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frontiers in NEUROSCIENCE



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Decoding of the spike timing of primary afferents during voluntary arm movements in monkeys

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INTRODUCTION

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Researchers have developed a brain-machine interface (BMI) that 040 allows patients or experimental animals to control a robotic arm 041 by translating neural signals into control signals for the device 042 (Hochberg et al., 2006, 2012; Velliste et al., 2008; Yanagisawa et al., 043 2012; Collinger et al., 2013). Furthermore, studies have shown 044 that monkeys can use cortical activity to control functional elec-045 **Q8** 046 trical stimulation of muscles (Moritz et al., 2008; Ethier et al., 29 Q10b47 2012) and the spinal cord (Nishimura et al., 2013), and restore volitional control of the paretic hand. In these approaches, the 048 control of a prosthetic device to a desired target has relied mainly 049 on visual feedback for the position of the prosthesis. Since the 050 ability to control hands and arms in a dexterous and compli-051 ant manner depends on somatosensory signals from the body 052 (Ghez et al., 1990; Gentilucci et al., 1994; Gordon et al., 1995), 053 somatosensory feedback should be provided for precise control of 054 the prosthetic limb precisely and exploratorily (Biddiss and Chau, 055 2007). Recently a somatosensory BMI with a tactile feedback sys-056 tem, such as direct electrical stimulation of the primary sensory 057

070 Understanding the mechanisms of encoding forelimb kinematics in the activity of 071 peripheral afferents is essential for developing a somatosensory neuroprosthesis. To 072 investigate whether the spike timing of dorsal root ganglion (DRG) neurons could 073 be estimated from the forelimb kinematics of behaving monkeys, we implanted two 074 multi-electrode arrays chronically in the DRGs at the level of the cervical segments 075 in two monkeys. Neuronal activity during voluntary reach-to-grasp movements were 076 recorded simultaneously with the trajectories of hand/arm movements, which were 077 tracked in three-dimensional space using a motion capture system. Sixteen and 13 078 neurons, including muscle spindles, skin receptors, and tendon organ afferents, were 079 recorded in the two monkeys, respectively. We were able to reconstruct forelimb joint 080 kinematics from the temporal firing pattern of a subset of DRG neurons using sparse linear 081 regression (SLiR) analysis, suggesting that DRG neuronal ensembles encoded information 082 about joint kinematics. Furthermore, we estimated the spike timing of the DRG neuronal 083 ensembles from joint kinematics using an integrate-and-fire model (IF) incorporating the 084 SLiR algorithm. The temporal change of firing frequency of a subpopulation of neurons 085 was reconstructed precisely from forelimb kinematics using the SLiR. The estimated firing 086 087 pattern of the DRG neuronal ensembles encoded forelimb joint angles and velocities as 088 precisely as the originally recorded neuronal activity. These results suggest that a simple 089 model can be used to generate an accurate estimate of the spike timing of DRG neuronal 090 ensembles from forelimb joint kinematics, and is useful for designing a proprioceptive 091 decoder in a brain machine interface. 092

Keywords: dorsal root ganglion, proprioceptive interface, multichannel recording, integrate-and-fire model, brain machine interface

> cortex, has been developed (O'Doherty et al., 2011; Tabot et al., 096 2013). Experimental animals perceived an electrical stimulation 097 train as if it was a mechanical stimulus of the limbs at the corre-098 sponding frequency. Proprioceptive information can also be used 099 to increase accuracy of prosthesis control (Johnson et al., 2013), 100 but proprioceptive information has not been returned directly to 101 the brain in the current frame of BMI research. 102

> Primary sensory nerves are an appropriate site for the delivery 103 of electrical stimulation to provide proprioceptive information to 104 the subject. First, movements with a high number of degrees of 105 freedom in three-dimensional space yield considerable positional 106 information of a prosthetic device. Ensemble neural recordings 107 in the dorsal root ganglia (DRGs) of anesthetized animals have 108 shown that the activity of neuronal ensembles encoded high 109 dimensional information of limb kinematics (Stein et al., 2004; 110 Wagenaar et al., 2011; Weber et al., 2011; Umeda et al., 2012). 111 Second, the sensation of limb movement may be induced artifi-112 cially by the delivery of vibrations to a tendon (Goodwin et al., 113 1972; Craske, 1977; McCloskey et al., 1983; Roll et al., 2009; 114

