Neuroplasticity Caused by Peripheral Proprioceptive Deficits

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ABSTRACT

SHITARA, H., T. ICHINOSE, D. SHIMOYAMA, T. SASAKI, N. HAMANO, M. KAMIYAMA, T. TAJIKA, A. YAMAMOTO, T. KOBAYASHI, T. HANAKAWA, Y. TSUSHIMA, K. TAKAGISHI, and H. CHIKUDA. Neuroplasticity Caused by Peripheral Propriocep-tive Deficits. *Med. Sci. Sports Exerc.*, Vol. 54, No. 1, pp. 28–37, 2022. **Purpose:** Proprioceptive feedback is crucial for motor control and stabilization of the shoulder joint in everyday life and sports. Shoulder dislocation causes anatomical and proprioceptive feedback damage that contributes to subsequent dislocations. Previous recurrent anterior shoulder instability (RSI) studies did not investigate functional neuroplasticity related to proprioception of the injured shoulder. Thus, we aimed to study the differences in neuroplasticity related to motor control between patients with RSI and healthy individuals, using functional magnetic resonance imaging, and assess the effects of peripheral proprioceptive deficits due to RSI on CNS activity. **Methods:** Using passive shoulder motion and voluntary shoulder muscles contraction tasks, we compared the CNS correlates of proprioceptive activity between patients having RSI ($n = 13$) and healthy controls ($n = 12$) to clarify RSI pathophysiology and the effects of RSI-related peripheral proprioceptive deficits on CNS activity. **Results:** Decreased proprioception-related brain activity indicated a deficient passive proprioception in patients with RSI ($P < 0.05$ family-wise error, cluster level). Proprioceptive afferent-related right cerebellar activity significantly negatively correlated with the extent of shoulder damage ($P = 0.001$, $r = -0.79$). Functional magnetic resonance imaging demonstrated abnormal motor control in the CNS during voluntary shoulder muscles contraction. **Conclusion:** Our integrated analysis of peripheral anatomical information and brain activity during motion tasks can be used to investigate other orthopedic diseases. **Key Words:** NEUROPLASTICITY, PROPRIOCEPTION, RECURRENT ANTERIOR SHOULDER INSTABILITY, CEREBELLUM

The glenohumeral (shoulder) joint has unique features, including its mobility and wide range of motion. The glenohumeral joint has a marked lack of bony con-straint and is highly dependent on the matching surfaces and surrounding soft tissue envelope for static and dynamic stability

(1). Shoulder movements require precise control by interactions of sensory feedback, which are represented by proprioception between dynamic/static stabilizers in the periphery, alongside motor control in the CNS.

Because of its unique anatomical features, the shoulder joint is most frequently dislocated among the human joints, and dis-location often occurs in the anterior direction (2). In fact, this is the most common first-time dislocation experienced by ath-letes (2), and once it has occurred, the risk of subsequent dis-location increases due to injury to its anatomical features. Furthermore, subsequent shoulder dislocations occur due to damage to the anatomical features and deficits in sensory feedback, particularly proprioception, which is crucial for motor control and stabilization of shoulder joint in daily life and sports practice.

Anatomical failure in the periphery in patients with recurrent anterior shoulder instability (RSI) involves the following three main lesions: (i) Bankart lesion (3), an injury to the anteroinferior labrum associated with the capsulolabral ligament from the glenoid rim and scapular neck; (ii) bone loss at the humeral head, commonly known as a Hill–Sachs lesion (4); and (iii) glenoid bone loss, which commonly occurs after RSI and is a major risk factor of recurrent dislocation or subluxation after shoulder sta-bilization surgery (5). Among these three lesions, the Bankart

lesion and the glenoid bone defect affect the generation of proprioception because mechanoreceptors are present in the capsulolabral–ligamentous structures (6), which form a complex with the labrum that attaches to the glenoid rim and scapular neck.

Previous studies have demonstrated that patients with RSI experience proprioceptive deficits, including deficits in sensing joint position and kinesthesia (7–9). However, proprioception tests conducted in these previous studies involved the measurement of proprioception of actively and passively reproduced shoulder positions using an isokinetic dynamometer and a proprioception testing apparatus, respectively. The evaluation involved assessing shoulder proprioception using a memory-based, joint position-matching task (10). The three submodalities of proprioception, including (i) sense of joint position, (ii) sense of motion (kinesthesia), and (iii) sense of force or tension, are initially relayed to the CNS. A joint position-matching task includes not only proprioception but also many other neural processes, such as attention, consciousness, and memory for reproduction of joint position matching. We believe that a joint position-matching task is inadequate for the evaluation of proprioception relevant to dynamic movements because we usually move our body without specific attention, consciousness, and memory in daily life. To directly measure proprioception on the CNS, a passive motion task was used during functional magnetic resonance imaging (fMRI) recording in the present study (11). Compared with the traditional joint position-matching task, the passive motion task/fMRI method can obtain pure brain activation, which is evoked by proprioceptive stimulation, whereas the traditional joint position-matching task includes many other neural processes, such as attention, consciousness, and memory for reproduction of joint position matching. Using the fMRI method for patients with RSI, previous studies elucidated brain activity related to shoulder apprehension (12) and abnormal brain activity during active shoulder flexion and abduction (13).

The purpose of this study was to detect changes caused by RSI in the motor control-related brain activation, including proprioception, using fMRI during shoulder motion tasks. CNS provides crucial contributions to shoulder joint control. Therefore, we hypothesized that fMRI would allow for the comprehensive detection of proprioception because CNS regions that receive proprioceptive information will be activated during both passive shoulder motion and voluntary shoulder muscles contraction tasks. To date, only peripheral assessments have been made in patients with RSI. No studies have reported any findings on the relationship between functional neuroplasticity, which is defined as an ability of neural networks in the CNS to change through reorganization due to RSI and proprioception of the injured shoulder in patients with RSI. However, evaluating neuroplasticity in patients with RSI is essential to understanding the pathophysiology underlying RSI and the effects of peripheral proprioceptive deficits in the CNS.

Thus, we used fMRI to study differences in neuroplasticity related to motor control between patients with RSI (who were used as a peripheral proprioceptive deficit model) and healthy individuals. Moreover, to assess changes in the CNS due to peripheral proprioceptive deficits, we applied the glenoid bone defect for the parameter of the damage in the proprioceptive generator because the glenoid bone defect has been used as the parameter of the severity of anterior instability of the shoulder joint (14). The glenoid bone defect was quantitatively evaluated using computed tomography (CT) images assessing the amount of anatomical failure in the shoulder joint.

