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Increasing cutaneous afferent feedback improves proprioceptive accuracy at the knee in patients with sensory ataxia

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Macefield VG, Norcliffe-Kaufmann L, Goulding N, Palma JA, Fuente Mora C, Kaufmann H. Increasing cutaneous afferent feedback improves proprioceptive accuracy at the knee in patients with sensory ataxia. *J Neurophysiol* 115: 711–716, 2016. First published December 9, 2015; doi:10.1152/jn.00148.2015.—Hereditary sensory and autonomic neuropathy type III (HSAN III) features disturbed proprioception and a marked ataxic gait. We recently showed that joint angle matching error at the knee is positively correlated with the degree of ataxia. Using intraneural microelectrodes, we also documented that these patients lack functional muscle spindle afferents but have preserved large-diameter cutaneous afferents, suggesting that patients with better proprioception may be relying more on proprioceptive cues provided by tactile afferents. We tested the hypothesis that enhancing cutaneous sensory feedback by stretching the skin at the knee joint using unidirectional elasticity tape could improve proprioceptive accuracy in patients with a congenital absence of functional muscle spindles. Passive joint angle matching at the knee was used to assess proprioceptive accuracy in 25 patients with HSAN III and 9 age-matched control subjects, with and without taping. Angles of the reference and indicator knees were recorded with digital inclinometers and the absolute error, gradient, and correlation coefficient between the two sides calculated. Patients with HSAN III performed poorly on the joint angle matching test [mean matching error 8.0 ± 0.8° (±SE); controls 3.0 ± 0.3°]. Following application of tape bilaterally to the knee in an X-shaped pattern, proprioceptive performance improved significantly in the patients (mean error 5.4 ± 0.7°) but not in the controls (3.0 ± 0.2°). Across patients, but not controls, significant increases in gradient and correlation coefficient were also apparent following taping. We conclude that taping improves proprioception at the knee in HSAN III, presumably via enhanced sensory feedback from the skin.

cutaneous afferents; familial dysautonomia; HSAN III; muscle spindles; proprioception

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY type III (HSAN III), also known as Riley-Day syndrome or, more commonly, familial dysautonomia (FD), is a rare autosomal recessive disorder that causes a deficiency of IκB kinase complex-associated protein (IKAP or elongator-1) (Anderson et al. 2001; Slaugenhaupt et al. 2001). The genotype affects the development (Pearson et al. 1978) and normal myelination (Cheishvili et al. 2007) of mainly afferent neurons. In addition to the well-known cardiovascular and respiratory complications of the disease (Filler et al. 1965; Norcliffe-Kaufmann et al. 2010), patients with HSAN III have a distinctive gait ataxia that progressively worsens with age and impacts severely their quality of life. Motor milestones are delayed in children with HSAN III, who are often described as having a "stumbling, shambling gait" (Yoslow et al. 1971); the average age at which a walking aid is required is 28 ± 1 yr. In adults, tandem walking is seldom possible and patients have a positive Romberg sign (Axelrod et al. 1981; Siggers et al. 1975).

The cause of the gait ataxia in patients with HSAN III is not definitively known. Autopsy studies show little evidence of cerebellar atrophy, while muscle tone and strength are normal (Brown et al. 1964; Cohen and Solomon 1955; Yatsu et al. 1964). The incidence of orthopedic problems, including kyphoscoliosis and Charcot joints (Axelrod and Gold-von Simpson 2007; Bar-On et al. 2000; Gold-von Simpson and Axelrod 2006; Yoslow et al. 1971) is increased in HSAN III, but gait ataxia occurs even in patients who do not have orthopedic complications. Tendon and H-reflexes are absent (Aguayo et al. 1971; Macefield et al. 2011; Mahloudji et al. 1970; Riley et al. 1974), which, given that these reflexes depend on mechanical and electrical activation of muscle spindle afferents, respectively, may account for the clinical observation of disturbed proprioception in these patients; it is known that muscle spindles play the dominant role in the perception of limb position and movement (Burke et al. 1988; McCloskey 1978; Proske and Gandevia 2009). Taken together, these findings suggest that the gait ataxia in HSAN III is predominantly of sensory origin.