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Thyrion and Roll, 2010) or the direct electrical stimulation of 115 afferents (Gandevia, 1985; Dhillon and Horch, 2005). Individuals 116 who felt the illusory movement of the stimulated hand could indi-117 cate the direction of the movement using the other hand. Thus, 118 artificial kinesthetic sensations may allow individuals to adapt 119 easily to such feedback signals containing considerable positional 120 121 information of a prosthesis. The rigid link between limb movements, the neural activity of peripheral afferents, and kinesthetic 122 sense suggests peripheral afferents as an appropriate site for a 123 proprioceptive interface. 124

Estimating the neuronal firing pattern from the positional 125 information of the upper limb is of obvious utility for the devel-126 opment of a sensory-motor BMI with a proprioceptive feedback 127 system. The development of a motor BMI has stemmed from 128 the establishment of decoding algorithms, which translate neu-129 ronal ensemble activity into limb movements and muscle activity 130 (Chapin et al., 1999; Wessberg et al., 2000; Serruya et al., 2002; 131 Morrow and Miller, 2003). Similarly, a decoding model would 132 help to determine the optimal stimulus parameters to elicit artifi-133 cial kinesthetic sensation. Spiking neuron models can reproduce 134 the timing of spikes elicited by an external stimulus with high 135 temporal precision (Gerstner and Kistler, 2002). An integrate-136 and-fire (IF) model is a simple phenomenological model of spike 137 generation. Recent studies have demonstrated that various IF 138 models accurately estimate spike timing, and describe some of the 139 important physiological properties of the recorded sensory neu-140 rons (Pillow et al., 2005; Kim et al., 2010; Dong et al., 2013). For 141 a model to have a practical use in an online BMI, it should be 142 simple, with a small computational overhead. Furthermore, the 143 reproduced spike patterns generated by the model should reliably 144 encode the external stimulus that elicited the original neural firing 145 pattern. 146

In the present study, we performed multichannel record-147 ings from the cervical DRGs of awake monkeys during volun-148 tary reach-to-grasp movements. First, we investigated whether a 149 population of DRG neurons recorded from behaving monkeys 150 could encode the forelimb joint kinematics. Next, we investi-151 gated whether the temporal firing pattern of DRG neurons can 152 be reconstructed from forelimb joint kinematics using an IF 153 model incorporating the sparse linear regression (SLiR) algo-154 rithm, which selects important input signals to reduce the com-155 putational time (Sato, 2001). Finally, we examined whether the 156 reconstructed spike pattern contained positional information to 157 validate the model. 158

160 MATERIALS AND METHODS

One adult male monkey (Monkey T) and one adult female mon-161 key (Monkey C) (Macaca mulatta) were used in the present study. 162 The experiments were approved by the experimental animal com-163 mittee of the National Institute of Natural Sciences of Japan 164 (Approval Nos.: 10A203, 11A168, and 12A139) and were per-165 formed in accordance with the Weatherall report, "The use of 166 non-human primates in research." Before the experiments, the 167 animals were housed individually on a 12-h light/dark cycle. 168

169 170 BEHAVIORAL TASK

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¹⁷¹ Monkey C was trained to perform a reach-to-grasp task with its right hand, as described previously (Shin et al., 2012). The object

to grasp was a small plastic knob that was attached to the end of 172 a joystick controller lever. To start a trial, the monkey placed its 173 hand on a button located in front of a chair for 2-2.5 s. After a 174 go cue was given as a beep sound, the monkey pulled the knob 175 and then returned its hand to the button. When the monkey suc-176 cessfully pushed the button and pulled the knob to the required 177 displacement of 6 cm, it received a reward. Monkey T was trained 178 to perform a reach-to-grasp task with its right hand. The object 179 was a small piece of potato. The monkey launched a trial by plac-180 ing its hand in front of a chair, and then a piece of potato was 181 presented in front of the monkey. The monkey was required to 182 take the potato, eat it, and then return its hand to the original 183 position. In the reach-to-grasp task, both the proximal and distal 184 forelimbs were active. This task allowed us to analyze the kine-185 matics from multiple joints of the forelimb. Monkey C performed 186 the task for 5 sessions of 10 min each, in which the monkey 187 conducted 136.8 \pm 5.3 (mean \pm standard deviation) trials per ses-188 sion. Monkey T performed the task for 1 session of 2 min, which 189 contained 21 trials. 190