METHODS

Subjects

All participants were right-handed. We consecutively enrolled the patients with RSI into this study from April 2012 to December 2013. The exclusion criteria used for the selection of healthy control volunteers were as follows: (i) younger than 16 yr, (ii) history of neuropsychiatric disorders, and (iii) contraindications for MRI. The criteria used for the selection of patients with RSI were as follows: (i) repeated traumatic shoulder dislocation, (ii) positive apprehension test (15) and relocation test (16) findings, and (iii) isolated, right-sided RSI associated with a Bankart lesion identified on magnetic resonance arthrography or arthroscopy. The exclusion criteria for patients were as follows: (i) younger than 16 yr, (ii) nontraumatic shoulder instability, (iii) multidirectional shoulder instability, (iv) history of neuropsychiatric disorders, (v) contraindications for MRI, and (vi) history of shoulder dislocation within 1 month before study participation. One patient was excluded from this study because their CT image obtained at another hospital was unclear. Eventually, 12 healthy volunteers (4 women; mean ± SD age, 23.2 ± 3.2 yr) and 13 RSI patients (2 women; mean ± SD age, 27.8 ± 9.2 yr) participated in this study. The Institutional Review Boards of Gunma University Hospital approved the study protocol (approval no. 769). All methods were carried out in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants and their parents.

Quantification of Glenoid Bone Defects

To assess the relationship between anatomical failure in the glenohumeral joint, as a producer of proprioceptive afferents, and brain activity, as a receiver of those proprioceptive afferents, we defined glenoid bone loss as reflective of mechanoreceptor damage in the injured shoulder. Although damage to the joint capsule and ligaments, where mechanoreceptors are located (17), should be used as a parameter of mechanoreceptor damage in the injured shoulder, it is difficult to evaluate this damage quantitatively. As an alternative, we used glenoid bone loss as a proxy because the labral capsular ligamentous complex attaches to the glenoid bone. We did not consider bone defects involving Hill–Sachs lesions because no mechanoreceptors are located around Hill–Sachs lesions.

A Picture Archiving and Communications Systems system (Konica Minolta, Tokyo, Japan) was used to quantify glenoid bone loss. According to previous studies (14), we drew a perfect circle at the inferior portion of the glenoid surface in a

three-dimensional CT image, and the circle diameter and bone defect width were subsequently calculated. The glenoid bone defect is defined as the percentage of the defect width (B) to the diameter of the assumed inferior circle of the glenoid (A) (see Figure, Method for quantifying glenoid bone defect, Supplementary Digital Content, Appendix, http://links.lww.com/MSS/C418).

The interrater reliability between two experienced shoulder surgeons (H.S. and N.H.) and the intrarater reliability of one of the surgeons (H.S., who measured the glenoid bone defect again 2 wk later) were calculated. The intraclass correlation coefficients for the interrater and intrarater reliabilities were 0.92 and 0.93, respectively. The interrater and intrarater reliabilities were almost perfect according to the criteria described by Landis and Koch (18). In this study, we used data measured by H.S.

MRI Acquisition

As in our previous study (12), image acquisition was performed on a 3-T Siemens MRI scanner with a head coil (MAGNETOM Trio, A Tim System 3T; Siemens Medical Solutions, Erlangen, Germany). fMRI data were acquired using T2-weighted echo planar images that were sensitive to the blood oxygenation level–dependent signal using the following parameters: 64×64 matrix, 38 slices, $3 \times 3 \times 3$ mm^3 spatial resolution, field of view (FOV) = 192 mm, repetition time (TR) = 2500 ms, echo time (TE) = 30 ms, and flip angle (FA) = 90°. For high-resolution anatomical image, T1-weighted three-dimensional structural images were acquired for each participant with a magnetization-prepared, rapid gradient-echo sequence using the following parameters: 256×256 matrix, $1 \times 1 \times 1$ mm^3 spatial resolution, FOV = 256 mm, TR = 2300 ms, TE = 3.26 ms, and FA = 8°.

Experimental Tasks

Based on a previous study, we tightly fixed the right body trunk and shoulder girdle to the scanner bed with nonelastic bandages to minimize head motion during scanning. We also used foam pads and vacuum cushions (Vac-Lock Cushion; CIVCO, Coralville, IA) to immobilize the head.

Passive shoulder motion task during fMRI. For the detection of brain activity related to proprioceptive afferents from the shoulder, a passive shoulder motion task was performed during fMRI (cited by Shitara et al. [12]). The participant's right shoulder was passively rotated in internal (range, 0°–20°) and external motion (range, 0°–90°) with approximately 90° abduction at approximately 1 Hz, by a single experienced orthopedic surgeon in response to cues projected on a screen located at the participant's feet. Resting and passive shoulder motion conditions were alternated every 20 s and repeated 12 times, respectively (see Figure, Experimental tasks, Supplemental Digital Content, Appendix, http://links.lww.com/MSS/C418). For patient safety, we ensured that the shoulder motion would not cause any protective muscle contraction, subluxation, or shoulder dislocation on the MRI bed before performing MRI scanning. A single experienced shoulder surgeon (H.S.) performed the task in all participants.

Voluntary shoulder muscles contraction task during fMRI. To investigate CNS activity related to the motor control and the sense of force or tension in proprioception during voluntary shoulder muscles contraction, we asked each participant to perform isometric flexion, abduction, or external rotation of the right shoulder during fMRI. We applied an isometric exercise at 0° abduction to prioritize safety because external and internal rotation with approximately 90° abduction is associated with a high risk of dislocation or subluxation of the shoulder. To restrict joint movement and limit any effect of the antagonistic muscles associated with stretching, we used a custom-made, nonmagnetic splint fixed tightly with nonelastic bandages to the right hand, wrist, and elbow joints.

Each shoulder movement was performed for 20 s and was triggered randomly by a visual presentation on a screen (approximately 1 Hz). Before scanning, each participant practiced the movement to perform the contraction intensity for each direction at approximately 19.6 N, measured using a PowerTrack II Commander handheld dynamometer (J-Tech Medical, Salt Lake City, UT). The movement was to be performed without exacerbation of shoulder pain or muscle fatigue; the responses were evaluated as subjective sensations to ensure stable and accurate performance levels across all trials (see Figure, Supplemental Digital Content 3, http://links.lww.com/MSS/C418). We applied a force of relatively weak intensity (19.6 N) for both healthy participants and patients because high intensity may cause body and head motion which would decrease fMRI data quality. Additionally, using the same contraction intensity minimizes the differences in brain activity by varying contraction intensities.