Recent work from our laboratory has shown that muscle spindle afferents, as recorded via intraneural microelectrodes inserted into muscle fascicles of the common peroneal nerve, are functionally absent in patients with HSAN III (Macefield et al. 2011). Moreover, we recently showed that there was a tight linear relationship between loss of proprioceptive accuracy seen in HSAN III patients and the severity of gait impairment, which we attributed to the loss of muscle spindle afferents (Macefield et al. 2013). Nevertheless, despite an absence of functional muscle spindle afferents in all patients studied, proprioception was not compromised equally in all; some patients had almost normal proprioception (Macefield et al. 2013).

Interestingly, histological studies have shown normal Meissner and Pacinian corpuscles in the skin (Pearson et al. 1971; Winkelmann et al. 1966), and these sensory cutaneous receptors appear to be functional in these patients; apparently normal activity of low-threshold mechanoreceptor afferents, including afferents sensitive to lateral skin stretch (slowly adapting type II afferents, believed to innervate the Ruffini ending), could be recorded from cutaneous fascicles of the peroneal nerve

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(Macefield et al. 2011). Cutaneous afferents, including Meissner, Merkel, and Ruffini endings, have been shown to be able to provide signals of joint movements in the hand (Burke et al. 1988; Collins et al. 2005; Edin 1992, 2004; Hulliger et al. 1979), ankle (Aimonetti et al. 2007, 2012), and knee (Edin 2001), with the slowly adapting type II (SAII) and SAIII (Edin 2001) afferents, both of which are sensitive to skin stretch, being the most likely candidates responsible for signaling limb movement and/or position (Chambers et al. 1972; Edin 1992, 2001, 2004). It should be pointed out that no receptor has yet been attributed to the SAIII afferent, which, unlike the SAII afferent, has very small, well-defined receptive fields (Edin 2001, 2004).

It has been shown that taping the knee joint, which has been suggested acts to increase proprioceptive afferent feedback without affecting mechanical stability of the joint, aids joint positioning at the knee in healthy subjects (Callaghan et al. 2002), as well as in patients with patellofemoral pain syndrome (Callaghan et al. 2008) or anterior cruciate ligament tears (Jerosch and Prymka 1996). We hypothesized that this technique could be of use in patients with HSAN III by increasing the tensile strain in the skin and hence increasing the afferent feedback provided by cutaneous afferents. Our aim, therefore, was to determine whether joint taping could enhance proprioceptive accuracy at the knee joint in patients with HSAN III. For comparison, we also applied tape to the knee joints in a sample of healthy age-matched controls.

METHODS

Twenty-five patients with HSAN III (19 females, 6 males, age 29 ± 2 yr, mean ± SE) and nine age-matched controls (5 females, 4 males, age 30 ± 4 yr) were recruited to participate in the primary study. All patients had typical clinical histories and molecular confirmation of the common HSAN-III 9q gene mutation. All had documented dulled temperature and pain perception and characteristic blood pressure abnormalities, and all reported difficulty walking. All were being actively followed by the Dysautonomia Center at New York University (NYU) School of Medicine. Informed consent was obtained from all participants before enrollment; all procedures were approved by the Institutional Review Board of NYU.

Protocol. After signing informed consent, patients first underwent a full neurological evaluation with assessment of myotatic reflexes. In 12 patients, the degree of ataxia was quantified using the 5-item Brief Ataxia Rating Scale (BARS; Schmahmann et al. 2009), in which a maximum score of 30 (severe ataxia) can be obtained from rating the following parameters: *1*) gait, assessed over a 10-m path, two back-and-forth journeys with each including turns (0 = normal, 8 = needs 2 people to assist, requires a wheelchair); *2*) knee-to-tibia test, which assesses decomposition of movement and intention tremor (0 = normal, 4 = lowering jerkily with extremely long lateral movements, or test impossible; left and right sides); *3*) the finger-to-nose test, which assesses decomposition of movement and dysmetria of the arm and hand (0 = normal, 4 = dysmetria preventing the patient from reaching the nose; left and right sides); *4*) dysarthria, in which the patient is asked to repeat a standard sentence (0 = normal, 4 = speech absent or unintelligible); and *5*) oculomotor abnormalities (0 = normal, 2 = prominently slowed pursuit, saccadic intrusions, hypo/hypermetric saccades, nystagmus). Patients were then randomized to determine the order in which their assessments were carried out (taped vs. nontaped) using a two-block random number generation scheme. Patients were fitted with a loose medical gown, leaving their legs uncovered. Although blinding to the randomization allocation was not possible because the tapes were visible, participants were unaware of the hypothesis that taping might improve proprioceptive score outcomes. Proprioceptive accuracy was assessed with and without the tape, which was applied to both knees.