SURGERY

A mixture of xylazine (0.4 mg/kg; Bayer Health Care, Monheim, 193 Germany) and ketamine (5 mg/kg; Daiichi Sankyo, Tokyo, Japan) 194 was used to induce satisfactory sedation of the monkeys. Then, 195 the monkeys were anesthetized with isoflurane (exhaled level; 196 1-2%) and nitrous oxide gas (33%). The monkeys were para-197 lyzed using pancuronium bromide (Mioblock; $0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$; 198 Schering-Plough Corporation, Kenilworth, NJ). Expiratory CO2 199 levels were maintained within the physiological range (3.3–4.2%). 200 Assessment of the depth of anesthesia was done continuously by 201 checking the stability of expiratory CO₂ levels and the heart rate. 202

After shaving the hair on the back, the C3 through Th2 verte-203 brae were exposed bilaterally, and stainless screws were inserted 204 into the lateral mass of each vertebra on the bilateral sides. After 205 the lateral mass of the C5-Th1 segments was dissected on the 206 right side, two multi-electrode arrays (Blackrock Microsystems, 207 Salt Lake City, UT) were inserted through the dura into two 208 DRGs (Monkey C: C6 and C7; Monkey T: C7 and C8) on the 209 right side using a high-velocity inserter (Rousche and Normann, 210 1992). Reference wires were placed over the dura. After insert-211 ing the arrays, a connector was positioned over the laminectomy 212 and cemented in place with dental acrylic. Before recovering 213 from anesthesia, neostigmine bromide (Vagostigmin; 0.1 mg/kg; 214 Shionogi, Osaka, Japan) was administrated to recover from 215 the paralyzing effects of pancuronium bromide. Dexamethasone 216 (Decadron; 0.82 mg; MSD, Tokyo, Japan), atropine (0.25 mg; 217 Mitsubishi Tanabe Pharma, Osaka, Japan), and penicillin (peni-218 cillin G potassium; 50000 units; Meiji Seika Pharma, Tokyo, 219 Japan) were administered preoperatively, and penicillin (50000 220 units) and ketoprofen (Capisten; 5 mg/kg; Kissei pharmaceutical, 221 Matsumoto, Japan) were given postoperatively. 222

NEURAL RECORDING AND SPIKE DETECTION

The implanted arrays consisted of 48 platinized-tip silicon electrodes (100–1000 k Ω at 1 kHz), arranged in a square grid (400 μ m pitch) with 1 mm in length, and in a 5 × 10-configuration. The size of the array (2 mm in width, 4 mm in length) covered a DRG of 2–3 mm in diameter and 4 mm in length. For Monkey

C, the electrode arrays were connected to a 96-channel amplifier 229 230 (Plexon MAP system; Plexon, Dallas, TX) with a gain of ×20000, and signals from each electrode were sampled at 40 kHz. Filtered 231 spikes (150-8000 Hz) above the amplitude threshold, which 232 was determined by the "auto threshold algorithm" of the soft-233 ware, were bracketed within a window running 0.3 ms before to 234 235 0.8 ms after the threshold crossing. For Monkey T, the electrodes were connected to a 128-channel amplifier (Cerebus; Blackrock 236 Microsystems, Salt Lake City, UT) with a gain of ×1000, and sig-237 nals from each electrode were sampled at 30 kHz. Filtered waves 238 (250-7500 Hz) above the amplitude threshold, which was 5 times 239 the estimated background noise based on the median of the abso-240 lute value of the bandpass filtered signals (Quiroga et al., 2004), 241 were captured within a window running 0.33 ms before to 0.73 ms 242 after threshold crossing. After the detection of signals crossing 243 the threshold in both monkeys, spikes with similar features on 244 the principal component analysis (PCA) projection were grouped 245 into clusters by semi-automatic spike sorting methods (Offline 246 sorter; Plexon, Dallas, TX) and further manual refinement. The 247 interval between 2 consecutive spikes was more than 1 ms for 248 51 units, which implied no contamination from other neurons. 249 For the remaining 32 units, the proportion of cases in which the 250 interval between two consecutive spikes was less than 1 ms was 251 less than 1% of the total number of spikes. The neuronal firing 252 rates for each unit were computed in 5-ms bins in synch with the 253 sampling rate of the motion capture system at 200 fps. 254

256 CLASSIFICATION PROCEDURE

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We identified the modality of some recorded units each day 257 in Monkey C right after the tasks was completed. Units that 258 were sorted using an online spike sorting method were analyzed. 259 260 Waves above the amplitude threshold, which was used in the above offline sorting, were sorted to the same units by selecting 261 waveforms that crossed time-amplitude windows that were set 262 manually. We considered that spikes constituting online sorted 263 units were similar to, but not coincident with those constituting 264 offline sorted units. The arm, hand, and fingers were stimulated 265 manually to identify the receptive field of each unit. Pressure 266 over the tendon and muscle belly was used to identify tendon 267 organs and muscle spindles, respectively. Brushing and pinching 268 were used to identify cutaneous receptors. Subtypes of cutaneous 269 receptors were classified into rapidly or slowly adapting units 270 based on their response to the stimuli. 271