After the task, each participant was asked to report any negative sensations, such as pain and apprehension, to ensure that the task did not cause any adverse effects. Because we focused on the effect of voluntary shoulder muscles contraction on brain activity, and considered that it was difficult to distinguish differences in brain activity among the types of shoulder movements, the data of flexion, abduction, and external rotation were evaluated under the same condition, i.e., voluntary shoulder muscles contraction.

fMRI Data Analysis

The analysis was performed for the whole brain, including the cerebellum. Similar to a previous study (12), we used SPM12 (http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MathWorks, Inc., MA) for preprocessing of imaging data. The first four functional images were removed because of unsteady magnetization. Then the time series fMRI data were aligned in both time and space, spatially normalized to fit to the Montreal Neurologic Institute template, and smoothed with a 8-mm full-width Gaussian kernel at half-maximum. Six motion parameters (translation: x, y, z; rotation: pitch, roll, yaw) were also included in the model to account for the effects of no interest, and only global signal normalization was performed between runs. A first-line, first-level general linear model analysis for each task was used to evaluate

correlations between fMRI signal changes and a block regressor convolved with a canonical hemodynamic response function.

A second-level random-effect group analysis was then performed to identify voxels that showed a significant difference in brain activity between movement condition and rest and between passive motion condition and rest. In all comparisons, the threshold was initially set at a cluster threshold of $P < 0.05$ family-wise error (FWE), corrected for multiple comparisons.

Between-Group fMRI Analysis

We directly compared differences between patients with RSI and healthy participants using a second-level random-effects analysis. We performed a between-group analysis to identify regions of brain activity that were greater in patients with RSI than in controls and *vice versa*. A significant difference in brain activity between the groups was defined at a cluster threshold of $P < 0.05$ FWE, corrected for multiple comparisons.

Glenoid Bone Defects and Brain Activity during Shoulder Motion Tasks

We used a general linear model to investigate the correlation between brain activity and glenoid bone defects to understand the changes in brain activity related to glenoid bone defects in RSI patients during each task. The threshold was initially set at a cluster threshold of $P < 0.05$ FWE, corrected for multiple comparisons. When significant correlations between brain activity and glenoid bone defects were not found at a cluster threshold of $P < 0.05$ FWE, we changed the threshold to $P < 0.005$, uncorrected. Next, we selected regions of interest (ROI) in which brain activity significantly correlated with glenoid bone defects at $P < 0.005$, uncorrected. Then, beta values were extracted from the ROI using Marsbar (http://marsbar.sourceforge.net). Finally, the beta values extracted for each patient were compared with the glenoid bone defect to assess whether the percentage of glenoid bone defect was related to a decrease in proprioceptive afferent-related brain activity. Pearson's correlation analysis was performed using GraphPad Prism8 (GraphPad Software, CA), and differences were considered significant for values of $P < 0.05$.

Controlling for Confounding Differences between Groups and by Head Motion

We ensured that our findings were not likely to be substantially influenced by the confounding effects of age and sex
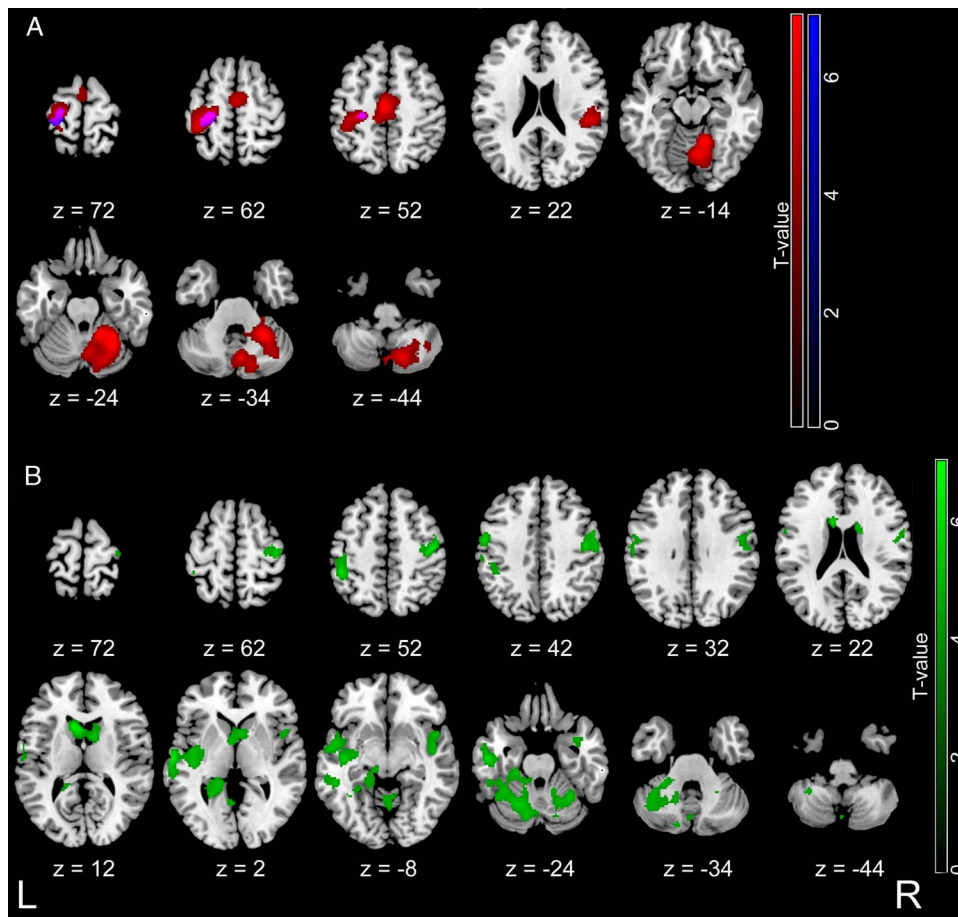
FIGURE 1—Brain activity during the passive shoulder motion task (image threshold at $P < 0.05$ FWE, cluster level). A, Overlapping brain activity between healthy participants and RSI patients. The *red* and *blue* areas represent brain activity in the healthy participants and RSI patients, respectively. The *purple* areas represent overlapping brain activity between healthy participants and RSI patients. B, Comparison of brain activity between healthy participants and RSI patients. The *green* areas represent regions where brain activity is higher in healthy participants compared with RSI patients. L, left; R, right.

differences between the groups or by head motion artifacts (see Text, Supplemental Digital Content, Appendix, http://links.lww.com/MSS/C418).

