Exp Brain Res (2013) 230:311–321
DOI 10.1007/s00221-013-3656-4

RESEARCH ARTICLE

Proprioceptive sensitivity in Ehlers–Danlos syndrome patients

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Received: 14 February 2013 / Accepted: 20 July 2013 / Published online: 3 August 2013

Abstract Reaching movements are rapidly adapted following training with rotated visual feedback of the hand. Our laboratory has also found that this visuomotor adaptation results in changes in estimates of felt hand position (proprioceptive recalibration) in the direction of the visuomotor distortion (Cressman and Henriques in J Neurophysiol 102:3505–3518, 2009; Cressman et al. in Exp Brain Res 205:533–544, 2010). In the current study, we investigated proprioceptive acuity and proprioceptive recalibration in a group of individuals with Ehlers–Danlos syndrome (EDS), a degenerative condition associated with collagen malformation. Some studies have suggested that these patients may have proprioceptive impairments, but the exact nature of the impairment is unclear (Rombaut et al. in Clin Rheumatol 29:289–295, 2010a). In this study, we measured the ability of EDS patients to estimate their felt hand position and tested whether these estimates changed following visuomotor adaptation. We found EDS patients were less precise in estimating their felt hand position in the peripheral workspace compared to healthy controls. Despite this poorer sensitivity, they recalibrated hand proprioception to the same extent as healthy controls. This is consistent with other populations who experience proprioceptive deficits (e.g. the elderly, Parkinson's disease patients), suggesting that sensory noise does not influence the extent of either motor or sensory plasticity.

Keywords Proprioception · Ehlers–Danlos syndrome · Generalized joint hypermobility · Reaches · Multisensory integration

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Introduction

Ehlers–Danlos syndrome (EDS) is a group of genetic connective tissue disorders, which is proposed to include hypermobility syndrome (HMS) and benign joint hypermobility syndrome (BJHS) (Tinkle et al. 2009). Although over 10 variations of the disorder have been documented, most geneticists agree that there are 3 main types of EDS: classic type I/II, hypermobility type III and vascular type IV (Beighton et al. 1997; Keer and Grahame 2003). While past research has indicated that EDS affects approximately 0.02 % of individuals, recent work suggests that this statistic is a gross underestimation and that the prevalence of EDS in the general population is much higher. In fact, the prevalence of EDS has been suggested to be closer to 0.75–2.00 % when including HMS and BJHS (Castori 2012).

In general, patients with EDS have mutated collagen present throughout their bodies, which results in a wide range of clinical manifestations. For example, patients often experience stretchy skin, vascular problems, chronic pain, dysautonomia, developmental delays, clumsiness, poor wound healing, and chronic fatigue (Beighton et al. 1988, 1992, 1997; De Paepe and Malfait 2004; Hollister 1978; Lawrence 2005; Malfait et al. 2010; Parapia and Jackson 2008; Rombaut et al. 2010b; Sacheti et al. 1997; Voermans and Knoop 2011).

As well, one of the main clinical features present in EDS is generalized joint hypermobility, as determined using the Beighton criteria, which rates a patient's hypermobility on a 9 point scale after performing 9 different movements (Keer and Grahame 2003). Moreover, it has been suggested by Rombaut et al. (2010a) that EDS patients may have proprioceptive impairments, perhaps because there is mutated collagen in proprioceptors (muscle spindles and Golgi tendons), which may be providing suboptimal afferent signals. However, little is known about the exact nature of these sensory impairments, or why mutated collagen (which often results in joint hypermobility) may result in these sensory deficits, as only a few studies have attempted to explore proprioceptive abilities in EDS patients or other patients exhibiting joint hypermobility.

In particular, a few studies have sought to investigate proprioceptive deficits in individuals with other similar connective tissue disorders, specifically HMS and BJHS. These inheritable connective tissue disorders share many of the same symptoms as EDS hypermobility type III and are generally considered to be variants of the same spectrum of connective tissue disorders (Keer and Grahame 2003; Tinkle et al. 2009). Thus, in reviewing these previous findings, we will consider them to be applicable to EDS.

Hall et al. (1995) were the first to explore proprioceptive abilities in HMS patients by studying the knee joint. Specifically, by using a static remembered joint matching threshold-detection paradigm, researchers found that HMS subjects showed significantly higher threshold detection levels (about 1.5°) at knee flexion angles of 5° and 30° in comparison with age-matched healthy controls (about 1°). These results were supported by Sahin et al. (2008) who showed that patients with BJHS had significantly higher absolute angular errors than healthy controls during a knee joint matching task. Recently, Rombaut et al. (2010a) explored proprioception and vibratory perception sense in hypermobility type III EDS patients, using both an active and passive shoulder and knee joint matching paradigm. They found that EDS patients showed significantly larger angular errors in joint matching at the knee joint, but not at the shoulder joint. However, vibratory perception did not significantly differ in EDS patients and healthy controls (Hall et al. 1995; Rombaut et al. 2010a; Sahin et al. 2008). Overall, these studies suggest that patients with joint hypermobility perform poorer than controls when having to report or match joint angles, particularly when judging the position of the leg.

Given that patients who exhibit joint hypermobility seem to have some proprioceptive impairments, our goal was to explore proprioceptive abilities in patients with EDS, and how they differ compared to controls. In particular, we sought to determine proprioceptive abilities in the hand, a body part that is required to frequently produce and monitor movement with a great deal of precision in order to manipulate objects in the environment. In contrast to previous studies examining proprioceptive abilities in patients with hypermobility disorders, which have patients complete joint matching tasks, we used a procedure that allowed us to precisely place the hand in a controlled manner at a variety of workspace locations and therefore acquire very acute measures of proprioception. Finally, we explored whether proprioceptive sensitivity was related to patients' degree of joint hypermobility (Beighton scores).

In addition to examining proprioceptive sensitivity, we also wanted to determine the ability of the proprioceptive system to recalibrate in the face of conflicting visual information about the hand; that is, we wanted to determine whether felt hand position would change. The ability of EDS patients to update their felt hand position was compared to control subjects to establish whether these potential proprioceptive impairments in EDS patients also lead to greater changes in proprioceptive estimates following what is known as visuomotor adaptation (i.e. changes in reaches in response to altered visual feedback). In previous studies from our laboratory, we have shown that in healthy young adults, as well as in older adults and adults suffering from Parkinson's disease, adapting reaching movements to altered feedback of the hand (visuomotor adaptation) leads to consistent changes in people's perceived location of their unseen hand (Cressman and Henriques 2009; Cressman et al. 2010; Salomonczyk et al. 2011). Here, we also tested whether visuomotor adaptation leads to recalibration of felt hand position in EDS like it does in healthy controls, which would tell us whether the deficit is related to higher-order CNS processes, such as multisensory integration. Since proprioceptive deficits can lead to accidental injuries, accompanied by lengthy recovery periods in EDS, the current study can prove to be a valuable addition to the current knowledge for individuals with EDS.