273 MOTION CAPTURE

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274 By tracking multiple reflective markers (4- or 6-mm-diameter 275 spheroids) with an optical motion capture system (Eagle-4 Digital RealTime System; Motion Analysis, Santa Rosa, CA), movements 276 of the upper limb, from the shoulder to the fingers, were recorded 277 and synchronized with the neural recordings. In the system, 12 or 278 279 11 infrared cameras operated at 200 frames/s to track the position of the reflective markers with submillimeter accuracy in Monkey 280 C and T, respectively. A total of 14 or 5 markers were attached to 281 the surface of the forelimb using a mild adhesive (LACE FX TAPE; 282 Vapon Inc., Fairfield, NJ, Aron Alpha Extra Jelly, Toagosei, Tokyo, 283 Japan) in Monkey C and T, respectively (Figure 1A). For Monkey 284 285 C, a total of 14 markers were attached to the left shoulder (marker 1; M1), the center of the chest (M2), the right shoulder (M3), the 286 biceps (M4), the triceps (M5), the medial epicondyle (M6), the 287 medial to the medial epicondyle (M7), the radial styloid process 288 (M8), the ulnar styloid process (M9), the metacarpophalangeal 289 joint of digit 2 (M10), the metacarpophalangeal joint of digit 4 290 (M11), the middle phalanx of digit 1 (M12), the middle pha-291 lanx of digit 2 (M13), and the middle phalanx of digit 4 (M14). 292 For Monkey T, a total of 5 markers were attached to the right 293 shoulder (M1), the medial epicondyle (M2), the center of the 294 forearm (M3), the ulnar styloid process (M4), and the metacar-295 pophalangeal joint of digit 4 (M5). The markers were placed at 296 almost identical positions on the two recording days for Monkey 297 C. The inter-marker distance between any two markers was sim-298 ilar between the 2 days. The ratio of the distance between the 2 299 days was 0.998 in the breast (M1-M2, M1-M3, and M2-M3), 300 1.01 in the upper arm (M1-M7), 1.03 in the lower arm (M7-M8 301 and M7-M9), 1.01 in the hand (M8-M9, M8-M10, M8-M11, 302 and M10-M11), and 1.09 in the fingers (M8-M12, M10-M13, 303 and M11-M14). A comprehensive catalog of 10 or 4 anatomically 304 defined upper extremity joint angles (Monkey C: shoulder flex-305 ion/extension (FE), shoulder adduction/abduction (AA), elbow 306 FE, pronation/supination (PS), wrist FE, wrist radial/ulnar (RU), 307 digit1 FE, digit1 AA, digit2 FE, and digit4 FE; Monkey T: elbow 308 FE, PS, wrist FE, and wrist RU) were analyzed in Monkey C and 309 T, respectively (Monkey C, Table1; Monkey T, Table2). In partic-310 ular, Euler angles were used to represent relative joint rotation. To 311 reduce noise from various sources, temporal changes in the joint 312 angles were smoothed using a 5 Hz low-pass digital filter. For con-313 venience, we refer to the first and second time derivatives of the 314 joint angles as "velocity" and "acceleration," respectively. 315

ENCODING OF JOINT KINEMATICS

Joint angle, velocity, and acceleration were modeled as a weighted linear combination of neuronal activity using multidimensional linear regression analysis as follows:

$$y_j(t) = \sum_{k,l} w_{j,k,l} \times x_k (t + l\delta) + b_j$$
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where: $y_i(t)$ is a vector of kinematic variables *j* (joint angle, veloc-325 ity, and acceleration) at time index t. $x_k(t + l\delta)$ is an input vector 326 of unit k at time index t and time-lag $l\delta$ ($\delta = 5 \text{ ms}$). $w_{i,k,l}$ is 327 a vector of weights on unit k at time-lag $l\delta$, and b_i is a vector 328 of bias terms to y_i . The units that showed no more than one 329 spike in the training data sets were omitted before the regres-330 sion analysis. We used a Bayesian SLiR algorithm that introduced 331 the automatic relevance determination (ARD) parameters $\alpha_{i,k}$ for 332 the weights $w_{i,k,l}$ assuming the same ARD parameters $\alpha_{i,k}$ for 333 different time-lags $l\delta$. Namely, sparse conditions were imposed 334 only for the unit dimension, and not for the temporal dimen-335 sion (Toda et al., 2011). By applying the variational Bayesian 336 approximation (Sato, 2001), this method iteratively estimates the 337 weights and the ARD parameters, which represent how much 338 the weight contributes to the reconstruction. On the basis of 339 the values of the estimated ARD parameters, the SLiR algorithm 340 automatically and effectively selects important feature sets and 341 prunes inappropriate signals from explanatory variables to attain 342