RESULTS

Passive shoulder motion task. There was a significant, widespread increase in brain activity in the left primary sensory area (S1), premotor cortex, and primary motor area (M1), as well as the supplementary motor area (SMA), the left premotor cortex, and the right cerebellum in healthy participants during the passive shoulder motion task. Conversely, there was a significant increase in brain activity only in M1 and S1 in patients with RSI during the passive shoulder motion task.

Brain activity was significantly higher in the bilateral M1, S1, cingulate cortices, inferior parietal cortices, caudate nuclei, parietal operculum, insula, area 44, gyrus fusiformis, and cerebellum; in the right premotor area; and in the left hippocampus, thalamus, auditory cortex, intraparietal sulcus, and superior parietal cortex in healthy participants than that in patients with RSI (Fig. 1, Table 1). Brain activity was not significantly higher in any brain region in patients with RSI as compared with healthy participants.

During the passive shoulder motion task, the examiner did not feel any protective muscle contractions, which could falsely appear as shoulder active movements on fMRI scans, in any of the participants' shoulders. Additionally, no adverse events, such as subluxation and dislocation, occurred.

Voluntary shoulder muscles contraction task. Significant brain activity was observed in the motor network, including the SMA, bilateral premotor cortices, M1, S1, thalamus, and cerebellum, in both healthy participants and participants with RSI. Brain activity was significantly increased in the bilateral superior temporal gyri and precentral gyri; in the right angular gyrus, middle frontal gyrus, inferior frontal and parietal lobules, and calcarine gyrus; and in the left precuneus, Rolandic operculum, middle cingulate cortex, and insula lobe in patients with RSI compared with healthy participants (Fig. 2, Table 1). Although brain activity in patients with RSI was more widespread than that in healthy participants, the differences in brain activity between the two groups were not significant. Brain activity did not significantly increase in any of these brain regions in healthy patients compared with patients with RSI. No participant reported any adverse effect during the task.

Glenoid bone defects and brain activity during shoulder motion tasks. There was no significant correlation between brain activity and glenoid bone defect during the passive shoulder motion task at $P < 0.05$ FWE, cluster level. The right cerebellum activity significantly negatively correlated with a glenoid bone defect at $P < 0.005$, uncorrected (Fig. 3A, Table 2). ROI were created, and beta values were extracted from the right cerebellum. The extracted beta values were compared with the percentage of glenoid bone defects to assess whether the glenoid bone defect ratio was related to a decrease in proprioceptive afferent-related brain activity.

TABLE 1. Results of brain activity with specific contrast for activity associated with passive shoulder motion and voluntary shoulder muscles contraction in each group and the differences between groups.

Anatomical Region	MNI Coordinates (mm)			t
	x	y	z	
Healthy participants				
Right cerebellum (lobule VI)	30	−54	−28	9.53
Right cerebellum (lobule V)	16	−46	−24	8.41
Left precentral gyrus	−26	−24	56	8.24
Left SMA	−4	−16	54	8.61
Left precentral gyrus (area 4a, 4p)	−24	−22	68	7.31
Right cerebellum (lobule VIIIa)	30	−54	−50	7.45
Right cerebellum (lobule VIIb)	20	−70	−50	6.95
Left postcentral gyrus (area 3b)	−40	−34	58	6.88
RSI patients				
Left precentral gyrus (area 4a, 4p)	−24	−26	58	6.22
Left precentral gyrus	−24	−22	70	4.67
Left postcentral gyrus	−28	−30	76	4.40
Healthy participants > RSI patients				
Left precentral gyrus (premotor area)	44	−14	56	5.99
Right precentral gyrus	50	−2	48	5.27
Left inferior temporal gyrus	−52	−14	−26	5.94
Left superior temporal gyrus	−62	−14	6	5.90
Left caudate nucleus	−10	18	12	5.55
Right cerebellum (lobule VI)	30	−54	−26	5.09
Right caudate nucleus	16	2	20	5.07
Right insula	44	−6	−6	4.64
RSI patients > healthy participants				
Right superior temporal gyrus	64	−34	10	6.94
Right inferior parietal lobule	54	−48	46	6.87
Left Rolandic operculum (area OP2)	−38	−28	20	6.05
Right inferior frontal gyrus	32	6	32	5.44
Left superior temporal gyrus	−44	−36	20	5.42
Left precentral gyrus (area 4a)	−14	−26	60	5.41
Left precuneus (area 7A)	−16	60	66	5.17
Right middle frontal gyrus	40	34	46	4.98
Right precentral gyrus (area 44)	58	8	32	4.98
Right calcarine gyrus (area 18)	10	−96	10	4.68
Right angular gyrus	62	−50	34	4.33
Left posterior-medial frontal gyrus	−8	−20	50	3.75
Left insula	−32	−24	12	3.67

$P < 0.05$ FWE cluster level.
MNI, Montreal Neurological Institute.

Our results demonstrated that there was a significant negative correlation between the percentage of glenoid bone defect and brain activity in the right cerebellum ($P = 0.001$, $r = −0.79$, 95% confidence interval (95% CI) of −0.93 to −0.43) (Fig. 3A). There was no significant positive correlation between the defect size of the glenoid surface and brain activity during the passive shoulder motion task.

In contrast, brain activity in the left pre-SMA, middle frontal gyrus, precentral gyrus (including Brodmann area 44), anterior cingulate cortex, superior and inferior parietal lobules, middle temporal gyrus and the bilateral precuneus, superior frontal and medial gyri, and caudate nuclei showed significant positive correlation with a glenoid bone defect during the voluntary shoulder muscles contraction task at $P < 0.05$ FWE, cluster level (Fig. 3B, Table 2). There was no significant negative correlation between glenoid bone defect and brain activity.

