	M	11.0	8	9°	(R)	0	l-SCM/r-SCM
5	74	F	25.0	12	22°	(L)	0	l-SPL/l-SEMI/r-SCM
6	45	M	4.0	16	13°	(R)	0	l-SCM/l-SEMI/r-SPL
7	63	F	6.0	17	15°	(L)	1	l-SPL/r-SCM/r-SEMI
8	60	F	10.0	15	35°	(L)	1	l-SPL/l-SEMI/r-SPL
9	56	M	13.0	7	2°	(R)	0	l-SCM/r-SPL
10	61	M	2.0	13	22°	(L)	0	r-SCM/r-SPL/r-SEMI

[a] 0: no visible tremor during the experiments 1: pronounced tremor during the experiments

9 FIGURE CAPTIONS

Figure 1: Illustration of the platform, a seated subject and patient mean head yaw orientation. A: side view of motion platform and chair. B: Subjects were seated on the chair while restrained using a four-point harness and passive markers were attached to the head and torso. The head local coordinate system as used in the motion analysis was positioned at the estimated centre of gravity (Yoganandan et al.,2009) oriented along the Frankfurt plane. Inset head pictures demonstrate patient absolute head yaw orientation during the head forward (HF) and dystonic posture (DP) tasks estimated from the no-perturbation trials. The group means are indicated by dotted lines and standard deviations are indicated by shaded regions. Note, for clarity, absolute patient yaw head orientation was drawn in a rightward direction, although for 4 patients the head yaw orientation was leftward (see Table 1).

Figure 2: Block diagram of closed-loop head-neck stabilization. The dark grey box depicts the kinematic dynamics (kFRF) including closed-loop feedback pathways (i.e., input perturbation to output head motion). The light grey box depicts the afferent feedback dynamics (eFRF). Time signals represent example measurements obtained from one control subject during the head forward task while exposed to LOW and HIGH bandwidth perturbations.

Figure 3: Head kinematics of patients (blue) and controls (red) plotted per perturbation condition (LOW and HIGH bandwidth) for each task (HF: head forward and DP: dystonic posture) averaged across subjects (error bars are ± SE, n = 7). Graphs represent root-mean-square velocity of global head motion (X_{GH}), relative head motion (X_{RH}) and head yaw (ω_H). A significant effect of group was found on head yaw velocity ($P = 0.026$) for perturbation trials only, a significant effect of task was found on global head velocity ($P < 0.001$), and a significant effect of perturbation (all $P < 0.001$) was found on all kinematic measures. See text for details.

Figure 4: Baseline EMG levels of patients (blue) and controls (red) plotted per perturbation condition (LOW and HIGH bandwidth) for each task (HF: head forward and DP: dystonic posture) averaged across subjects (error bars are ± SE, n = 7). Graphs represent the sternocleidomastoid (SCM), splenius capitis (SPL) and semispinalis (SEMI). Although the mean patient responses are 1.5-2 time greater than mean control responses, no significant effect of group was found on all muscles. A significant effect of task was found on SPL and SEMI muscles and no significant effect of perturbation was found on all muscles. See text for details.

Figure 5: Effects of bandwidth in healthy controls in the head forward (HF) task. **A**: Kinematics (kFRF), **B**: Afferent feedback (eFRF). Results were averaged across subjects (shaded region is ± SE) for LOW and HIGH bandwidth perturbations. Magnitude was log transformed before calculating group averages and SE (n = 7). With increasing perturbation bandwidth kFRF magnitude increases (i.e. decreasing neck stiffness) and eFRF magnitude decreases (i.e. decreasing afferent feedback gains).

Figure 6: Effects of bandwidth (LOW and HIGH) and task (DP: dystonic posture and HF: head forward) in controls (left column) and patients (right column). **A**: Kinematics (kFRF), **B**: Afferent feedback (eFRF). Magnitude was log transformed before calculating group averages. See text for detailed description of responses.