Methods

Subjects

Twenty-two healthy control subjects (mean age 21 years, range 16–27, 15 females) and ten subjects with EDS (mean age 24 years, range 16–43, 7 females), all of whom were right handed, participated in the experiment outlined below. Initially, there were 26 healthy control subjects, but 4 subjects were removed from analyses due to the fact that they were not consistent in reporting their hand position, suggesting that they did not understand the requirements of the task.

Control subjects were either laboratory volunteers or were recruited through the undergraduate research

Table 1 EDS clinical demographics

Subject	Age	Sex	Type	Beighton score
SG	27	F	Hypermobility (III)	4
NH	30	F	Classic (I/II)	8
TH	27	F	Classic (I/II)	8
AL	16	M	Hypermobility (III)	5
DL	43	M	Hypermobility (III)	5
CM	23	F	Hypermobility (III)	7
RO	28	F	Hypermobility (III)	8
NO	28	F	Hypermobility (III)	9
LW	22	F	Classic (I/II)	4
TW	24	M	Classic (I/II)	3

participant pool at York University (and given course credit for their participation). Subjects in the patient group were recruited through various Internet support groups related to EDS. Patient clinical demographics are provided in Table 1. Four of the EDS patients were classic type I/II (mean age 26 years, range 22–30, 3 females, from 2 family groups), while all of the others were hypermobility type III (mean age 28 years, range 16–43, 4 females, from 4 family groups, including a set of identical twins). To our knowledge, we are the first to study proprioceptive abilities in classic type (I/II), which is a common EDS subtype. By including these subjects, we hoped to obtain a wider range of Beighton scores, enabling us to examine the relationship between degrees of joint hypermobility and proprioceptive abilities. All subjects provided informed consent, and the study was conducted in accordance with the ethical guidelines set by the York Human Participants Review Subcommittee. All subjects had normal or corrected-to-normal vision. None of the EDS patients were on any medication known to affect their cognitive abilities during the experiment. Only patients with confirmed clinical diagnoses, who were not in extreme discomfort from pain on the day of the experiment, were admitted into the study. Patients' Beighton scores were first based on physician diagnoses and were confirmed by the experimenter prior to testing. Each patient who participated in this study was found to be hypermobile in their right elbow.

Apparatus

A view of the experimental set-up is provided in Fig. 1a. Subjects were seated in a chair that could be adjusted with respect to height and distance from the display, so that subjects could comfortably see and reach to each of the target locations presented on a reflective screen. With their right hand, subjects held onto the vertical handle on a two-joint robot manipulandum (Interactive Motion Technologies Inc., Cambridge, MA, USA) such that their thumb rested on top of the handle. The reflective screen was mounted on a horizontal plane 8.5 cm above the two-joint robotic arm. Visual stimuli were projected from a monitor (Samsung 510 N, refresh rate 72 Hz) located 17 cm above the robotic arm, such that images displayed on the monitor appeared to lie in the same horizontal plane as that of the robotic arm. The lights were dimmed, the subject's view of their own hand was blocked by the reflective surface, and a black cloth was draped over their shoulders to conceal the experimental set-up.

Procedure

The experiment consisted of both proprioceptive and reaching tasks (when visual feedback of the hand was or was not present), the goal of which was to assess proprioceptive acuity of hand position in EDS patients and to determine whether hand proprioception changes following visuomotor adaptation in EDS patients are similar to those for controls (hence the reaching task). All tasks were completed in 2 test sessions, which explored the influence of different visual feedback conditions on proprioceptive recalibration (change in felt hand position). Patients completed both sessions on the same day, while controls completed both sessions within a 2-week period. For the purpose of our first goal, subjects made proprioceptive estimates of their felt hand's position in the first session, after training to reach to targets with a cursor that was *aligned* with their hand's position (Fig. 2a). The aligned session also served to familiarize subjects with the experimental tasks. For the second session, subjects made the same estimates of their hand's location, but this time they completed these proprioceptive estimates after training with a cursor that was *misaligned* with their hand's position (Fig. 2b). The misaligned cursor was rotated 50° CW from their actual hand position, with this rotation being introduced gradually by 0.75° per trial.

Stimuli

During training, there were 6 reach targets, represented by 1-cm-diameter yellow circles. The reach targets were located radially, 10 cm from the home position at 5°, 30° and 60°, both CW and CCW of centre (body midline) (indicated by yellow circles in Fig. 1b). For the no-cursor reach tasks, we added two novel peripheral targets located 45° CW and CCW of centre and two novel central targets, one visual and one proprioceptive (body midline, which was indicated by a beep), for a total of 10 reach targets (circles in Fig. 1c; novel indicated by orange). The proprioceptive estimation task had 3 visual reference markers, represented by 1-cm-diameter yellow circles, as well as a proprioceptive reference marker (the body midline). Reference