DISCUSSION

We compared differences in CNS correlates of proprioceptive activity between patients with RSI and healthy controls to gain insights into the pathophysiology of RSI and assess the effects of peripheral proprioceptive deficits due to RSI on
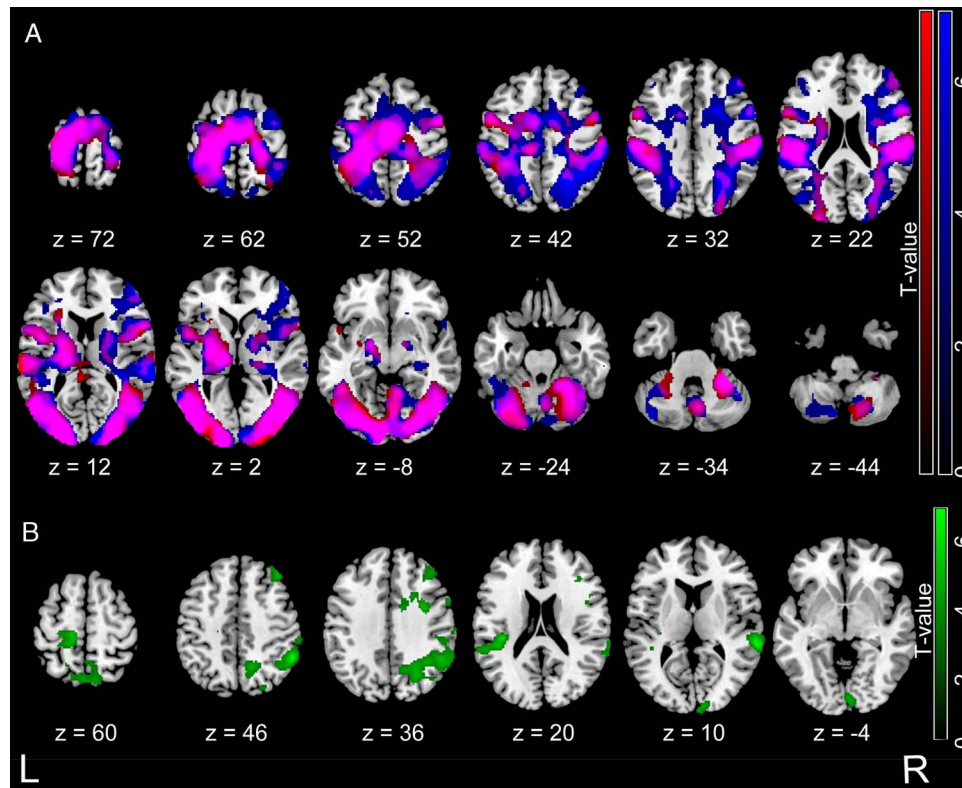
FIGURE 2—Brain activity during the voluntary shoulder muscles contraction task (image threshold at *P* < 0.05 FWE cluster level). A, Overlapping brain activity between healthy participants and RSI patients. The *red* and *blue* areas represent brain activity in the healthy participants and RSI patients, respectively. The *purple* areas represent overlapping brain activity between healthy participants and RSI patients. B, Brain activity comparison between RSI patients and healthy participants. The *green* areas represent regions where brain activity was higher in RSI patients compared with healthy participants. L, left; R, right.

CNS activity. We found that decreases in proprioception-related brain activity supported deficits of passive proprioception in patients with RSI. Brain activity in the right cerebellum, related to proprioceptive afferents, significantly negatively correlated ($P = 0.001$, $r = -0.79$) with the amount of damage in the recurrently dislocated shoulder (determined as a percentage of the glenoid bone defect). Moreover, abnormal motor control in the CNS was demonstrated by fMRI scans during voluntary shoulder muscles contraction. Thus, neuroplasticity, which may be caused by compensation for proprioceptive deficits, was significantly positively correlated with the amount of damage in the recurrently dislocated shoulder as a percentage of glenoid bone defect. To the best of our knowledge, no previous studies have revealed a connection between the anatomical factors in the periphery and the abnormal motor control-related brain activity in the CNS in patients with RSI.

A passive shoulder motion task was used to detect sensory afferents that mainly consisted of proprioceptive afferents. Proprioceptive afferents provide essential information for somatosensory–motor integration, which likely arises at multiple levels in the CNS from the spinal cord to the motor network in the brain.

According to previous studies the bilateral inferior parietal lobes (Fig. S2, http://links.lww.com/MSS/C418), contralateral S1, and secondary sensorimotor cortex were central processing sites for proprioceptive information (19). Howard et al.

(13) demonstrated that patients with complex shoulder instability showed significantly greater brain activity than controls in M1, supramarginal gyrus, inferior frontal gyrus, and premotor cortex using fMRI during an active shoulder motion task. Moreover, passive and voluntary movements induced activation in the same parts of the cerebellar hemispheres and dentate nuclei (19). The results of those studies are consistent with our findings, suggesting that there is a decline in proprioceptive sensitivity in the affected shoulder.

The findings of Zuckerman et al. (9) were consistent with our results with respect to decreased proprioceptive sensitivity; however, conversely to their evaluation (10), we consider that our testing approach using fMRI during the passive motion task is superior because, unlike the joint position-matching task, fMRI is not dependent on memory. Additionally, joint-position matching that assesses the static position may not reflect proprioceptive deficits during dynamic movement in daily life. Further, fMRI may be more suitable for detecting passive proprioceptive deficits during the passive motion task than the traditional joint position-matching task because the clinical relevance of a difference of approximately 2° in the joint-position matching appears to remain unclear.

To the best of our knowledge, no previous studies have investigated the relationship between peripheral anatomical failure in any joints and voluntary and passive motion-related brain activity. In patients with RSI, the capsuloligamentous
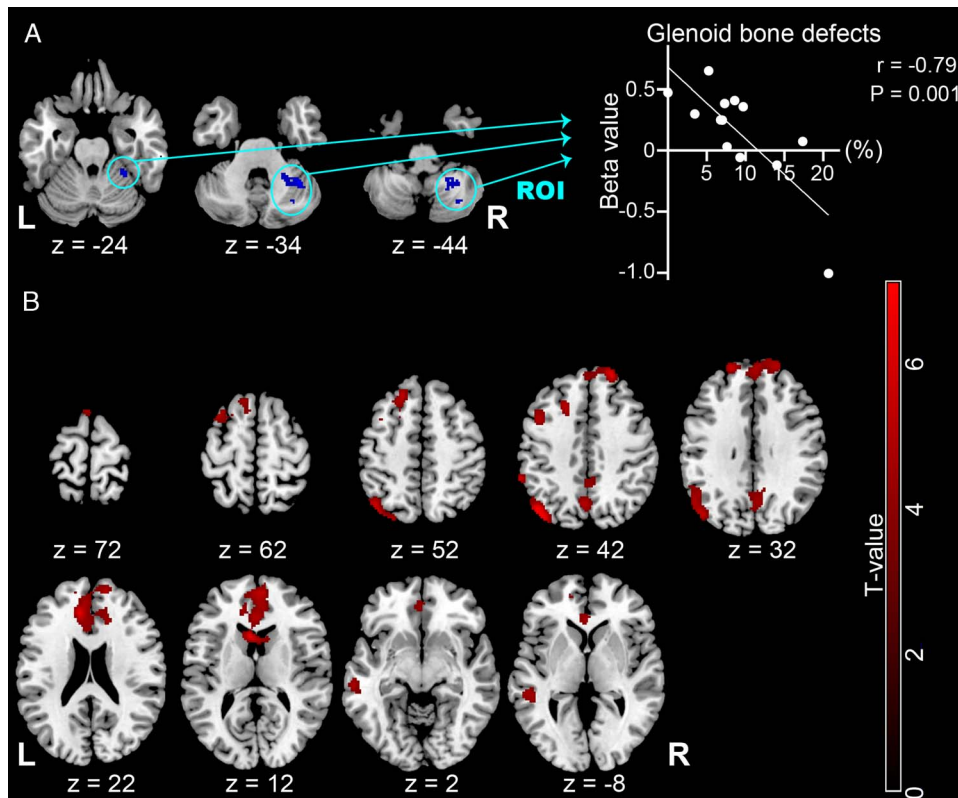
FIGURE 3—Brain activity correlates with the extent of glenoid bone defects in RSI patients. A, Passive shoulder motion task (image threshold at *P* < 0.005, uncorrected). The *blue* areas represent brain activities that significantly negatively correlated with the glenoid bone defects in patients with RSI. The right scatter plot shows the correlation between the beta value extracted from the ROI of the right cerebellum and the percentage of the glenoid bone loss. B, Voluntary shoulder muscles contraction task (image threshold at *P* < 0.05 FWE, cluster level). The *red* areas represent brain activities that significantly positively correlated with glenoid bone defects in patients with RSI. *r*, correlation coefficient; L, left; R, right.