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monkeys. Microelectrode arrays were implanted in the right DRGs. Markers were placed on both shoulders and the right arm and hand. The blue dots represent 6-mm-diameter spheroid markers, and the red dots represent 4-mm-diameter spheroid markers. (B) Simultaneous recording of DRG

reach-to-grasp movements of the right hand. (Bottom) Shoulder, elbow, wrist, and finger (digit 2 MCP) joint angles. Extension (Ext.) is represented by an upward deflection (arrow) of the traces: the length of the arrow represents the magnitude of the angle.

Table 1 | Calculation of the joint angles in Monkey C. Joint angles were calculated from the two vectors presented in the right columns.

Joint angle	Two vectors	
Shoulder FE	Cross product of vector M3–M2 and vector M3–M1	Vector M3–M7
Shoulder AA	Vector M3–M1	Vector M3–M7
Elbow FE	Vector M7–M3	Vector M7–M8/M9
PS	Projection of vector M7–M3 on the plane with the normal vector M7–M8/M9	Projection of vector M8–M9 on the same plane
Wrist FE	Cross product of vector M8–M10 and vector M8–M9	Vector M8/M9–M7
Wrist RU	Vector M9–M8	Vector M8/M9–M10
Digit1 FE	Projection of vector M8–M10 on the plane including M8, M10, and M11	Projection of vector M8–M12 on the same plane
Digit1 AA	Projection of vector M8–M10 on the plane with the normal vector M11–M10	Projection of vector M8–M12 on the same plane
Digit2 FE	Cross product of vector M8–M10 and vector M8–M11	Vector M10–M13
Digit4 FE	Cross product of vector M8–M10 and vector M8–M11	Vector M11–M14

Table 2 | Calculation of the joint angles in Monkey T. Joint angles were calculated from the two vectors presented in the right columns.

Joint angle	Two vectors		
Elbow FE	Vector M2–M1	Vector M2–M4	
PS	Projection of vector M2–M1 on the plane with the normal vector M2–M4	Projection of vector M3–M4 on the same plane	
Wrist FE	Cross product of vector M4–M2 and vector M4–M3	Vector M5–M4	
Wrist RU	Vector M4–M3	Vector M4–M5	

a better generalized performance compared to the regularized linear model (Figueiredo and Nowak, 2003; Ganesh et al., 2008; Umeda et al., 2012). This is because having too many parame-ters relative to a limited number of training data sets is known to lead to poor generalized performance (Akaike, 1974; Geman et al., 1992). As external stimulation induced afferent activity, the time-lag was set at future, positive values. The recorded neuronal population consisted of different types of sensory neu-rons. Even muscle spindle discharges are determined not only by the current kinematic state of their parent muscles but also by the simultaneous activation of the fusimotor systems during

active movements. Thus, it is difficult to determine the opti-mum value of the time window during the ensemble coding based on physiological knowledge elicited from previous experiments using single afferent recordings. In this study, we used a time window in which maximum accuracy was achieved for the esti-mation of joint kinematics. When we changed the length of the time window, 400 and 150 ms were obtained in Monkey C and T, respectively (data not shown). If we consider the conduction velocity of afferent nerves to be more than 10 m/s (Loeb, 1976) and their length to be \sim 30 cm, the propagation delay should be less than 30 ms. One possible explanation for such long windows

is that good prediction of the encoding of joint kinematics for 457 458 3-dimensional movements requires sufficient amounts of DRG activity, but the firing frequency of individual DRG neurons is 459 quite low. 460

To examine what timing of DRG neuronal activity encoded 461 joint kinematics, joint kinematics were modeled as a weighted 462 linear combination of activity of DRG neurons using the SLiR 463 algorithm. In the analysis, the model was generated from the spike 464 number in a fixed time window (25 ms; 5 bins) at a variable time-465 lag relative to joint kinematics. We assessed each model generated 466 from input-output pairs with a different time-lag by calculating 467 the correlation coefficient between the observed kinematics and 468 its prediction. 469