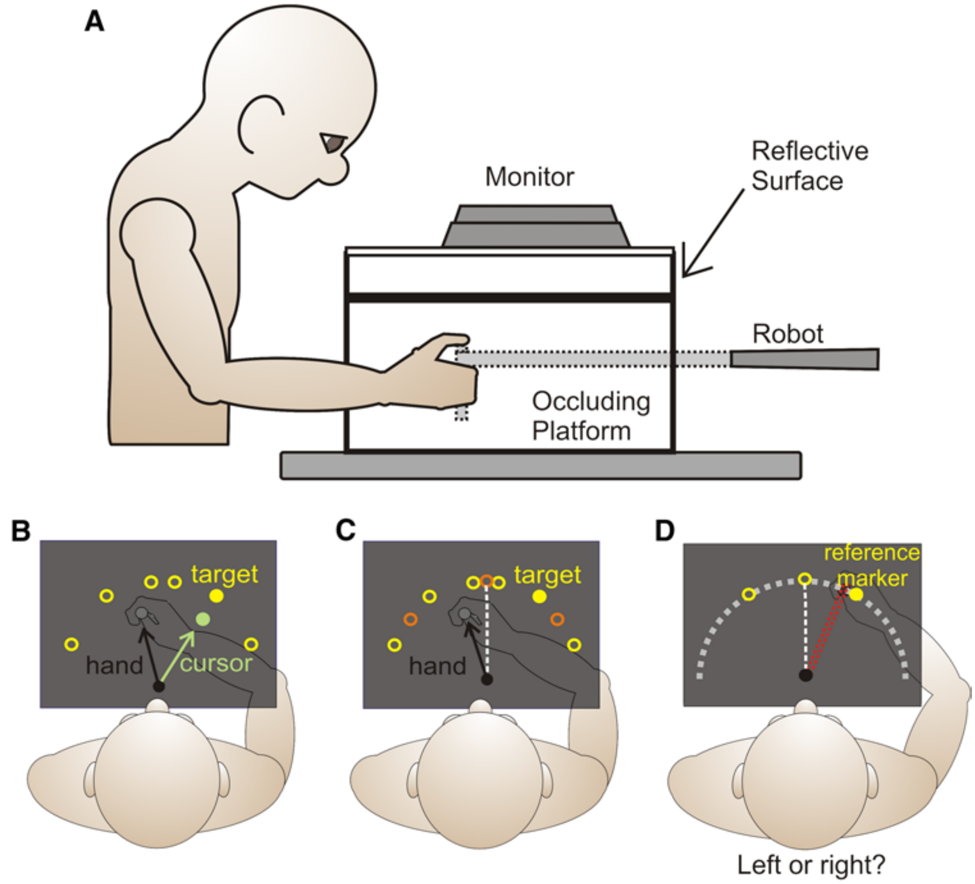

Fig. 1 **a** *Side view* of the general experimental set-up. **b–d** *Top views* of the experimental set-up. **b** *Reach training* The centre home position was represented by a 1 cm *circle* (shown in *black*), which was visible only before the trial began and was located about 20 cm in front of subjects' torso. Targets are represented by *yellow circles* and were located along a *circular arc* at a distance of 10 cm from the home position. Reach targets were located at 5°, 30° and 60° CW and CCW from the body midline (0°). The *green cursor* (representing the hand) was aligned with the actual hand position during session 1 (not shown). The *green cursor* was rotated 50° CW with respect to the actual hand position during the rotated-reach training condition (shown in *green*). **c** *Reaching without a cursor* Trained targets are represented by *yellow circles* at 5°, 30° and 60° CW and CCW from the centre. Novel targets are represented by *orange circles* at 0°, as well as 45° CW and CCW from the centre. Additionally, there was a novel proprioceptive midline target at the body midline (shown by the *white dashed line*). All targets were located at a distance of 10 cm from the home position. **d** *Proprioceptive estimation* For this task, subjects actively moved their hand along a robot-generated groove (shown by the *red rectangle*) to a location at the end of the *grey dotted arc*. Once the hand had arrived at this location, a reference marker appeared: either a visual dot (*yellow circles*) or a beep to signify the body midline reference marker (*white dashed line*). Visual references were located at 0°, as well as 45° CW and CCW from the centre, and were 10 cm from the home position (colour figure online)

markers for the proprioceptive estimation task were located radially, along an arc 10 cm from the home position, at 45° both CW and CCW of centre, as well as at centre (0°) (Fig. 1d). The centre reference marker was presented visually or proprioceptively. Next, we describe the three main tasks in the order by which subjects performed them for each session.

Task A: Reach training

Subjects held onto the robotic manipulandum with their right hand and were instructed to reach to one of the six reach targets as quickly and as accurately as possible, with either an aligned (session 1) or rotated (session 2) cursor representing their hand's position (Fig. 1b). During both sessions, the cursor was a green circle 1 cm in diameter. The home position, which was not visible in this task, was located 20 cm in front of the subjects, along their body midline. After placing the hand at the home position for 300 ms, 1 of the 6 reach targets would appear. Visual feedback of the hand's position became available only when subjects had travelled 4 cm away from the home position. A reach trial was complete when the centre of the hand cursor intersected the target (i.e. within 0.5 cm of the target's centre). After the reach was complete, both the cursor and target vanished and the subject moved their hand