Figure 1

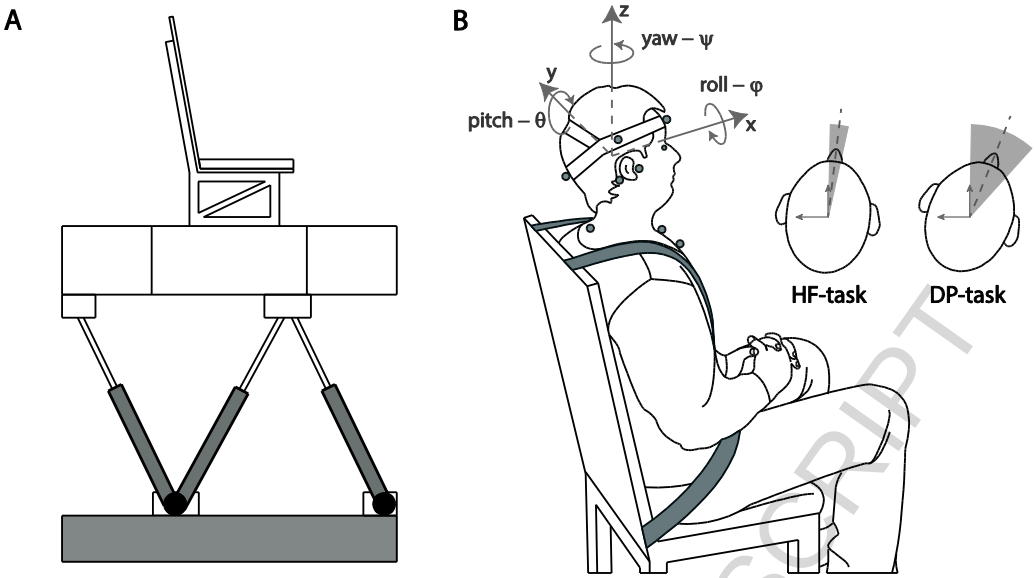

Figure 2

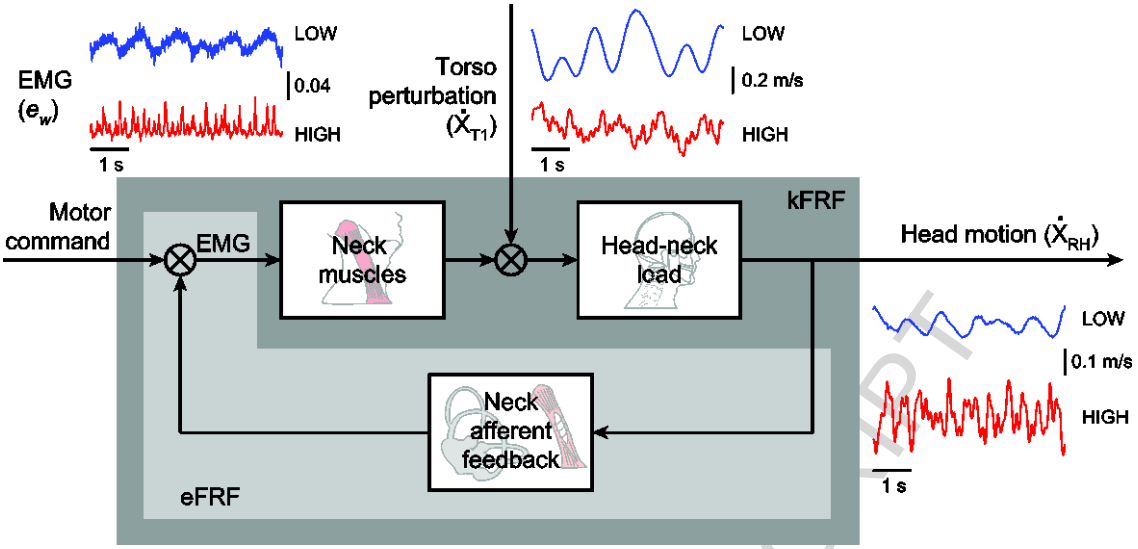

Figure 3

