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Supporting Data

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Intact Organization of Tactile Space Perception in Isolated Focal Dystonia

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ABSTRACT: Background: Systematic perceptual distortions of tactile space have been documented in healthy adults. In isolated focal dystonia impaired spatial somatosensory processing is suggested to be a central pathophysiological finding, but the structure of tactile space for different body parts has not been previously explored.
Objectives: The objective of this study was to assess tactile space organization with a novel behavioral paradigm of tactile distance perception in patients with isolated focal dystonia and controls.
Methods: Three groups of isolated focal dystonia patients (cervical dystonia, blepharospasm/Meige syndrome, focal hand dystonia) and controls estimated perceived distances between 2 touches across 8 orientations on the back of both hands and the forehead.
Results: Stimulus size judgments differed significantly across orientations in all groups replicating distortions of tactile space known for healthy individuals. There were no differences between groups in the behavioral parameters we assessed on the hands and forehead.
Conclusions: Tactile space organization is comparable between patients with isolated focal dystonia and healthy controls in dystonic and unaffected body parts.

Key Words: focal dystonia; somatosensation; tactile distance perception; cervical dystonia; blepharospasm; somatosensory receptive fields

Isolated focal dystonias (IFDs) are phenomenologically characterized by abnormal movements and/or postures.[1] Although overt sensory deficits are absent, abnormalities in somatosensory processing have been documented in various types of IFDs not only in dystonic, but also in nonaffected body parts (reviewed in reference 2). While changes in temporal somatosensory processing in IFDs are well documented with an array of different assessment tools,[2,3] the role of spatial somatosensory findings remains less well understood.

Already in 1834, Weber observed that the perceived distance between 2 tactile stimuli relates systematically to tactile sensitivity, a finding that was later associated with cortical receptive field (RF) size.[4] RFs for body regions with hairy skin are usually oval shaped.[5,6] This asymmetric structure leads to varying size estimations depending on stimulus orientation: tactile distances are perceived as larger in the mediolateral than in the proximodistal body axis, an effect called anisotropy (Fig. 1A).[4,7-11] Recently, a paradigm has been developed that allows testing of tactile spatial perception across 8 orientations to provide a more accurate estimation of RF size, shape, and orientation.[7] Indeed, perceptual distortions of tactile space match cortical tactile space organization in the primary somatosensory cortex.[12]

Previous literature shows impaired tactile spatial acuity in different forms of IFD[13-17] that is suggested to reflect a degradation of somatotopic organization in the somatosensory cortex.[18-22] We therefore employed a novel behavioral paradigm to examine the perceptual organization of tactile space in IFD. Specifically, we assessed affected and unaffected body parts across a comparatively large patient population with different IFDs (cervical dystonia [CD], blepharospasm [BSP]/Meige syndrome, and focal hand dystonia [FHD]) and healthy controls with the aim to establish their relation with the expression of dystonic symptoms. We hypothesized that owing to their phenotypic variability, the different forms of IFD would demonstrate systematic changes in tactile space organization in the body parts we assessed.

Methods

Fifty seven right-handed patients diagnosed with IFD[1] (n = 21, cervical dystonia; n = 16, BSP/Meige syndrome; n = 20, task-specific FHD of the dominant hand) and 21 age-matched healthy controls participated. The study was approved by the Charité University Medicine Berlin ethics committee. All participants gave written informed consent. Exclusion criteria were acquired causes of dystonia (eg, medication, brain lesions), peripheral neuropathy, skin conditions (eg, eczema, scars) in assessed areas, inability to perform the task (eg, dementia), and prior botulinum toxin treatment ≤ 12 weeks.

We investigated the perceived distance between 2 tactile stimuli separated 25, 30, 35, and 40 mm[4,7,10,23] (Fig. S1) at eight 22.5°-spaced orientations[7] on the back of the dominant right and nondominant left hand and the forehead (Fig. 1B,C). We touched the skin simultaneously with both stimuli for approximately 1 second in alignment with 1 of the 8 orientations on each trial and asked participants to verbally estimate the perceived distance between the tactile stimuli in centimeters.