Since the available data volume was limited in the encod-470 ing of joint kinematics by reconstructed DRG neuronal activ-471 ity (Monkey C, 3 blocks; Monkey T, 1 block, result shown in 472 Figure 7), the models generated with the data sets were assessed 473 using the same data sets. When we changed the length of the time 474 window in the analysis, maximum accuracy was achieved for the 475 estimation of joint kinematics at approximately 150 and 500 ms 476 in Monkey C and T, respectively (data not shown). We used this 477 time window in the analysis. 478

DECODING OF SPIKE TIMING 480

Neuronal firing frequency (dimensions; per second) was gener-481 ated by calculating the inverse of the inter-spike-interval of each 482 unit. The values were assigned to 5-ms bins corresponding to the 483 intervals. The firing frequency of the DRG neuronal ensembles 484 was modeled as a weighted linear combination of joint kinemat-485 ics (joint angle, velocity, and acceleration) using the following 486 multidimensional linear regression algorithm: 487

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$$x_j(t) = \sum_{k,l} w_{j,k,l} \times y_k \left(t + l\delta\right) + b_j$$

where: $x_i(t)$ is a vector of the firing frequency *j* at time index 492 t. $y_k(t+l\delta)$ is an input vector of kinematics k at time index 493 494 t and time-lag $l\delta$ ($\delta = 5 \text{ ms}$). $w_{i,k,l}$ is a vector of weights on 495 unit k at time-lag $l\delta$, and b_i is a vector of bias terms to x_i . We 496 used a Bayesian SLiR algorithm that introduced sparse conditions for the kinematic dimension. As external stimulation was 497 498 the cause of afferent activity, the time-lag was set at past, neg-499 ative values. When we varied the length of the time window, 500 maximum accuracy of estimation of the joint kinematics was achieved at -150 ms (data not shown). We used this time win-501 502 dow when decoding neuronal firing frequency from forelimb 503 kinematics.

To acquire the spike timing of the DRG neuronal ensembles 504 from their firing frequency, the inverse operation was employed. 505 Firing frequency values in 5-ms bins were summed cumulatively 506 507 until they hit a constant threshold of 200. The threshold value, 200, was set because the firing frequency values (dimension; per 508 second) were assigned to 5-ms bins. At this time, a spike occurred 509 and the cumulative sum was reset to zero. Then, the integra-510 tion process started again. When the firing frequency is replaced 511 with the membrane potential, the procedure corresponds to the 512 513 ordinary IF model.

DATA ANALYSIS

In both the encoding of joint kinematics by the population activ-515 ity of DRG neurons and the estimation of firing frequency from 516 the kinematics, a model generated from the training data set 517 was tested against a test data set. For Monkey C, continuously 518 recorded data of each session were partitioned into 24 blocks (1 519 block for 25 s data). Among the 24 blocks, 21 randomly selected 520 blocks were used as the training data set, and the remaining 3 521 blocks as the test data. For Monkey T, continuously recorded data 522 were partitioned into 6 blocks (1 block for 12.5 s data). Among 523 the 6 blocks, 5 randomly selected blocks were used as the train-524 ing data set, and the remaining block was used as the test data. 525 To assess the ability of the model encoding joint kinematics, a 5-526 and 6-fold cross-validation was performed in Monkey C and T, 527 respectively. To validate the prediction power of the model, we 528 created surrogate training data sets in which the temporal firing 529 profiles of inputs were shuffled independently across different tri-530 als and tested subsequently for their prediction of each output 531 parameter. 532

To assess the fine structures of the spike pattern, cross correla-533 tion between the observed firing pattern and its prediction in the 534 test data sets was calculated. Then, an absolute value of time-lag 535 at which the maximum correlation was achieved was obtained. 536

STATISTICAL ANALYSIS

The data were analyzed using the Kolmogorov-Smirnov test, a 539 One-Way analysis of variance (ANOVA), or the non-directional 540 paired Student's t-test, with Bonferroni correction if necessary. 541 An alpha level of significance was set at 0.05 for all statistical tests. 542 We found 95% confidence intervals for proportions based on the 543 inverse of the appropriate cumulative Beta distribution. We used 544 MATLAB (MathWorks, Natick, MA) for all statistical analyses. 545

RESULTS

(2)