Proprioceptive accuracy. Evaluations were carried out with the patient in the seated position with the back supported. The height of the bed was adjusted so that the legs could hang freely, at 90° to the thigh, and subjects could comfortably perform full flexion and extension of the knee without feeling the edge of the bed. Digital inclinometers, with a resolution of 0.01° (Digital 360 Angle Cube; Quint Graphics) were positioned at mid-calf height on the lateral aspect of each leg. Marks were placed on the legs so that the inclinometer could be positioned in the same place on each run. Subjects were instructed to keep their hands by their sides and keep their eyes closed, and when necessary blindfolds were used to prevent the subjects from seeing their lower legs. As described previously, proprioceptive accuracy was assessed at the knee joint (Macefield et al. 2013). The reference knee was determined to be the dominant leg, i.e., the right knee if the patient was right-handed. Before each leg movement the digital inclinometers were calibrated to 0.00° in the free-hanging vertical position. Patients were told not to actively move their leg themselves, but to allow the investigator to take the weight of their leg and move their leg passively. Flexion and extension movements were imposed on the reference leg about the axis of rotation of the knee by gently guiding the patient's foot (at the shoe) at a rate of ∼2°/s, as described previously (Macefield et al. 2013). The indicator leg was then moved by a second investigator until the subject reported that the legs were perceived to be at the same angle. Several trial runs were carried out until the subject understood the requirements. The reference leg was moved to varying degrees of flexion or extension (target angles of 7°, 14°, and 21°) in random order and was then returned to the neutral (vertical) position (0°) after each movement by letting this leg and the

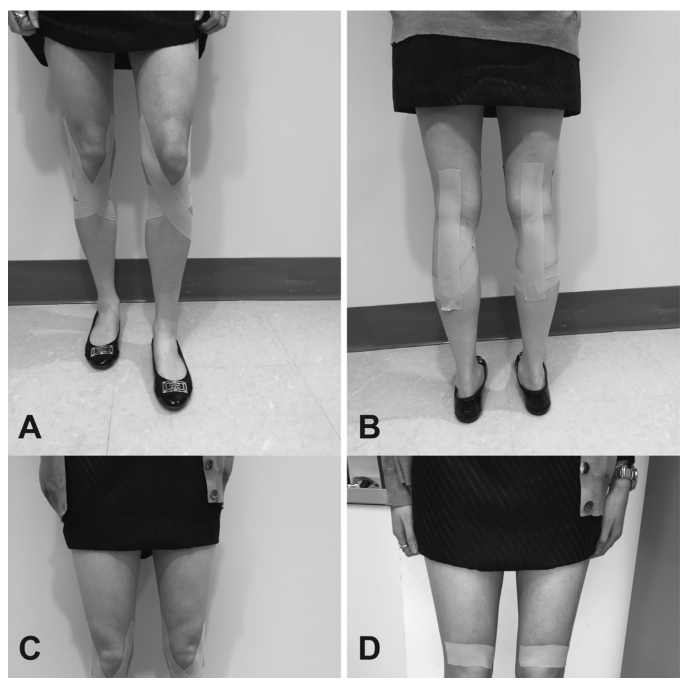

Fig. 1. Photographs of the taping technique used to assess the effects of taping on proprioceptive accuracy at the knee joint in one hereditary sensory and autonomic neuropathy type III (HSAN III) patient. The patient provided written consent for the photographs to be reproduced. *A*: each tape was stretched around the knee to the opposite side of the thigh in an X-shaped formation to allow maximum tension in the flexed position. *B*: an additional strip of tape was applied to the back of the leg, from the mid hamstring to mid calf, to create tension in the extended position. *C*: close-up view of the front of the knee in the normal taping position. *D*: close-up view of the front of the knee in the sham taping position.

indicator leg drop back under gravity to their natural pendent position. Each block of movements, comprising the three angles in both flexion and extension, was repeated four times, in a random sequence (Schultz and Grimes 2002); the total number of trials delivered was 24. Both the reference and indicator angles were recorded and the absolute difference, slope, and correlation coefficient between the two angles calculated, as described previously (Macefield et al. 2013). Subjects were not given feedback on their performance during the procedure. Other sets of 24 trials were delivered following application of kinesiology tape and again with sham taping.