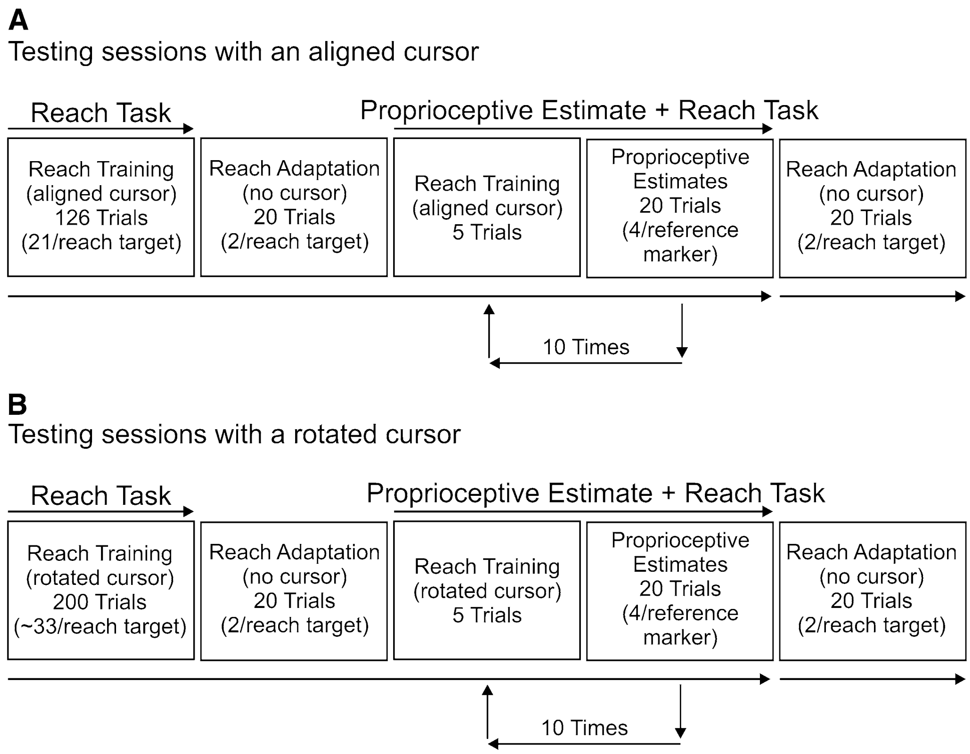

Fig. 2 Breakdown of the experimental tasks within each session. **a** Tasks completed during the first session of the experiment, which provided baseline measures of performance. Subjects began the session by reaching to visual targets while a cursor accurately represented the location of their *right hand* (*box 1*). After completing 126 visually guided reach trials, subjects reached to each of the 10 reach targets (6 trained and 4 novel targets) twice without the cursor, to assess visuomotor adaptation (reach after-effect trials, *box 2*). This was followed by 20 sets of 5 visually guided reaches (*box 3*) and 20 proprioceptive estimates (*box 4*). After completing the proprioceptive estimate + reach task, subjects completed 20 reaches without the cursor, reaching twice to each of the 10 reach targets (*box 5*). **b** Tasks completed during the second session of the experiment, where the cursor was rotated 50° CW with respect to the actual hand location during the visually guided reach training trials (*boxes 1* and *3*)

back towards the non-visual home position, guided by the robot that constrained the movement along a grooved path that ended at the home position. If subjects tried to move outside of the path, a resistance force [proportional to the depth of penetration with a stiffness of 2 N/mm and a viscous damping of 5 N/(mm/s)] was generated perpendicular to the grooved path (Henriques and Soechting 2003). The 6 reach targets were presented pseudo-randomly such that each target was presented once before any target from the set was repeated. Each subject completed 126 reach trials in the aligned session and 200 in the misaligned session.

Task B: Reaching without a cursor

One of the traditional methods for assessing reach adaptation is to look at changes in reaches made without any visual feedback before and after training with a misaligned cursor. These changes are known as after-effects. Thus, after training (Task A) in each session, subjects performed 10 more reaches without the cursor to the same six targets (yellow circles in Fig. 1c), as well as four additional ones including the proprioceptive midline location (white dashed line in Fig. 1c) and three other visual targets (orange circles in Fig. 1c). "Midline reaches" were cued by a beep. After the hand had moved out towards the target and been held in the same position for 500 ms, the target disappeared indicating that trial was over. Subjects returned their hand back to the home position by following the grooved path.

Task C: Proprioceptive estimates and reaching

To assess proprioceptive acuity and sensitivity, we used a similar proprioceptive estimation task as in previous studies from our laboratory (Fig. 1d). The purpose of the proprioceptive estimation trials was to determine the position at which subjects perceived their unseen hand was aligned with each of the reference markers (as a measure of accuracy), as well as the uncertainty ranges (precision) associated with these estimates. These estimation trials were interleaved with reach training trials completed after training an aligned cursor (session 1) and with a misaligned cursor (session 2), so that we could assess baseline proprioceptive sensitivity of hand position (in session 1), in addition to whether these estimates of felt hand position change with visuomotor adaptation of the hand movements (in session 2).

Reach trials and proprioceptive estimate trials were systematically interleaved during this task, to ensure that adaptation was maintained. Subjects began by reaching 5 times to the same visual reach targets as in the training trials with either an aligned cursor (session 1) or rotated cursor (session 2). The reaches were immediately followed by 20 proprioceptive estimates, in which subjects were instructed to push their right hand out along a linear robot-generated path until the path ended at a particular location. Once the hand arrived at this location, a reference marker appeared, which could be either a dot (yellow circles in Fig. 1d) or a beep to indicate the body midline (white dashed line). Subjects then pressed a left or right key to indicate whether their hand felt left or right of the reference marker, respectively. The position of the hand relative to each marker (and thus the direction of the robot-generated groove) was determined using an adaptive staircase algorithm (Kesten 1958; Treutwein 1995). Each of the four reference markers had 2 staircases: one starting 20° CCW (left) of the reference marker and another 20° CW (right) (Fig. 3a). The two staircases were randomly interleaved and adjusted independently as stipulated by Cressman and Henriques (2009, 2010). This procedure repeated itself 10 times until a total of 250 trials had been completed (50 reach trials and 200 proprioceptive estimates).

Data analysis

To determine the locations at which subjects felt their hand was aligned with the reference markers in the proprioceptive estimation task, we fitted a logistic function to each subject's responses for each reference marker in each testing session (Fig. 3b, c). Based on these logistic functions, we calculated the bias (the point of 50 % probability) and uncertainty range (the difference between the values at which the response probability was 25 and 75 %). Bias is a measure of the accuracy of hand-reference marker alignment, and the uncertainty range defines its precision. Additionally, the uncertainty range relates to the slope of the logistic fit, such that a steeper slope indicates a smaller uncertainty range (Fig. 3b, c).

To assess proprioceptive acuity in EDS patients and control subjects, we compared biases and uncertainty ranges from the proprioceptive estimation task using a mixed ANOVA that included group (healthy vs. EDS) as a between-group factor and reference marker (visual markers located at 0° centre, 45° left and right, as well as the proprioceptive midline) as repeated factors. We also included a third repeated measure factor of visual feedback

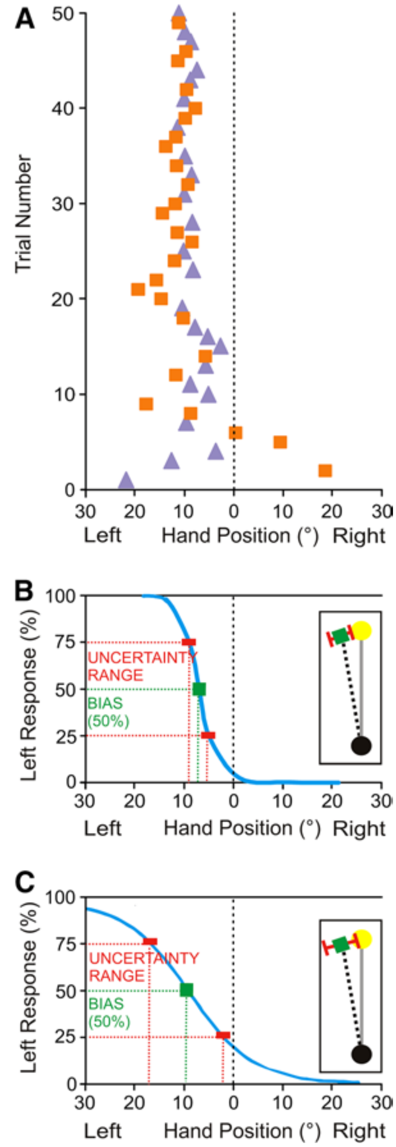

Fig. 3 **a** Example of a control subject's hand position during the proprioceptive estimation task for a single reference marker in session 2. Adjustments to the hand's position, with respect to the reference marker, were determined by 2 randomly interleaved and independently adjusted staircases. The *right staircase* is shown by *orange squares*, and the *left staircase* is shown by *purple triangles*. **b**, **c** Percentage of left responses for different hand positions for a typical healthy subject (**b**) and a typical EDS subject (**c**), when a peripheral visual reference marker was displayed (but normalized to 0° here) in the proprioceptive estimate trials (Task C) after the subject trained to reach with misaligned feedback of the hand's location. We can see that, although the bias (*green squares*) is quite similar between the control subject (**b**) and patient (**c**), the *curve* is not as steep for the patient (**c**) because the uncertainty range (*red rectangles*) is almost double that of the control (**b**) (colour figure online)