complex is not normally stretched by shoulder motion because of the slight tension in the capsuloligament caused by a large glenoid bone defect. Hence, mechanoreceptors are not activated, and proprioceptive afferents are not generated normally in the damaged shoulder. Thus, we used the severity of the glenoid bone defect as a quantitative measurement of the passive proprioceptive afferent-generator. We found that brain activity in the cerebellum during the passive shoulder motion task was significantly negatively correlated with the extent of glenoid bone defect ($P = 0.001$, $r = -0.79$).

Clinical studies in patients with cerebellar injuries (20), degenerative cerebellar disorders, and Parkinson's disease (21) did not detect deficits of conscious awareness of limb position (kinesthesia). To detect limb positioning, the cerebrobasal ganglia loop integrity is essential (21). The cerebellum gains proprioceptive afferents from various receptors mainly through the tractus spinocerebellaris (22), and previous positron emission tomography and fMRI studies demonstrated that there was widespread activation of the cerebellum during active and passive movements. These findings suggest that the cerebellum plays an important role in proprioception (19). We demonstrated that cerebellar activity significantly negatively correlated with the severity of peripheral proprioceptive deficits in patients with RSI who have normal cerebellar function. Much like findings from previous studies, our results indicate that the

cerebellum gains proprioceptive afferents mainly through the tractus spinocerebellaris.

Neuroplasticity, including compensatory changes, have been demonstrated in spinal cord side (23) and musculoskeletal injuries. In an experimental model of spinal cord injury, animals that exhibited almost complete recovery showed elevated brain

TABLE 2. Correlation between brain activity and glenoid bone defects in patients with RSI during passive shoulder motion and voluntary shoulder muscles contraction tasks.

Anatomical Region	MNI Coordinates (mm)			
	x	*y*	*z*	*t*
Passive shoulder motion (*P* < 0.005 uncorrected)				
Right cerebellum (lobule VIIa)	38	−50	−34	4.55
Right cerebellum (lobule VI)	34	−44	−30	4.33
Right cerebellum (lobule VIIIb)	20	−44	−50	4.14
Voluntary shoulder muscles contraction (*P* < 0.05 FWE cluster level)				
Left inferior parietal lobule (area PGa)	−38	−78	46	6.59
Left angular Gyrus (area PGp)	−46	−72	40	6.43
Left inferior parietal lobule (area PF)	−62	−44	42	5.33
Left superior medial gyrus	−12	40	18	6.28
Left caudate nucleus	−6	16	12	6.12
Right superior frontal gyrus	22	50	42	5.91
Left precuneus (area 7A)	−4	−66	44	4.90
Left precentral gyrus (area 44)	−44	10	42	4.72
Right precuneus	8	−52	36	4.44
Left superior frontal gyrus	−18	30	52	4.89
Left middle frontal gyrus	−34	14	62	4.73
Left middle temporal gyrus	−62	−28	−6	4.66

P < 0.005 uncorrected and *P* < 0.05 FWE, cluster level, respectively.
MNI, Montreal Neurological Institute.

activity on positron emission tomography, suggesting compensation on the affected side (23). Heroux and Tremblay (24) delivered transcranial magnetic stimulation to patients with anterior cruciate ligament injury and showed that corticospinal excitability increases and targets muscles adjacent to an immobilized or painful joint. In patients with Stanmore Classification Polar type II/III shoulder instability compared with healthy participants, during an active shoulder motion, fMRI detected that there were differences in cortical activation suggesting neuroplasticity including compensatory changes (13). In our study, brain activity was higher in regions that involved sensorimotor and visuomotor networks in patients with RSI compared with healthy controls. Thus, our results are consistent with the findings of previous studies, indicating that neuroplasticity occurs in the CNS to compensate for right shoulder dysfunction caused by RSI. In contrast to the findings in patients with Stanmore Classification Polar type II/III shoulder instability (13), we demonstrated that brain activity was elevated in the right superior temporal, angular, and calcarine gyri and the left Rolandic operculum, superior temporal gyrus, precuneus, posterior-medial frontal gyrus, and insula lobe in patients with RSI compared with healthy participants. These activities can be divided into (i) task-specific activation and (ii) unpleasant memory, emotion, and pain-related activation. With regard to task-specific activation, previous studies have demonstrated that activities in the bilateral superior temporal gyri were related to spatial perception (25). In addition, activity in the angular gyrus was related to visuospatial processing (26) and executive control of behavior (27); activity in the calcarine gyrus, including the primary visual cortex, was related to visual attention (28) and tracking visual motion patterns (29); and activity in the left precuneus was related to motor imagery and execution (30) and visuomotor attention (31). However, with regard to unpleasant memory, emotion, and pain-related activation, previous studies have shown that activities in the calcarine gyrus, including the secondary visual cortex and Rolandic operculum, were related to retrieval of unpleasant experiences (30) and responses to

emotion/attention in visual processing (32); activity in the left precuneus was related to conscious recollection of previously experienced events (33) and pain perception (34); activity in the posterior-medial frontal gyrus was related to emotion, pain, and cognitive control (35); and activity in the insula lobe was related to pain processing (36). Although no adverse events occurred during the task in our study, the high activity observed in these regions may indicate that shoulder motion induced the unwanted memory of shoulder dislocation in RSI patients.