For each trial we expressed judged size as a proportion of actual size, which was then averaged across stimulus sizes for each of the 8 orientations. First, we examined whether perceived stimulus size depends on orientation and whether this differs between groups via mixed analysis of variance (ANOVA). Second, we calculated the magnitude of anisotropy (judged stimulus size in mediolateral [0°] vs proximodistal [90°] axis) for each group and ran group comparisons using 1-factor ANOVA. To verify that anisotropy is >1 (ie, stimuli are

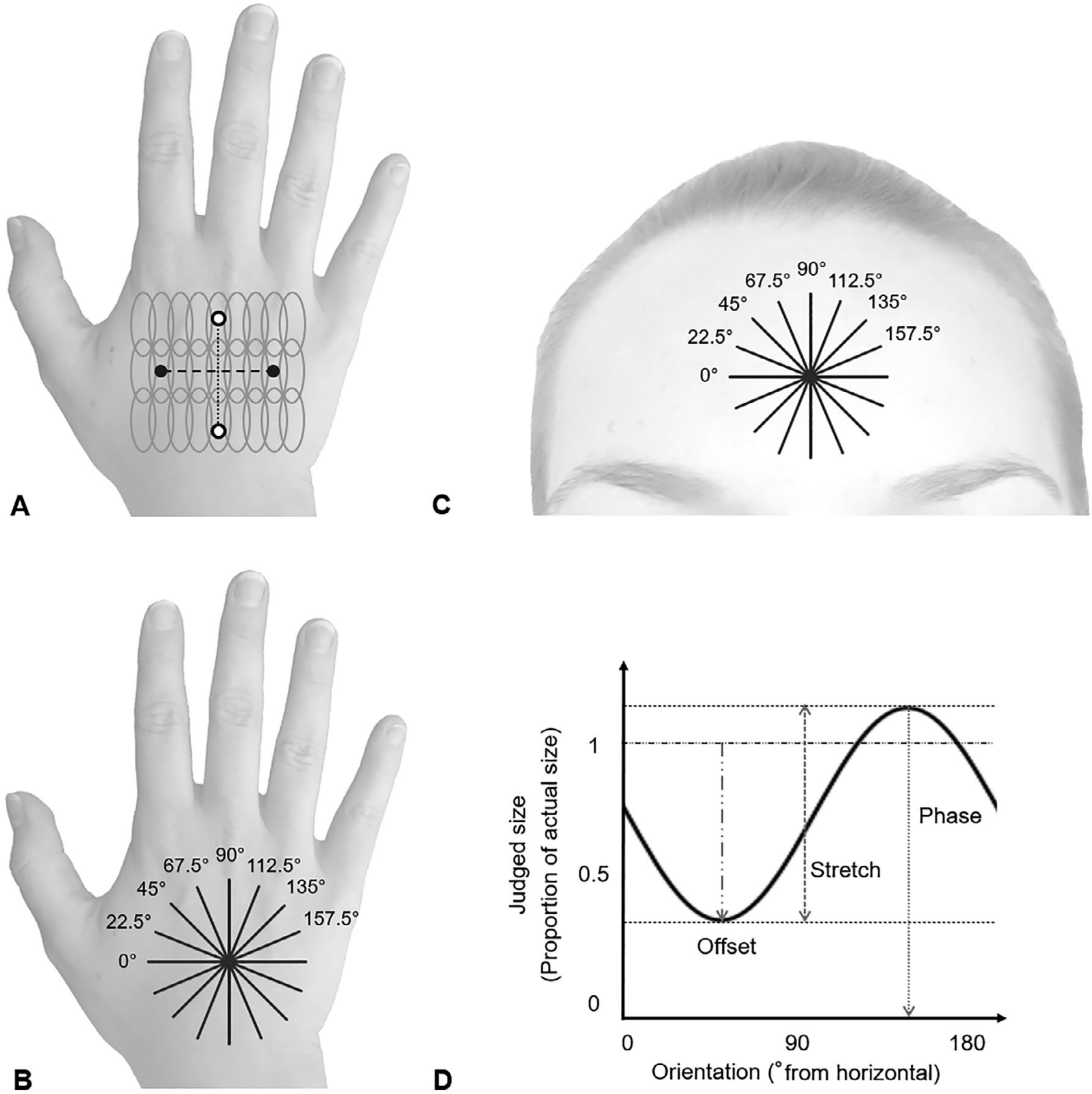

FIG. 1. (**A**) Tactile distance perception according to the pixel model proposed by Longo and Haggard.[4] The oval shape of receptive fields leads to different perception of equal tactile distances along the proximodistal and mediolateral body axis. More receptive fields lie between the 2 tactile stimuli in the mediolateral axis (black circles, dashed line) than in the proximodistal axis (white circles, dotted line). Thus, the perceived distance between 2 stimuli with equal gaps is longer in the mediolateral than in the proximodistal axis, an effect known as anisotropy. (**B, C**) The formation of the 8 stimulus orientations spaced in 22.5° intervals on the dorsum of the dominant right hand (**B**) and on the forehead (**C**). The 90° orientation was placed between the center of the wrist and the metacarpophalangeal joint of the middle finger, and of the middle hairline and the tip of the nose, respectively. Accordingly, the 0° orientation represented the mediolateral axis of the hands and the ear-to-ear axis of the face, respectively. Note, that the orientations were mirrored on the nondominant left hand, that is, arranged counterclockwise so that specific orientations referred to similar reference points on both hands. (**D**) The 3 essential parameters of the experimental model: the stretch parameter controls the sinusoid's amplitude (peak-to-trough distance) and reveals the magnitude of anisotropy. The phase parameter shifts the sinusoid along the *x* axis and determines at which orientation tactile distances are perceived as largest. The offset parameter shifts the sinusoid along the *y* axis (expressed as the distance of the sinusoid's trough from 1) and informs how large stimuli were rated. [Color figure can be viewed at wileyonlinelibrary.com]

judged longer in the mediolateral axis), 1-sample *t* tests were performed for each group. We used ANOVA to compare the magnitude of anisotropy between groups. Third, to evaluate the precision of stimulus size ratings, we compared their variance between groups via mixed ANOVA.