(aligned vs. misaligned cursor) in order to explore how these felt hand positions changed with motor adaptation. We used a similar mixed ANOVA to examine whether subjects adapted their reaches after reaching with the rotated cursor. In particular, to assess whether hand proprioception changed with visuomotor adaptation for EDS patients, we needed to analyse reaching errors (after-effects) made in the "Reaching without a Cursor" task to confirm that reach adaptation occurred and was maintained throughout all tasks of the experiment for both groups. Thus, we compared no-cursor reach endpoints as a function of group (healthy vs. EDS), target location (visual targets located at 0° centre, 5°, 30°, 45° and 60° left and right, as well as a proprioceptive target, which was an imagined location on the screen projected from the body midline) and visual feedback (aligned vs. misaligned cursor), using another three-way mixed ANOVA.

All ANOVA results are reported with Greenhouse–Geisser corrected P values to compensate for violations of sphericity. Differences with a probability of $P \le 0.05$ were considered to be significant. Bonferroni post hoc tests were administered to determine the locus of these differences ($\alpha = 0.05$).

Results

Proprioceptive acuity

We see that for both groups (Fig. 4), subjects' estimates of their unseen hand positions (diamonds) were quite accurate after training with an aligned cursor, in which they fell close to the reference markers (yellow circles). On average, the mean bias collapsed across all reference markers for EDS patients (striped symbols) was 2.57° to the left of the reference marker, while the mean bias for controls (solid symbols) was 4.77° to the left of the reference markers. Further analyses revealed that both EDS and control subjects had similar biases during the aligned condition [$F(1, 30) < 1$, $P = 0.46$] and that biases were similar across all reference markers [$F(1.51, 48.53) < 1$, $P = 0.90$].

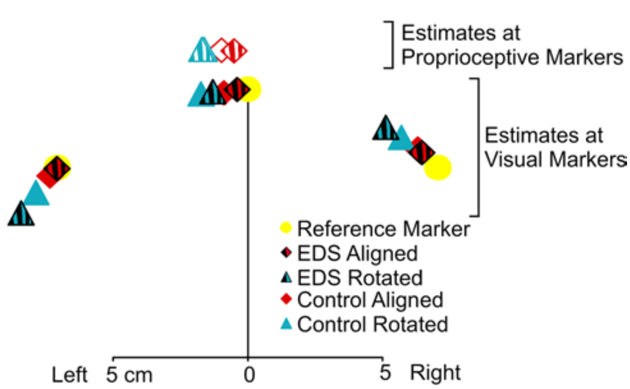

Fig. 4 Mean 2-D estimates of felt hand position after subjects trained with an aligned (*red diamonds*) or rotated (*blue triangles*) cursor. Estimates with respect to visual reference markers (*yellow circles*) are represented by the *black zebra pattern symbols* for EDS subjects and *colour filled symbols* for controls. The proprioceptive estimates relative to the body midline (or proprioceptive marker) are shifted above those for the central visual reference marker to avoid overlap; here, the biases for EDS subjects are represented by a *white zebra pattern symbol*, and those for controls by *white filled symbols* (colour figure online)

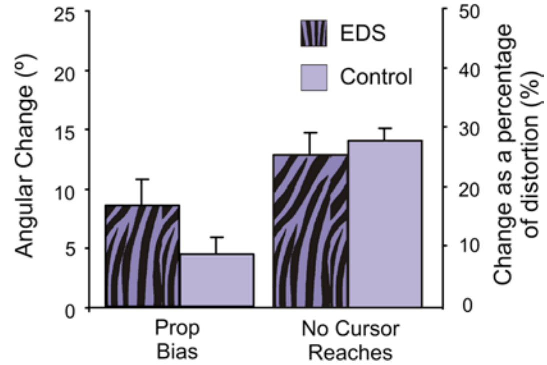

Fig. 5 Summary of changes in angular error at reach endpoints in the no-cursor reaches and proprioceptive biases after training to reach with a rotated cursor. Changes are shown for all tasks in degrees and as a percentage of the distortion. *Error bars* reflect standard error of the mean

Proprioceptive recalibration (estimates)

After subjects trained with a rotated cursor, their estimates of hand position (Fig. 4, blue triangles) were shifted more to the left than those in the aligned session (red diamonds), suggesting both groups recalibrated their sense of hand position [$F(1, 30) = 26.82$, $P < 0.001$]. Specifically, patients' estimates (Fig. 5, left zebra bar) were 8.42° more left after training with a rotated cursor and controls' estimates (Fig. 5, left purple bar) were 4.39° more left following training. Furthermore, these changes in estimates of hand position were similar across all reference markers [$F(1.89, 56.67) < 1$, $P = 0.39$].