Taping. Each subject's left and right knees were taped using kinesiology tape, the unidirectional elasticity of which permitted stretch in length as the knee bent but no stretch in width. Two tapes, 30 cm in length, were anchored on either side of the lower leg just below the knee. To allow maximum tension in the flexed position, each tape was stretched around the knee to the opposite side of the thigh in an X-shaped formation (Fig. 1, *A* and *C*). An additional 30-cm strip of tape was applied to the back of the leg, from the mid hamstring to mid calf, to create tension in the extended position (Fig. 1*B*). In seven subjects, sham taping was applied as a single horizontal 10-cm strip of tape above the knee such that there was negligible stretching of the tape during either flexion or extension of the knee (Fig. 1*D*).

Statistical analysis. For each patient, proprioceptive accuracy was determined from the average mean absolute error (i.e., difference) between the reference leg and indicator knee joint angle, as well as from the gradient (slope) and the correlation coefficient between the two angles. All statistical analyses were performed using GraphPad (version 6.00 for Mac; GraphPad Software, La Jolla, CA). Paired *t*-tests were used to compare normally distributed data. For data that was not normally distributed, the Wilcoxon matched-pairs signed rank test was used to compare differences in proprioceptive accuracy across patients before and after taping, whereas the unpaired Mann-Whitney test was used to compare proprioceptive accuracy between patients and control data obtained in a previous study. Other specific tests are reported in RESULTS. Significance was taken at $P < 0.05$. All data are means ± SE.

RESULTS

Clinical features. All patients had obvious difficulty walking and all had noticeable postural sway. Five patients used walking aids and one was wheelchair bound. The mean composite BARS score, which included all elements of the BARS assessment, was 13 ± 2. The score for gait alone ranged from 1 to 8, with 1 being almost normal and 8 meaning that walking was impossible, with a group average of 4 ± 1.

Proprioception without taping. Proprioceptive accuracy with and without tape was measured in all 25 patients with HSAN III. Without the tape, patients performed poorly at matching joint angle. Eleven patients were not able to perceive the direction of movement of their indicator leg at all; the remaining patients had obvious difficulty matching the joint angle. Regardless, all patients completed the proprioceptive assessments. Mean absolute error was 8.0 ± 0.8°. For comparison, a group of 9 age-matched control subjects had a mean matching error of 3.0 ± 0.3° ($P < 0.0001$; unpaired Mann-Whitney test), as reported previously (Macefield et al. 2013). Patients with the highest composite BARS score had the highest mean absolute error in angle matching, as determined in 12 patients ($r = 0.67$, $P < 0.02$). The mean gradient (slope)