Distortions of tactile distance perception reflect a simple and coherent stretch of tactile space. Thus, individual experimental data can be fitted to a model predicting tactile distance judgments as a sinusoidal function of stimulus orientation.[7] This model is based on 3 parameters: *stretch* — regulates the sinusoid's amplitude (peak-to-trough distance), that is, the magnitude of anisotropy across orientations; *phase* — shifts the sinusoid along the *x* axis, that is, determines orientation at which tactile distances are perceived as largest; and *offset* — shifts the sinusoid along the *y* axis (distance of curve's trough from 1), that is, informs how large the stimuli were rated (Fig. 1D). Models were fitted to grand mean and individual participant data.

We used ANOVAs to compare the stretch and offset parameter and also conducted Bayesian ANOVAs[24,25] to determine whether nonsignificant results provide support for the null hypothesis. We examined phase alignment across participants using Rayleigh's test.[26,27] We performed the Watson–Williams test to examine whether the phase differs between groups.[27] Calculations were run separately for each body part. Complete methods and analyses are provided as a supplement.

Results

Dystonic patients and controls did not differ in age (60.9 ± 12.7 vs 58.2 ± 9.4 years; $P = 0.17$) and distribution of sex ($P = 0.65$). Disease duration did not differ, albeit marginally, between patient groups ($P = 0.06$; Table S1).

Stimulus size judgments differed significantly across orientations (nondominant hand, $P < 0.0001$; dominant hand, $P < 0.0001$; forehead, $P < 0.0001$). There was no effect of group (nondominant hand, $P = 0.67$; dominant hand, $P = 0.14$; forehead, $P = 0.62$) or group × orientation interaction (nondominant hand, $P = 0.83$; dominant hand, $P = 0.6$; forehead, $P = 0.27$).

The mediolateral was judged significantly larger than the proximodistal axis for each group on each body part (eg, nondominant hand; controls, $P < 0.0001$; CD, $P < 0.0001$; BSP, $P = 0.04$; FHD, $P = 0.001$). However, the magnitude of anisotropy did not differ between groups (nondominant hand, $P = 0.82$; dominant hand, $P = 0.18$; forehead, $P = 0.83$). Also, the variance of stimulus size ratings did not differ between groups (nondominant hand, $P = 0.78$; dominant hand, $P = 0.45$; forehead, $P = 0.51$).