SIMULTANEOUS RECORDING OF ENSEMBLE ACTIVITY OF DRG NEURONS

We recorded neuronal activity from the DRGs at the C6/7 and 550 C7/8 segments with two multi-electrode arrays in Monkey C 551 and T, respectively. For Monkey C, a couple of units could still 552 be recorded by the fifth post-operative day. We used recording 553 data in 3 sessions on the third post-operative day and 2 ses-554 sions on the fourth post-operative day for further analysis. A 555 total of 15 or 16 units were discriminated from 13 channels on 556 the third post-operative day, and a total of 12 units were dis-557 criminated from 9 to 10 channels on the fourth post-operative 558 day. The recorded units included muscle spindles, cutaneous 559 receptors (both rapidly and slowly adapting units), and a ten-560 don organ in Monkey C. In Monkey T, a total of 13 units 561 were discriminated from 12 channels in one session on the second post-operative day. After the recording, due to accidental damage to the head holder, further recordings could not be performed.

RECONSTRUCTION OF FORELIMB JOINT KINEMATICS

Population recordings during voluntary reach-to-grasp move-568 ments showed that the temporal discharge patterns of individual 569 isolated units were correlated with temporal changes in the joint 570

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angles and that the temporal firing pattern of each unit was different among the isolated units (**Figure 1B**).

To investigate whether the neuronal activity in the DRGs 573 conveyed information about joint kinematics, we applied the 574 SLiR model to encoding of kinematic variables using the activ-575 ity of all units. As the excitation of peripheral afferents can be 576 elicited by external stimulation, we considered that the periph-577 eral afferents contained information concerning limb position 578 immediately before firing (Umeda et al., 2012). Therefore, the 579 kinematic variables were defined as a weighted sum of neu-580 ral activity for the upcoming 400 and 150 ms (here grouped 581 into 80 and 30, 5-ms bins) in the SLiR algorithm in Monkey 582 C and T, respectively. Figure 2 shows the results for the recon-583 struction of angle (Figures 2A,B), velocity (Figures 2C,D), and 584 acceleration (Figures 2E,F) of forelimb joints in a test data 585 set, from the activity of a neuronal ensemble. The predic-586 tion accuracy of 3 kinematics of all 10 joints encoded by 587 the actual neural firing pattern was much better than that 588 obtained by the shuffled data (paired Student's t-test, p <589 0.0001). Thus, the SLiR model provided accurate predictions of 590 joint kinematics. The prediction accuracy for angle was higher 591 than that for velocity and acceleration in all joints (One-Way 592 ANOVA, $F_{(2, 2319)} = 254.03$, $p = 1.76 \times 10^{-100}$; paired Student's 593 *t*-test with Bonferroni correction (n = 3), p < 0.0001). These 594 results demonstrate that the a population of DRG neurons 595 convey rich information about joint kinematics, especially for 596 angle. 597

The SLiR model reduced the number of units used in the pre-598 diction (Figure 3). Note that the proportion of selected units was 599 higher in the prediction of angle than that of velocity and accel-600 eration [angle, 0.66 (0.61-0.70); mean, (confidence interval)]; 601 velocity, 0.52 (0.47-0.56); acceleration, 0.41 (0.36-0.45); One-602 Way ANOVA, $F_{(2, 90)} = 22.34$, $p = 1.32 \times 10^{-8}$; paired Student's 603 *t*-test with Bonferroni correction (n = 3), p < 0.0001), suggest-604 ing that a larger number of units contribute to the encoding 605 of joint angle than velocity and acceleration. This result was 606 correlated with the prediction accuracy of the respective kine-607 matics shown in Figure 2. In any case, the SLiR model accurately 608 encoded temporal changes in joint kinematics from the activity of 609 the DRG neuronal ensembles using a reduced number of units. 610

Next, we examined how the timing of neuronal activity 611 encoded the joint kinematic information. We generated models 612 from neuronal activity in a short time window (25 ms) with vari-613 able time-lag against joint kinematics and assessed each model by 614 calculating the correlation coefficient between the observed kine-615 matics and its prediction (Figure 4A). The activity of DRG neu-616 ronal ensembles with similar timing as the kinematics provided 617 the most accurate prediction of all three measures of kinematics 618 (Figure 4B). Neuronal activity for 375 ± 44.3 ms (mean \pm SE, 619 n = 6) reconstructed a joint angle at 80% of the highest accu-620 racy. On the other hand, neuronal activity for 150 ± 15.8 ms and 621 150 ± 9.1 ms reconstructed the velocity and acceleration at the 622 highest accuracy of 80%, respectively. The range for the predic-623 tion of a joint angle was significantly larger than that of velocity 624 and acceleration (One-Way ANOVA, $F_{(2, 15)} = 22.09, p = 3.38 \times$ 625 10^{-5} ; paired Student's *t*-test with Bonferroni correction (n = 3), 626 p < 0.05). 627