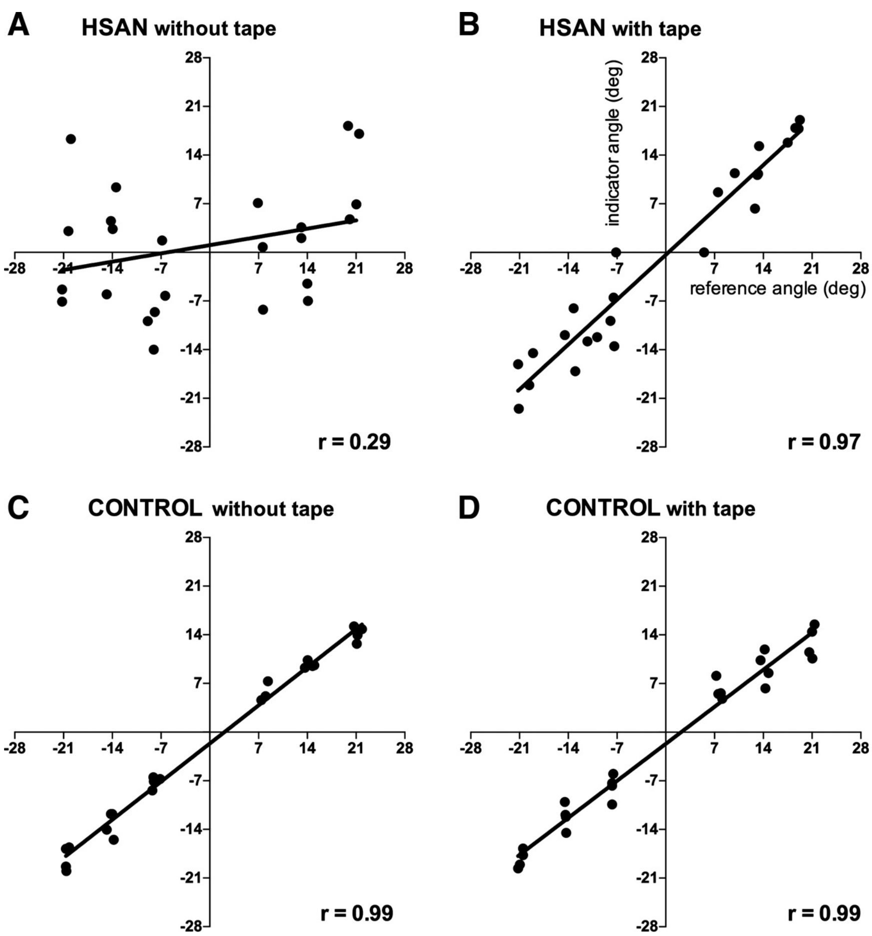

Fig. 2. Correlation between reference and indicator angles for one HSAN III patient before (*A*) and after (*B*) taping of the knee joints and for an age-matched control subject before (*C*) and after (*D*) taping. Angles of the reference knee are shown on the *X*-axis and angles of the indicator knee on the *Y*-axis. Extension of the knee joint is shown as a positive value and flexion as a negative value. Taping increased the gradient (slope) of the relationship between the reference and indicator knee joint angles and decreased the scatter of the matched joint angles, representing an improvement in proprioceptive accuracy. Correlation values are also indicated in each condition.

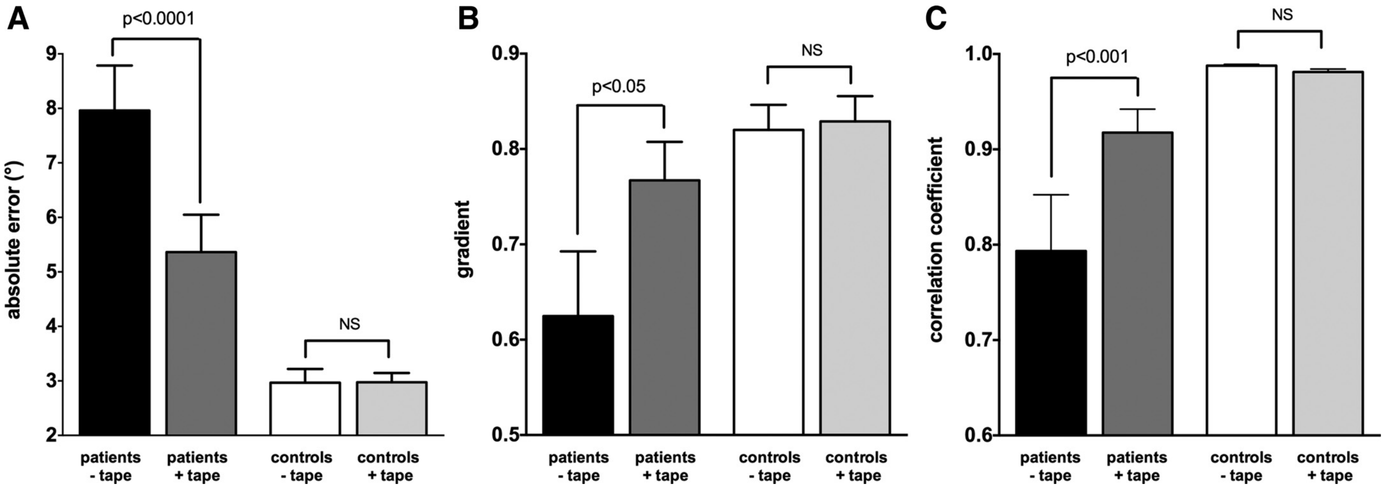

Fig. 3. Changes in mean (±SE) knee-joint angle matching error (*A*), gradient (*B*), and correlation coefficient (*C*) for 25 HSAN III patients and 9 age-matched control subjects before and after taping. NS, not significant.

of the relationship between the reference and indicator angles was 0.62 ± 0.07, whereas the mean correlation coefficient between these angles was 0.79 ± 0.06. Conversely, both the gradient and correlation coefficient should be close to 1 for individuals with normal proprioception; these were 0.82 ± 0.03 and 0.99 ± 0.00, respectively, which were significantly different from the gradient ($P < 0.0001$; unpaired *t*-test) and correlation ($P < 0.0001$; unpaired Mann-Whitney test) of the patients.