Best-fitting sinusoids to grand mean and individual participant data fit well. R^2 as well as residuals, representing deviations from the model, did not differ between groups (R^2, nondominant hand, $P = 0.11$; dominant hand, $P = 0.54$; forehead, $P = 0.48$; residuals, nondominant hand, $P = 0.57$; dominant hand, $P = 0.41$; forehead, $P = 0.65$).

Experimental results and best-fitting sinusoids for each group and body part are provided in Figure 2A.

No differences between groups in the sinusoid's amplitude and therefore in the magnitude of anisotropy were detected (nondominant hand, $P = 0.61$; dominant hand, $P = 0.22$; forehead, $P = 0.5$; Fig. 2B, amplitude). In addition, Bayes factor provided decisive evidence in favor of the null hypothesis, that is, no difference in amplitudes between groups (nondominant hand: $BF_{01} = 7.47$; dominant hand: $BF_{01} = 2.91$; forehead: $BF_{01} = 6.15$).

A directed distribution of the phase, that is, orientation at which distances are perceived as largest, was seen for each group and body part. However, the phase did not differ between groups (nondominant hand, $P = 0.69$; dominant hand, $P = 0.34$; forehead, $P = 0.51$; Fig. 2B, phase).

Curve offsets, that is, global size estimation of stimuli ratings, did not differ between groups (nondominant hand, $P = 0.62$; dominant hand, $P = 0.16$; forehead, $P = 0.62$; Fig. 2B, offset). Again, Bayes factor strongly supported the null hypothesis (nondominant hand: $BF_{01} = 7.83$; dominant hand: $BF_{01} = 2.28$; forehead: $BF_{01} = 7.5$). Complete results are provided as a supplement.

Discussion

We explored tactile space organization across IFD patients using a novel behavioral paradigm, which allows quantification of distortions in tactile spatial perception and matches cortical tactile space organization in the primary somatosensory cortex.[7,12] Clearly, stimulus size judgments differed across orientations in controls *and* in groups of patients with CD, BSP/Meige syndrome, and FHD, replicating distortions of tactile space previously shown for healthy individuals.[7] However, contrary to our hypothesis, we found that there was neither a change in the magnitude of anisotropy nor in the axis at which tactile distances were perceived as largest or in the global stimulus size estimation between groups. These findings suggest that the shape, orientation, and magnitude of somatosensory RF are widely comparable between patients and controls in unaffected (eg, hands in BSP/Meige syndrome) and dystonic body parts (eg, dominant hand in FHD).

RF overlap is physiological. However, its extent in health and disease remains unclear.[28,29] In FHD, functional magnetic resonance imaging,[19] magnetoencephalography,[20] and somatosensory-evoked potentials[18] indicate abnormal somatotopic organization in the primary and secondary somatosensory cortices with "merged" representation of single fingers, which was also seen in a primate model of FHD.[30,31] Behavioral measures such as spatial acuity, suggested to reflect cortical RF size, have corroborated this pathophysiological view.[13-17] It is surprising, therefore, that we found no evidence of abnormal representation of tactile space in the 3 different IFD phenotypes for all tested body parts. Indeed, IFD patients showed distortions of tactile space similar in nature and magnitude to those observed in healthy controls, possibly indicating that the structure and order of somatosensory RF in different IFD phenotypes is overall intact (Fig. S2A).

Lack of significant group differences could also be due to the body parts we assessed. Most previous