Uncertainty range

Figure 6 shows the magnitude of the uncertainty ranges for both the EDS (zebra bars) and control subjects (dashed lines) following training with an aligned (red) and misaligned (blue) cursor. Levels of precision in estimating the location of their unseen hand positions after training with an aligned and rotated cursor were similar for both groups [$F(1, 30) < 1$, $P = 0.42$]. However, the estimates of EDS subjects were less precise than estimates by control subjects, but only for those estimates made at peripheral reference marker locations [$F(2.76, 88.82) = 5.30$, $P < 0.01$]. In fact, the uncertainty ranges at the left and right locations were almost double those at central

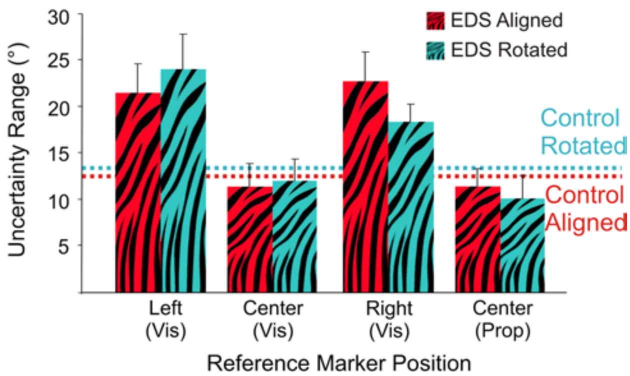

Fig. 6 Magnitude of the uncertainty ranges for estimates of felt hand position following training with an aligned (*red*) and rotated (*blue*) cursor. Uncertainty ranges of EDS subjects are shown with *zebra bars* for the different reference markers (*left visual*, *centre visual*, *right visual* and *centre proprioceptive*), while control subjects' measures of precision are collapsed across reference marker locations/modalities and shown by *dashed lines*. *Error bars* reflect standard error of the mean (colour figure online)

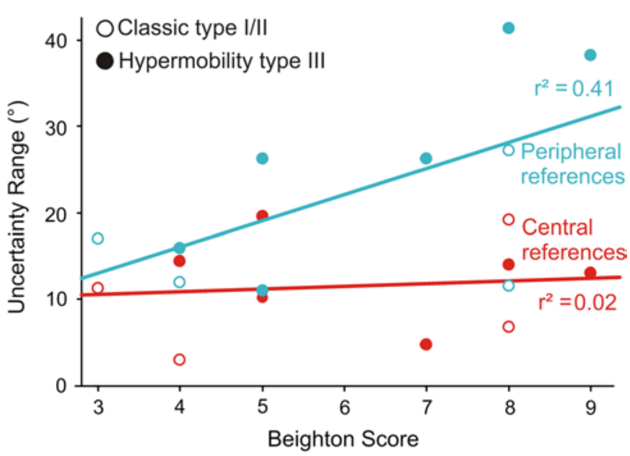

Fig. 7 Uncertainty ranges of estimates of felt hand position are plotted as a function of Beighton score for each EDS subject after training with an aligned cursor (*hollow symbols* classic type (I/II) EDS subjects, *solid symbols* hypermobility type (III) EDS subjects, *blue* peripheral reference markers, *red* central reference markers) (colour figure online)

locations, which were no different in controls. Furthermore, if we plot these measures of precision for EDS subjects, after reaching with an aligned cursor, as a function of their Beighton scores (measure of joint hypermobility), we find a significant positive correlation between Beighton score and uncertainty range at peripheral reference marker locations (Fig. 7, $P = 0.05$, $r^2 = 0.41$). However, measures of precision at central reference marker locations were not found to be significantly correlated with Beighton score (Fig. 7, $P = 0.73$, $r^2 = 0.02$). Since there were no differences in precision between peripheral and central reference markers for control subjects, we did not conduct this analysis for our control group.

Visuomotor adaptation

Patients showed similar reaching endpoint errors to controls when reaching to targets without a cursor [$F(1, 30) = 1.91$, $P = 0.18$]. The size of these after effects were similar for both novel and trained targets after training to reach with a rotated cursor; on average, they were 12.73° more left for patients (Fig. 5, right zebra bar) and 13.89° more left for controls (right solid bar) and did not significantly differ across the groups [$F(4.13, 123.81) < 1$, $P = 0.42$]. This suggests that EDS and control subjects adapted their reaches in a similar manner in response to training with the rotated cursor.

Discussion

The goal of the present study was to examine proprioceptive abilities in EDS patients and determine whether proprioceptive sensitivity is related to the degree of joint hypermobility. Additionally, we wanted to know whether EDS patients would recalibrate their felt hand position to a similar extent as healthy controls following visuomotor adaptation. To address these questions, we determined the positions at which subjects felt their hand to be aligned with reference markers before and after adapting their reaches to a rotated cursor. Then, we compared these positions (proprioceptive estimates of hand position) to those of healthy controls. EDS patients showed similar estimates of felt hand position as controls, both before and after learning to reach with a cursor that was rotated 50° CW with respect to their hand's position. However, patients had significantly larger (almost twice the size) uncertainty ranges for estimates made at peripheral reference marker locations, when compared to controls. These uncertainty ranges did not differ across aligned and rotated sessions. They were also found to be significantly correlated with patients' Beighton scores, suggesting that those who are the most hypermobile were the least precise at these peripheral locations. Overall, these results suggest that EDS patients exhibit some deficits in proprioceptive sensitivity that may be related to the degree of joint hypermobility.

Proprioceptive acuity and joint hypermobility

There have been a handful of studies that suggest that individuals with hypermobility syndromes also experience proprioceptive deficits. Most of these studies include patients with HMS or BJHS because HMS, BJHS and EDS type III are generally considered to be the same condition (Tinkle et al. 2009). These studies exploring proprioceptive abilities in hypermobile patients typically have subjects performing remembered joint matching tasks in which they reproduce a remembered target joint angle, passively displaced, in the absence of vision with the same limb. In most cases, absolute matching errors are reported and results indicate a significant deterioration in one's ability to report the position of their limb if they have EDS or one of the other syndromes of joint hypermobility. For example, Rombaut et al. (2010a) found that patients had significantly larger absolute angular errors when repositioning their knee joint compared to healthy controls. In other studies using a similar task, patients with hypermobility were also found to have significantly larger absolute angular errors when repositioning their leg after experiencing passive placement (Fatoye et al. 2009; Hall et al. 1995; Rombaut et al. 2010a; Sahin et al. 2008). Hall et al. (1995) also found that HMS patients could not reproduce more extended limb positions as well as healthy controls. Overall, these studies suggest that those exhibiting joint hypermobility may have proprioceptive deficits.

Sahin et al. (2008) found that BJHS patients could overcome some of their proprioceptive impairments after participating in proprioceptive exercises (walking backwards, heel walking, walking with eyes closed, etc.). Improvements, this time in balance, were also found after repetitive muscle vibration in an adolescent with HMS (Celletti et al. 2011), in which their absolute angular errors became similar to control subjects. These results suggest that exercises and stimulation may improve proprioception in patients with joint hypermobility.