Proprioception with taping. Figure 2, *A* and *B*, shows experimental records of proprioceptive performance in a 56-year-old female HSAN III patient, with and without taping. The scatter of joint angles between the reference and indicator sides was very wide before taping (Fig. 2*A*) but decreased when the patient was retested following application of the tape (Fig. 2*B*). This resulted in a reduction in mean matching error, as well as an increase in gradient and an increase in the correlation coefficient. Conversely, data from a 57-year-old female control subject showed no such improvement following taping, although her proprioception was clearly very good in the absence of tape (Fig. 2, *C* and *D*).

On average, as indicated in Fig. 3*A*, mean absolute error decreased significantly in the patients with taping (8.0 ± 0.8 vs. 5.4 ± 0.7°, $P < 0.0001$; Wilcoxon matched-pairs signed rank test), but, as shown in Fig. 3*B*, there were no significant changes in the controls (3.0 ± 0.3 vs. 3.0 ± 0.2°, $P = 0.97$; paired *t*-test). Across patients, significant increases in gradient (0.77 ± 0.04 vs. 0.62 ± 0.07, $P = 0.035$; paired *t*-test) and correlation coefficient (0.92 ± 0.02 vs. 0.79 ± 0.06, $P = 0.0002$; Wilcoxon matched-pairs signed rank test) were also apparent following taping, but there were no such changes in the controls (0.83 ± 0.03 vs. 0.82 ± 0.03, $P = 0.60$; paired *t*-test) and (0.98 ± 0.00 vs. 0.99 ± 0.00, $P = 0.12$; Wilcoxon matched-pairs signed rank test).

Figure 4 shows data from a subset of seven patients in whom we assessed proprioceptive accuracy without and without taping, and in a sham taping condition in which a strip of tape was applied horizontally above the knee (see Fig. 1*D*). There was no significant effect of sham taping on proprioceptive performance: mean joint angle matching errors were not significantly different. Conversely, as expected, the standard (vertical) taping caused a significant fall in error (ANOVA: Friedman test with Dunn's correction for multiple comparisons).

DISCUSSION

The aim of this study was to investigate whether increasing the proprioceptive feedback provided by cutaneous afferents around the knee would improve proprioceptive accuracy in patients with HSAN III. We have shown in a large sample of patients with HSAN III ($n = 25$) that taping the skin in a vertical pattern around the knee improved proprioceptive joint angle matching errors; in a subset of patients we have shown that horizontal (sham) taping, which did not increase tensile strain in the skin, had no effect. Not surprisingly, taping did not improve proprioception in the control subjects.

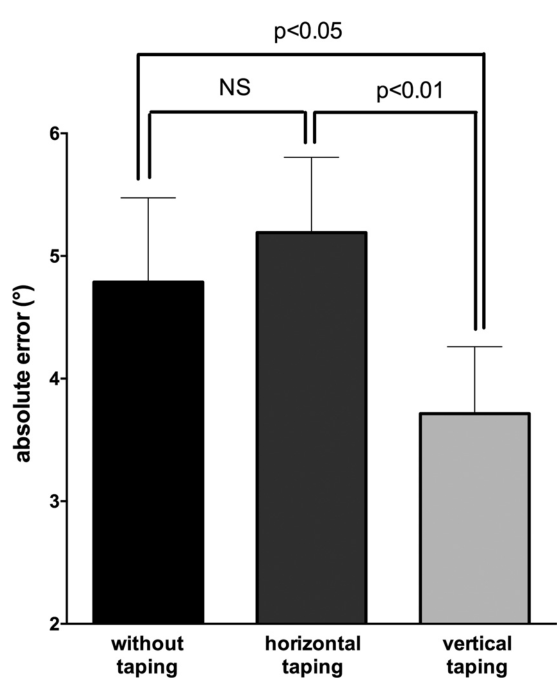

Fig. 4. Changes in mean (±SE) angle matching error for 7 HSAN III patients before and after vertical taping and horizontal (sham) taping. Only vertical taping produced an improvement in proprioceptive accuracy.