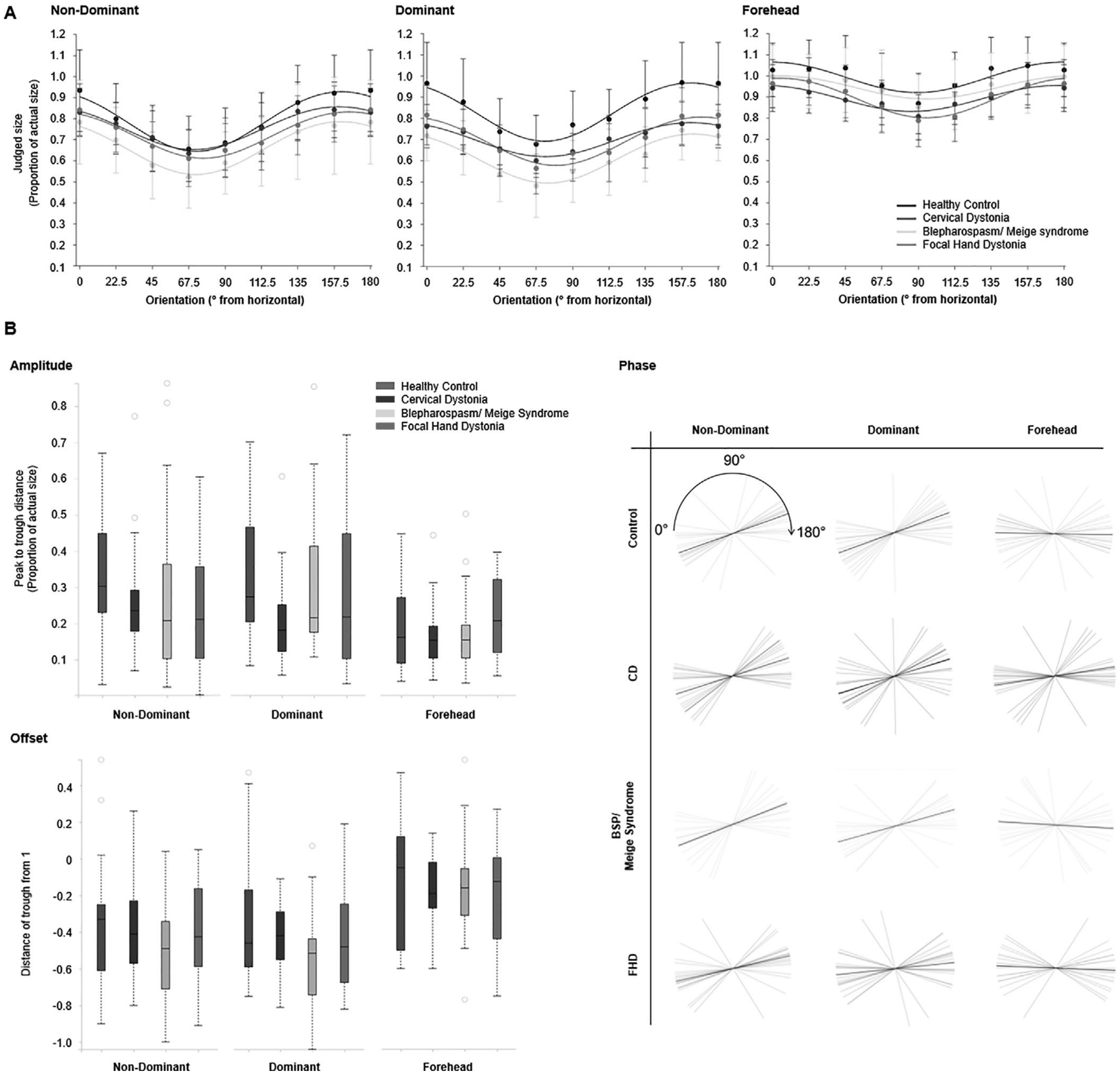

FIG. 2. (**A**) Experimental results showing judged size as a function of stimulus orientation (degrees from mediolateral). Experimental data are plotted as mean ± 95% confidence interval. Lines show the best-fitting sinusoid according to our model for each group (healthy controls, n = 21; cervical dystonia, n = 21; blepharospasm and Meige syndrome, n = 16; focal hand dystonia, n = 20) and each body part. Note that the same data point is shown as both 0° and 180° for illustrative purposes. (**B**) Model parameters. The stretch parameter represented by the sinusoid's amplitude (peak-to-trough distance) and the offset parameter (distance of the sinusoid's trough from 1) are displayed as box plots for each group (healthy controls, n = 21; cervical dystonia, n = 21; blepharospasm and Meige syndrome, n = 16; focal hand dystonia, n = 20) and each body part (nondominant and dominant hands, forehead). Lines within the box indicate the sample median, Whiskers indicate 1.5× the interquartile range. For the phase, each line indicates the orientation at which tactile distances were perceived largest for a single participant. Black lines indicate the average orientation at which distances were perceived as largest across participants of each group for each body part. Note that the phases are mirrored for the nondominant hand to allow better visual comparison of data between body parts. [Color figure can be viewed at wileyonlinelibrary.com]