For the most part, the impairments and improvements in proprioception discussed above have been investigated in the lower limbs. It is less clear whether the same is true for the upper limbs. For example, Jeremiah and Alexander (2010) and Rombaut et al. (2010a) found that although BJHS patients and EDS hypermobility type III patients, respectively, had a significantly higher range of shoulder motion, there were no significant differences in absolute angular error between patients and controls during a remembered joint matching task of this upper limb. However, somewhat similar to our findings, patients were shown to have significantly higher variability than controls during this joint angle reproduction task (Jeremiah and Alexander 2010). Our study is unique in that we went beyond just measuring the sensitivity of joint angles, instead testing participants' estimates of hand position. Moreover, we tested hand position sense at locations relatively near the body, which is where most of our hand movements take place. Yet, we found that EDS patients' estimates of felt hand location were as accurate as controls, and only their precision of these estimates was impaired at more peripheral locations.

Another group known to have poor proprioceptive sensitivity is older adults (Goble et al. 2009). Interestingly, EDS is sometimes considered to resemble a disorder of aging. In testing proprioceptive abilities in older adults using a similar paradigm (Cressman et al. 2010), our laboratory specifically found that although older adults were just as accurate at estimating their felt hand position as younger adults, their uncertainty ranges were about 1.5 times larger than those of controls for the same three reference locations tested in the current study. This was somewhat smaller than the uncertainty ranges of our EDS patients, which were double those of our controls, but only at peripheral reference marker locations. Furthermore, given that the joints of older adults become less flexible with age, yet also show larger uncertainty ranges, it is possible that overall changes in joint flexibility have a global effect on proprioceptive sensitivity. We are the first to examine and show hypermobility is related to proprioceptive impairment, at least in EDS. We found that patients who were the most hypermobile were also the least precise when estimating felt hand in the periphery (showed larger uncertainty ranges). While Classic EDS and the hypermobility types indeed have distinctive genetic causes, in our small sample size, we found no difference in the overall effect of hypermobility on proprioceptive sensitivity (see Fig. 7).

The reasons for these deficits are currently unclear, but a few possible mechanisms for this impairment have been suggested by Rombaut et al. (2010a). For example, it is possible that damage to the proprioceptors (muscle spindles and Golgi tendon organs) has occurred due to joint hyperextension, which often results in the production of unsafe limb positions. Another possibility is that activation of these proprioceptors is diminished due to overall joint laxity. Finally, it is also possible that chronic pain could be mediating this proprioceptive deficit, but to our knowledge, this aspect has not been investigated in those exhibiting EDS (Rombaut et al. 2010a). Additional research efforts are needed to determine whether hypermobility *causes* proprioceptive deficits or whether it merely interferes with typical proprioceptive tuning that occurs with optimal motor performance.

The effect of visuomotor adaptation on proprioceptive recalibration

As expected, we found that EDS patients adapted their reaches to a similar extent as healthy controls after training with a misaligned cursor, suggesting that the proprioceptive deficits do not interfere with motor adaptation. These results are similar to studies on deafferented subjects, who lack proprioceptive input, yet are able to adapt to a novel visuomotor rotation and show after-effects of a similar magnitude as healthy controls (Bernier et al. 2006;

Ingram et al. 2000). Similarly, older adults, who also show poorer proprioceptive sensitivity, have also been shown to adapt just as well as younger controls, especially when the visuomotor rotation is introduced gradually (Bock and Girgenrath 2006; Buch et al. 2003; Cressman et al. 2010), although some studies have shown deficits (Anguera et al. 2011; Bock 2005; Bock and Girgenrath 2006; Seidler 2006), typically when the rotation is large and introduced abruptly. For the purposes of this study, equivalent visuomotor adaptation between controls and EDS patients allowed us to measure the effect of this adaptation on hand proprioception.

Our second aim of this study was to test whether visuomotor adaptation affected hand proprioception in EDS patients to the same extent as it did in healthy adults. It is possible that people with poor proprioception may be more vulnerable to proprioceptive recalibration, but this is not what we found. Although patients showed changes in felt hand position (i.e. leftward shifts) that were almost double those of controls (as illustrated in Fig. 4), these results were not found to be statistically significant. This is likely due to increased variability found in the patient group, but could also be because results from our controls do not show changes of the same magnitude as those found in previous studies from our laboratory (Cressman and Henriques 2009; Cressman et al. 2010; Salomonczyk et al. 2011); the changes in patients are similar to those of healthy controls in these other studies. Specifically, our controls showed a change in felt hand position of only about 10 % of the size of the visuomotor distortion, while healthy subjects in our previous studies have shown a change closer to 20 %, which is what we found in the EDS patients.

This proprioceptive recalibration, despite increased levels of uncertainty associated with proprioceptive estimates, is consistent with our previous study with older adults, which showed that, although they had poorer proprioceptive sensitivity, their felt hand position was shifted to the same extent as healthy controls after training with a rotated cursor (Cressman et al. 2010). This shift was approximately 20 % of the visuomotor distortion (30° CW) introduced and is similar to the shift seen in our EDS patients.

In contrast, cerebellar patients have been shown to recalibrate their felt hand position to a lesser extent following visuomotor adaptation (Izawa et al. 2012; Synofzik et al. 2008). Specifically, Synofzik et al. (2008) and Izawa et al. (2012) showed that, after training with rotated visual feedback of their hand movements, patients misperceived their hand movements as being in the direction of the rotated feedback to a lesser extent than healthy controls. This is not what we found given that EDS patients recalibrated their felt hand position in a similar manner as healthy controls. This suggests that proprioceptive recalibration may be less affected by possible noise in sensory afferents and may have more to do with subcortical processing.

Conclusions

The goal of the present study was to explore proprioceptive abilities in EDS patients and determine whether the degree of joint hypermobility is related to the degree of proprioceptive impairment. EDS patients showed similar proprioceptive biases to control subjects. However, despite this similarity in bias, patients showed significantly larger uncertainty ranges (less precision) at peripheral reference marker locations compared to control subjects. Interestingly, these uncertainty ranges were found to be significantly correlated with patients' Beighton scores, such that those who were the most hypermobile were the least precise when estimating their felt hand's position in the periphery. A second goal of this study was to examine proprioceptive recalibration in EDS patients following visuomotor adaptation. We found that EDS patients were able to recalibrate their felt hand's position to a similar extent as healthy controls. Overall, these findings suggest that EDS, or joint hypermobility, leads to mild impairments in proprioception such that peripheral proprioceptive signals may be noisier in this group. While the clinical implications of these peripheral proprioceptive deficits are presently unclear, it is possible that mild impairments in proprioception could cause mechanical stress leading to injury. Specifically, these deficits may permit suboptimal joint positions to be incorporated into movements, resulting in nerve and other tissue damage. More research efforts are needed to determine the reasons why joint hypermobility (resulting from mutations in collagen) is related to proprioceptive deficits and the resulting clinical implications.