Muscle spindles, as the primary proprioceptors, play a major role in the sensations of limb position and movement (McCloskey 1978; Proske and Gandevia 2009). Conversely, joint receptors are sensitive primarily at the limits of joint rotation (Burke et al. 1988) and play a very minor role in proprioception, as evidenced by the lack of proprioceptive loss in patients who have had joint replacement surgery, in whom the ability to detect joint position was unaffected despite removal of all capsular and ligamentous components of the hip joint (Grigg et al. 1973). This was confirmed by further studies involving intracapsular injection of a local anesthetic into both knee joints, after which the ability to detect angular changes in joint position was unaltered (Clark et al. 1979). In addition, compelling evidence supporting the primary role of the muscle spindles was seen in studies looking into the effects of muscle vibration, a potent excitatory stimulus for muscle spindles (Fallon and Macefield 2007; Goodwin et al. 1972), and studies that assessed proprioceptive performance after muscles were disengaged from joints (Gandevia and McCloskey 1976) or by directly pulling on the surgically isolated tendon (McCloskey et al. 1983).

Recent work from our laboratory has shown that proprioception is essentially normal in patients with multiple system atrophy of the cerebellar phenotype (MSA-C); by definition, these patients have an ataxic gait because of cerebellar atrophy (Macefield et al. 2013). As described previously (Macefield et al. 2013), patients with HSAN III performed poorly in their assessment of proprioceptive accuracy, with high levels of error when matching the indicator leg with the reference leg. Moreover, proprioceptive performance correlated positively with gait scores and overall ataxia scores in the BARS. This indicated that intact proprioception is important for the control of gait in HSAN III. Although functional muscles spindle afferents appear to be absent in HSAN III, and small-diameter tactile afferent function is affected (Macefield et al. 2014), large-diameter cutaneous afferent innervation is intact (Macefield et al. 2011). It is known that input from cutaneous afferents can contribute to the awareness of joint position (Collins et al. 2005; Edin 2001); slowly adapting type II or III afferents in the skin around the knee (Edin 2001) are likely to be responsible for providing this proprioceptive information.

Limitations. Although movements were imposed passively, and participants were instructed not to assist in moving their indicator leg, we do need to acknowledge that EMG was not recorded, so we cannot be absolutely certain that the legs were fully relaxed. Nevertheless, the investigators could feel if any resistance or assistance to the passive movements occurred and could repeat any trials in which they judged the participant to be actively resisting or assisting. Importantly, despite this potential methodological limitation, the proprioceptive performance was worse in the patients than in the controls and was improved by taping in the patients but not in the controls. Another limitation was that we did not have the same number of patients ($n = 25$) and age-matched controls ($n = 9$), but given that proprioceptive performance in the controls was so consistently superior, we did not consider it warranted to increase the number of control subjects simply to obtain parity between the two groups. Moreover, mean matching errors for the control subjects in the current study (3.0 ± 0.2°) were identical to those of a larger cohort of 14 subjects (3.0 ± 0.2°) reported previously (Macefield et al. 2013); the same was true for the gradient of the relationship between reference and indicator angles (0.82 ± 0.03 vs. 0.86 ± 0.03) and for the correlation coefficient (0.99 ± 0.00 vs. 0.98 ± 0.00).

Conclusions. We have shown that proprioceptive accuracy at the knee joint improved after vertical taping over the knee. We postulate that the elastic tape attached to the skin increases the tensile strain in the skin during joint rotation and thereby increases the sensory feedback from the intact large-diameter tactile afferents in patients with HSAN III. Applying a strip of tape horizontally above the patella as a sham procedure had no effect on proprioceptive performance, presumably because in this condition there was negligible stretch of the tape during flexion and extension of the knee and hence little change in tensile strain about the knee. Whether applying tape around a joint improves sensorimotor control in patients with HSAN III remains to be determined.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

V.G.M. conception and design of research; V.G.M., L.N.-K., N.G., J.-A.P., and C.F.M. performed experiments; V.G.M., L.N.-K., N.G., J.-A.P., and C.F.M. analyzed data; V.G.M., L.N.-K., N.G., and H.K. interpreted results of experiments; V.G.M. and N.G. prepared figures; V.G.M., L.N.-K., N.G., J.-A.P., C.F.M., and H.K. edited and revised manuscript; V.G.M., L.N.-K., N.G., J.-A.P., C.F.M., and H.K. approved final version of manuscript; N.G. drafted manuscript.

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