studies on tactile spatial discrimination assessed the fingertips or lips.[2,22] It could be, therefore, that dystonic changes are confined to these specific areas, and are less pronounced in adjacent body parts (eg, affection of somatosensory finger, but not hand representation in FHD; Fig. S2B). However, given a previous neurophysiological study in FHD, which showed abnormal sensorimotor processing for areas beyond the fingertips,[32] this appears improbable. As cortical finger and lip representation are particularly large, it might be that changes in other areas are comparatively subtler and therefore were harder to detect with our behavioral testing paradigm. Indeed, smaller stimulus sizes closer to the discrimination threshold might have been more sensitive to reveal such differences between patients and controls (Fig. S2C), but would not accurately inform on the perceptual organization of tactile space, which we specifically aimed to explore here.[2,22]

Lack of changes in our model's stretch and phase parameters could also be explained by RF enlargement with fixed proportions, that is, without change in shape and directionality of RFs (Fig. S2D). Indeed, dystonia has been linked to reduced cortical inhibition[33] that could increase RF size.[34,35] However, this explanation would require similar structural transformations of *each* RF, which seems statistically improbable and therefore biologically unlikely. Also, such changes would create systematic tactile distance underestimation, which we did not find.

In conclusion, based on the behavioral paradigm we employed, we have demonstrated that organization of tactile space is widely intact in IFD patients in both affected and unaffected body parts. This questions the role of a specific and overarching deficit of tactile spatial organization in IFD. It also highlights the need for further research across well-characterized IFD phenotypes, ideally combining hypothesis-driven behavioral, neurophysiological, and functional neuroimaging methods. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

CME

Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Focal Hand Dystonia: A Pilot Study

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ABSTRACT: Background: The efficacy of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy for the treatment of focal hand dystonia (FHD) is not well known.
Objective: We aimed to prospectively investigate the efficacy of MRgFUS thalamotomy for the treatment of FHD.
Methods: We performed MRgFUS thalamotomy of the ventro-oral (Vo) nucleus in 10 patients with FHD. We evaluated the scores of the Writer's Cramp Rating Scale (WCRS, 0–30; higher scores indicating greater severity), Tubiana Musician's Dystonia Scale (TMDS, 0–5; lower scores indicating greater severity), and Arm Dystonia Disability Scale (ADDS, 0%–100%; lower scores indicating greater disability) at baseline and 3 and 12 months post-treatment.
Results: WCRS, TMDS, and ADDS scores significantly improved from 6.3 ± 2.7, 1.4 ± 0.5, and $58.7\% \pm 14.3\%$ at baseline to 1.6 ± 3.1 ($P = 0.011$), 5.0 ± 0 ($P = 0.0001$), and $81.6\% \pm 22.9\%$ ($P = 0.0229$) at 12 months, respectively. There was one prolonged case of dysarthria at 12 months.
Conclusion: We show that MRgFUS Vo-thalamotomy significantly improved FHD. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: magnetic resonance-guided focused ultrasound thalamotomy; focal hand dystonia; ventro-oral nucleus

Introduction

Focal hand dystonia (FHD) is an idiopathic, adult-onset disorder in most cases and manifests only while performing specific tasks.[1] Writer's cramp and musician's dystonia are the most well-known types of FHD, both of which cause dystonic muscle contractions in hand muscles only while writing or playing musical instruments. The prevalence of this condition is 1.2–1.5 per 100,000 persons.[2-4] In some specific populations, such as professional musicians or athletes, the prevalence is much higher than in the general population; approximately 1%–2% of professional musicians are affected by FHD.[5,6]

The ventro-oral (Vo) nucleus is one of the main output terminators from the basal ganglia, and lesioning or stimulation of this nucleus has been reported to improve FHD.[7,8] Magnetic resonance (MR)-guided focused ultrasound (MRgFUS) thalamotomy, which allows intracranial focal lesioning without an incision, has been reported to be an effective and less invasive procedure for the treatment of tremor and Parkinson's disease.[9,10] MRgFUS thalamotomy produces thermal lesions, similarly to radiofrequency thalamotomy, and is expected to have similar effects to radiofrequency Vo-thalamotomy on FHD. However, its efficacy for the treatment of FHD has been investigated in only two patients thus far.[11,12] Therefore, we prospectively

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