Acknowledgments Special thanks to each of the patients who participated in this study, as well as the Ehlers–Danlos Syndrome Ontario Support Group for promoting awareness of this project. This work has been funded by an NSERC Discovery Grant to DYPH.

References

Anguera JA, Reuter-Lorenz PA, Willingham DT, Seidler RD (2011) Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. J Cogn Neurosci 23:11–25

Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, Hall JG, Hollister DW, Horton W, McKusick VA (1988) International nosology of heritable disorders of connective tissue, Berlin, 1986. Am J Med Genet 29:581–594

Beighton P, De Paepe A, Hall JG, Hollister DW, Pope FM, Pyeritz RE, Steinmann B, Tsipouras P (1992) Molecular nosology of heritable disorders of connective tissue. Am J Med Genet 42:431–448

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ (1997) Ehlers–Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers–Danlos National Foundation (USA) and Ehlers–Danlos Support Group (UK). Am J Med Genet 77:31–37

Bernier PM, Chua R, Bard C, Franks IM (2006) Updating of an internal model without proprioception: a deafferentation study. Neuroreport 17:1421–1425

Bock O (2005) Components of sensorimotor adaptation in young and elderly subjects. Exp Brain Res 160:259–263

Bock O, Girgenrath M (2006) Relationship between sensorimotor adaptation and cognitive functions in younger and older subjects. Exp Brain Res 169:400–406

Buch ER, Young S, Contreras-Vidal JL (2003) Visuomotor adaptation in normal aging. Learn Mem 10:55–63

Castori M (2012) Ehlers-danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. ISRN Derm 2012:1–22

Celletti C, Castori M, Galli M, Rigoldi C, Grammatico P, Albertini G, Camerota F (2011) Evaluation of balance and improvement of proprioception by repetitive muscle vibration in a 15-year-old girl with joint hypermobility syndrome. Arthritis Care Res (Hoboken) 63:775–779

Cressman EK, Henriques DYP (2009) Sensory recalibration of hand position following visuomotor adaptation. J Neurophysiol 102:3505–3518

Cressman EK, Salomonczyk D, Henriques DYP (2010) Visuomotor adaptation and proprioceptive recalibration in older adults. Exp Brain Res 205:533–544

De Paepe A, Malfait F (2004) Bleeding and bruising in patients with Ehlers–Danlos syndrome and other collagen vascular disorders. Br J Haematol 127:491–500

Fatoye F, Palmer S, Macmillan F, Rowe P, van der Linden M (2009) Proprioception and muscle torque deficits in children with hypermobility syndrome. Rheumatology (Oxford) 48:152–157

Goble DJ, Coxon JP, Wenderoth N, Van Impe A, Swinnen SP (2009) Proprioceptive sensibility in the elderly: degeneration, functional consequences and plastic-adaptive processes. Neurosci Biobehav Rev 33:271–278

Hall MG, Ferrell WR, Sturrock RD, Hamblen DL, Baxendale RH (1995) The effect of the hypermobility syndrome on knee joint proprioception. Br J Rheumatol 34:121–125

Henriques DY, Soechting JF (2003) Bias and sensitivity in the haptic perception of geometry. Exp Brain Res 150:95–108

Hollister DW (1978) Heritable disorders of connective tissue: Ehlers–Danlos syndrome. Pediatr Clin North Am 25:575–591

Ingram HA, van Donkelaar P, Cole J, Vercher JL, Gauthier GM, Miall RC (2000) The role of proprioception and attention in a visuomotor adaptation task. Exp Brain Res 132:114–126

Izawa J, Criscimagna-Hemminger SE, Shadmehr R (2012) Cerebellar contributions to reach adaptation and learning sensory consequences of action. J Neurosci 32:4230–4239

Jeremiah HM, Alexander CM (2010) Do hypermobile subjects without pain have alteration to the feedback mechanisms controlling the shoulder girdle? Musculoskelet Care 8:157–163

Keer R, Grahame R (2003) Hypermobility syndrome: recognition and management for physiotherapists. Butterworth-Heinemann, New York

Kesten H (1958) Accelerated stochastic approximation. Ann Math Stat 29:41–59

Lawrence EJ (2005) The clinical presentation of Ehlers–Danlos syndrome. Adv Neonatal Care 5:301–314

Malfait F, Wenstrup RJ, De Paepe A (2010) Clinical and genetic aspects of Ehlers–Danlos syndrome, classic type. Genet Med 12:597–605

Parapia LA, Jackson C (2008) Ehlers–Danlos syndrome—a historical review. Br J Haematol 141:32–35

Rombaut L, De Paepe A, Malfait F, Cools A, Calders P (2010a) Joint position sense and vibratory perception sense in patients with Ehlers–Danlos syndrome type III (hypermobility type). Clin Rheumatol 29:289–295

Rombaut L, Malfait F, Cools A, De Paepe A, Calders P (2010b) Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers–Danlos syndrome hypermobility type. Disabil Rehabil 32:1339–1345

Sacheti A, Szemere J, Bernstein B, Tafas T, Schechter N, Tsipouras P (1997) Chronic pain is a manifestation of the Ehlers–Danlos syndrome. J Pain Symptom Manag 14:88–93

Sahin N, Baskent A, Cakmak A, Salli A, Ugurlu H, Berker E (2008) Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int 28:995–1000

Salomonczyk D, Cressman EK, Henriques DY (2011) Proprioceptive recalibration following prolonged training and increasing distortions in visuomotor adaptation. Neuropsychologia 49:3053–3062

Seidler RD (2006) Differential effects of age on sequence learning and sensorimotor adaptation. Brain Res Bull 70:337–346

Synofzik M, Lindner A, Thier P (2008) The cerebellum updates predictions about the visual consequences of one's behavior. Curr Biol 18:814–818

Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D (2009) The lack of clinical distinction between the hypermobility type of Ehlers–Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet A 149A:2368–2370

Treutwein B (1995) Adaptive psychophysical procedures. Vision Res 35:2503–2522

Voermans NC, Knoop H (2011) Both pain and fatigue are important possible determinants of disability in patients with the Ehlers–Danlos syndrome hypermobility type. Disabil Rehabil 33:706–707