Proprioception with muscle contraction during active (voluntary) movements is more precise than proprioception in the absence of muscle contraction during similar passive movements. This precision in active movements is assumed to follow heightened peripheral muscle feedback, direct transmission of a copy of motor commands from motor to sensory processing areas, and/or the involvement of predictive models through the cerebellum (37,38). Bhanpuri et al. (39) showed that patients with cerebellar disorders had no deficits in passive proprioception, and unlike healthy controls, patients with cerebellar disorders showed no improvement in passive and active proprioception. Thus, intact cerebellar function strengthens active proprioception by predicting movement terminations. This predication is based on dynamic models of the arm rather than a general increase in sensitivity of proprioceptive receptors in the active arm.

In our study, cerebellar activity was not correlated with peripheral proprioceptive deficits during active shoulder motion tasks. This may be due to the fact that intact cerebellar function enhances peripheral proprioceptive deficits during active movements.

When patients with RSI start to move their injured shoulder, the following takes place: (i) brain activity occurs in the motor network and descends to the cerebellum; (ii) a forward model is created to predict sensory feedback for accuracy adjustment in motion; (iii) target muscles contract; (iv) proprioceptive afferents are produced, and sensory feedback, including proprioception, ascends to the cerebellum and the sensory cortex; (v) the sensory feedback is compared with the forward model in
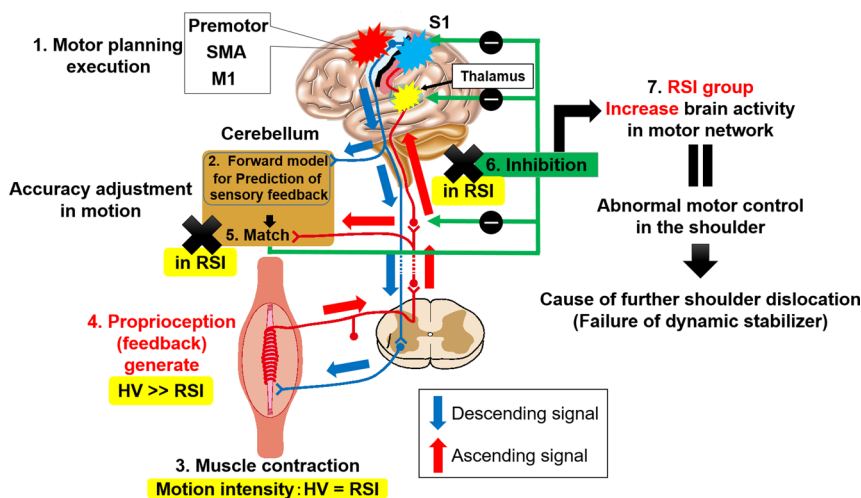

FIGURE 4—Recurrent shoulder instability pathophysiology. The cross mark indicates "failure."

the cerebellum; (vi) the compared feedback and forward models are usually matched, and brain activity is inhibited, but in RSI, the actual sensory feedback is reduced compared with the one in the predicted forward model, and the inhibition mechanism fails; and (vii) brain activity increases compared with the one in healthy controls. Although significantly elevated brain activity may reflect compensation for the injured shoulder, the abnormal motor control may cause recurrent dislocation (Fig. 4).

Our study had several limitations. First, the voluntary shoulder muscles contraction task may not have been optimal. To compare with the amount of proprioceptive feedback in actual active shoulder motion tasks, the amount of proprioceptive feedback in voluntary shoulder muscle contraction may be smaller because proprioceptive feedback-related sense of joint position and sense of motion (kinesthesia) is minimally evoked without joint movement.

In the MRI scanner, the evaluation of shoulder motion similar to that in daily life was impossible because the subject was in the supine position, and the space for shoulder motion was greatly restricted. Therefore, we were compelled to select isometric shoulder muscles contraction for the voluntary shoulder muscles contraction task, although there are differences in brain activity between isometric and nonisometric normal motion. However, our isometric voluntary shoulder muscles contraction task presented with a number of advantages for acquiring fMRI data as compared with an inadequate active motion task because it helped minimize head motion and achieve uniformity in the intensity of shoulder motion. Second, slight motion, which is not detectable by visual observation, was not measured because an electromyogram was not obtained. Although slight motion may have affected the results of the passive shoulder task, the effects are expected to be limited because brain activity was less widespread in patients with RSI compared with healthy controls during the passive shoulder motion task. Third, passive movements were applied by a surgeon who knew who the patients and who the controls were. This may have represented unconscious bias, although the surgeon was careful to ensure task consistency among all participants. We prioritized ensuring patients' safety rather than preventing bias. Finally, the brain activity during both tasks might be affected by nociceptive feedback. To reduce the effects of nociceptive feedback, we asked participants to report any negative sensations, such as pain and apprehension. No participant reported any adverse effect during the task. Thus, we believe that the effects of nociceptive feedback might be minimal, although it is hard to completely exclude the effect of nociceptive feedback.

In summary, this study laid forth previously unreported evidence that brain activity associated with proprioception and compensation for motor dysfunction altered in patients with RSI. Furthermore, three-dimensional CT and fMRI findings during shoulder motion tasks have determined the presence of dysfunction involving proprioceptive afferents in the affected right shoulder and decreased brain activity in the right cerebellum. We demonstrated the utility of the combined approach, which involves integrated analysis between peripheral anatomical information and brain activity, with comparison of passive motion and voluntary shoulder muscles contraction. This approach can be broadly applied to pathological investigations in patients with orthopedic diseases. Investigations of such diseases have typically been limited in terms of the CNS. However, functional changes in the CNS, including motor control, are crucial to understanding the underlying pathophysiological mechanisms of these conditions.