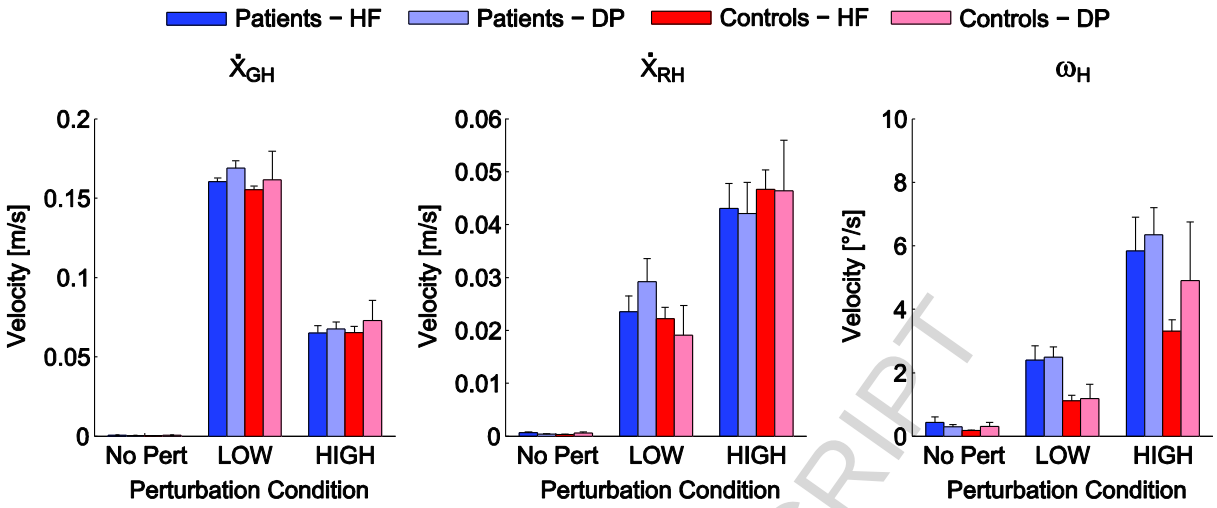

Figure 4

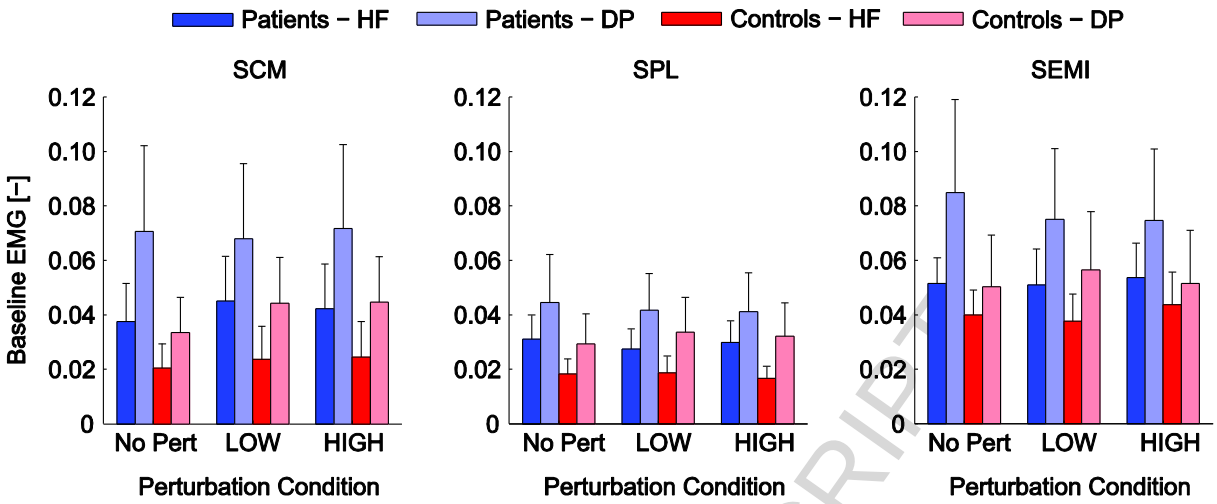

Figure 5

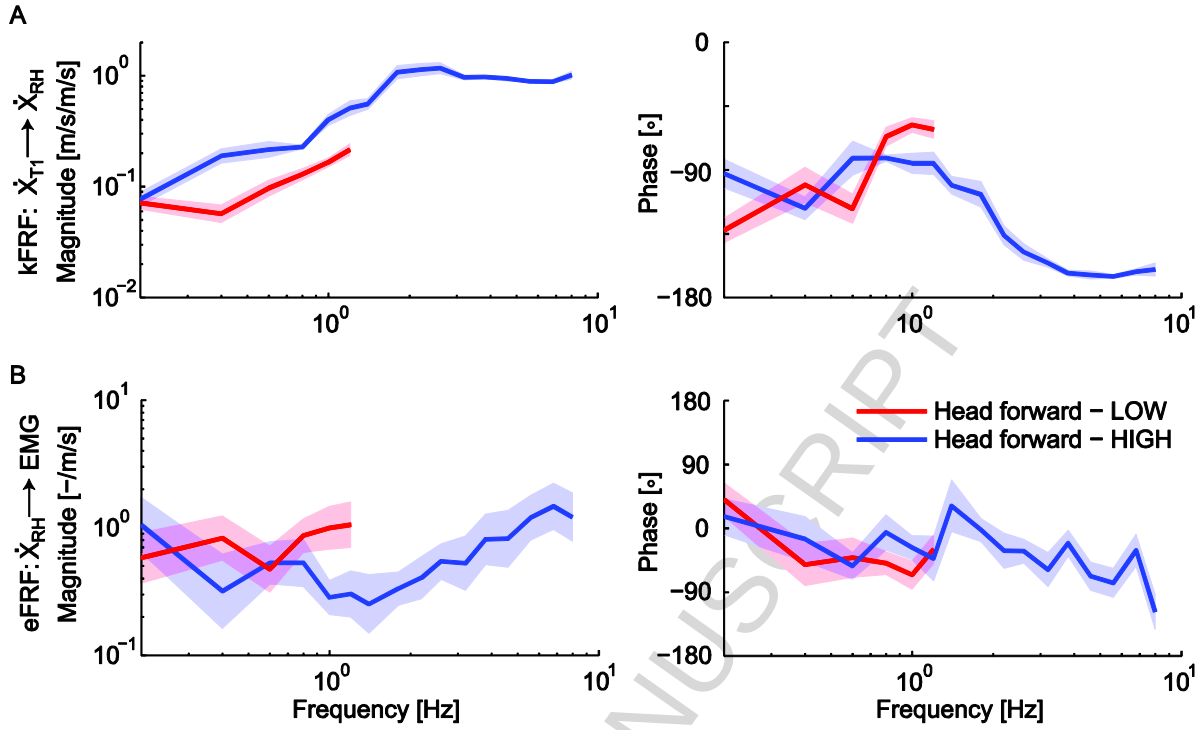

Figure 6