REFERENCES

1. Bigliani LU, Kelkar R, Flatow EL, Pollock RG, Mow VC. Glenohumeral stability. Biomechanical properties of passive and active stabilizers. *Clin Orthop Relat Res*. 1996;330:13–30.
2. Dodson CC, Cordasco FA. Anterior glenohumeral joint dislocations. *Orthop Clin North Am*. 2008;39(4):507–18.
3. Rowe CR, Patel D, Southmayd WW. The Bankart procedure: a long-term end-result study. *J Bone Joint Surg Am*. 1978;60(1):1–16.
4. Burkhart SS, De Beer JF. Traumatic glenohumeral bone defects and their relationship to failure of arthroscopic Bankart repairs: significance of the inverted-pear glenoid and the humeral engaging Hill-Sachs lesion. *Arthroscopy*. 2000;16(7):677–94.
5. Milano G, Grasso A, Russo A, et al. Analysis of risk factors for glenoid bone defect in anterior shoulder instability. *Am J Sports Med*. 2011;39(9):1870–6.
6. Vangsness CT Jr, Ennis M, Taylor JG, Atkinson R. Neural anatomy of the glenohumeral ligaments, labrum, and subacromial bursa. *Art Ther*. 1995;11(2):180–4.
7. Lephart SM, Warner JJP, Borsa PA, Fu FH. Proprioception of the shoulder joint in healthy, unstable, and surgically repaired shoulders. *J Shoulder Elbow Surg*. 1994;3(6):371–80.
8. Rokito AS, Birdzell MG, Cuomo F, Di Paola MJ, Zuckerman JD. Recovery of shoulder strength and proprioception after open surgery for recurrent anterior instability: a comparison of two surgical techniques. *J Shoulder Elbow Surg*. 2010;19(4):564–9.
9. Zuckerman JD, Gallagher MA, Cuomo F, Rokito A. The effect of instability and subsequent anterior shoulder repair on proprioceptive ability. *J Shoulder Elbow Surg*. 2003;12(2):105–9.
10. Goble DJ. Proprioceptive acuity assessment via joint position matching: from basic science to general practice. *Phys Ther*. 2010;90(8):1176–84.

11. Nasrallah FA, Mohamed AZ, Campbell ME, Yap HK, Yeow CH, Lim JH. Functional connectivity of brain associated with passive range of motion exercise: proprioceptive input promoting motor activation? *Neuroimage*. 2019;202:116023.
12. Shitara H, Shimoyama D, Sasaki T, et al. The neural correlates of shoulder apprehension: a functional MRI study. *PLoS One*. 2015;10(9):e0137387.
13. Howard A, Powell JL, Gibson J, Hawkes D, Kemp GJ, Frostick SP. A functional magnetic resonance imaging study of patients with polar type II/III complex shoulder instability. *Sci Rep*. 2019;9(1):6271.
14. Sugaya H, Moriishi J, Dohi M, Kon Y, Tsuchiya A. Glenoid rim morphology in recurrent anterior glenohumeral instability. *J Bone Joint Surg Am*. 2003;85(5):878–84.
15. Rowe CR, Zarins B. Recurrent transient subluxation of the shoulder. *J Bone Joint Surg Am*. 1981;63(6):863–72.
16. Walch G. Chronic anterior glenohumeral instability. *J Bone Joint Surg Br*. 1996;78-B(4):670–7.
17. Grigg P. Peripheral neural mechanisms in proprioception. *J Sport Rehabil*. 1994;3(1):2–17.
18. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–74.
19. Gao J-H, Parsons LM, Bower JM, Xiong J, Li J, Fox PT. Cerebellum implicated in sensory acquisition and discrimination rather than motor control. *Science*. 1996;272(5261):545–7.
20. Holmes G. The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain*. 1917;40(4):461–535.
21. Maschke M, Gomez CM, Tuite PJ, Konczak J. Dysfunction of the basal ganglia, but not the cerebellum, impairs kinaesthesia. *Brain*. 2003;126(10):2312–22.
22. Bosco G, Poppele RE. Proprioception from a spinocerebellar perspective. *Physiol Rev*. 2001;81(2):539–68.
23. Nishimura Y, Onoe H, Morichika Y, Perfiliev S, Tsukada H, Isa T. Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury. *Science*. 2007;318(5853):1150–5.
24. Héroux ME, Tremblay F. Corticomotor excitability associated with unilateral knee dysfunction secondary to anterior cruciate ligament injury. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(9):823–33.
25. Ellison A, Schindler I, Pattison LL, Milner AD. An exploration of the role of the superior temporal gyrus in visual search and spatial perception using TMS. *Brain*. 2004;127(10):2307–15.
26. Köhler S, Kapur S, Moscovitch M, Winocur G, Houle S. Dissociation of pathways for object and spatial vision: a PET study in humans. *Neuroreport*. 1995;6(14):1865–8.
27. Kübler A, Dixon V, Garavan H. Automaticity and reestablishment of executive control-an fMRI study. *J Cogn Neurosci*. 2006;18(8): 1331–42.
28. Smith AT, Cotillon-Williams NM, Williams AL. Attentional modulation in the human visual cortex: the time-course of the BOLD response and its implications. *Neuroimage*. 2006;29(1): 328–4.
29. Dieterich M, Bauermann T, Best C, Stoeter P, Schlindwein P. Evidence for cortical visual substitution of chronic bilateral vestibular failure (an fMRI study). *Brain*. 2007;130(8):2108–16.
30. Hanakawa T, Dimyan MA, Hallett M. Motor planning, imagery, and execution in the distributed motor network: a time-course study with functional MRI. *Cereb Cortex*. 2008;18(12):2775–88.
31. Caplan JB, Luks TL, Simpson GV, Glaholt M, McIntosh AR. Parallel networks operating across attentional deployment and motion processing: a multi-seed partial least squares fMRI study. *Neuroimage*. 2006;29(4):1192–202.
32. Ushida T, Ikemoto T, Tanaka S, et al. Virtual needle pain stimuli activates cortical representation of emotions in normal volunteers. *Neurosci Lett*. 2008;439(1):7–12.
33. Tulving E, Kapur S, Markowitsch HJ, Craik FI, Habib R, Houle S. Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition. *Proc Natl Acad Sci U S A*. 1994;91(6): 2012–5.
34. Apkarian AV, Darbar A, Krauss BR, Gelnar PA, Szeverenyi NM. Differentiating cortical areas related to pain perception from stimulus identification: temporal analysis of fMRI activity. *J Neurophysiol*. 1999;81(6):2956–63.
35. Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci*. 2011;12(3):154–67.
36. Schoedel ALA, Zimmermann K, Handwerker HO, Forster C. The influence of simultaneous ratings on cortical BOLD effects during painful and non-painful stimulation. *Pain*. 2008;135(1):131–41.
37. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. *Physiol Rev*. 2012;92(4):1651–97.
38. Miall RC, Wolpert DM. Forward models for physiological motor control. *Neural Netw*. 1996;9(8):1265–79.
39. Bhanpuri NH, Okamura AM, Bastian AJ. Predictive modeling by the cerebellum improves proprioception. *J Neurosci*. 2013;33(36): 14301–6.