RECONSTRUCTION OF THE FIRING FREQUENCY OF DRG NEURONS

We estimated the temporal firing pattern of DRG neuronal 629 ensembles using an IF model. We performed the calculation in 630 two steps (Figure 5A). For the first step (integration process), we 631 applied the SLiR model to estimate the firing frequency of DRG 632 neuronal ensembles from all kinematic variables. We then calcu-633 lated the spike timing of individual units from the decoded firing 634 frequency as the second step (fire process). In the fire process, the 635 firing frequency values were summed cumulatively until a con-636 stant threshold was reached. At this time, a spike occurred and the 637 cumulative sum was reset to zero, and integration started again. 638

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We considered that peripheral afferents carried information 639 concerning limb position within time windows preceding the 640 spiking events. Then, we defined firing frequency as a weighted 641 sum of joint kinematics for the previous 150 ms (here grouped 642 into 30, 5-ms bins) in the SLiR model. Figure 5B shows the 643 results of the estimation of firing frequency of 6 units in a 644 test data set from the joint kinematics in Monkey C. In the 645 previous analysis in Figure 3, the SLiR model selected impor-646 tant units that contributed to the encoding of joint kinemat-647 ics and pruned irrelevant units (selected, 63 units; pruned, 20 648 units). For 61.9% of the selected units, the prediction accu-649 racy (correlation coefficient) was more than 0.4 (Figure 5C). 650 The prediction accuracy from the actual joint kinematics was 651 much better than that from the shuffled data in 95.2% of the 652 selected units and 65% of the pruned units (paired Student's t-653 test, p < 0.05; Figure 5C). The prediction accuracy of the selected 654 units was higher than that of the pruned units (selected units, 655 0.47 ± 0.02 (mean \pm SE); pruned units, 0.17 ± 0.02 ; Student's 656 *t*-test, p < 0.0001; **Figure 5C**). The SLiR model reduced the num-657 ber of inputs used in the prediction (Figure 5D). Note that 658 the proportion of the selected angle was higher than that of 659 velocity and acceleration in the prediction of the firing fre-660 quency [angle, 0.94 (0.91–0.96); mean, (confidence interval)]; 661 velocity, 0.74 (0.69-0.80); acceleration, 0.55 (0.54-0.65); One-662 Way ANOVA, $F_{(2, 90)} = 42.6$, $p = 9.56 \times 10^{-14}$; paired Student's 663 *t*-test with Bonferroni correction (n = 3), (p < 0.05), suggest-664 ing that a higher number of angle variables contributed to the 665 encoding of the firing frequency than those of velocity and 666 acceleration. These results show that the kinematic informa-667 tion of forelimb joints, especially joint angles, can be trans-668 lated to the firing frequency of DRG neurons using the SLiR 669 model. 670

To demonstrate the importance of individual kinematic vari-671 ables in the reconstruction of the firing frequency, we calculated 672 the correlation coefficient between the observed firing frequency 673 and the predictions derived from each kinematic and the cor-674 responding weight values determined through the SLiR model 675 among all the kinematics. The joint angle contributed most to 676 the decoding of the firing frequency of the selected units (angle, 677 0.29 ± 0.02 (mean \pm SE, n = 63); velocity, 0.18 ± 0.02 ; accel-678 eration, 0.07 \pm 0.01; One-Way ANOVA, $F_{(2, 186)} = 47.83$, p =679 1.74×10^{-17} ; paired Student's *t*-test with Bonferroni correction 680 (n = 3), p < 0.05; Figure 5E), but not of the pruned units. This 681 result agrees with the preceding analysis that the activity of the 682 DRG neuronal ensembles encoded the joint angle more accurately 683 than the velocity and acceleration of the joints (Figure 2). 684



movements. (A,C,E) Examples of recorded kinematics of the shoulder, elbow, wrist, and finger (digit 2 MCP) joints of Monkey C (black line) and their prediction using the SLiR model (red line). The correlation coefficient (R) between the recorded and predicted kinematics is shown in the upper right corner of each trace. The angular changes at the joints are shown in

of the forelimb joints. The indicated values are averages of the results of 5 or 6 pairs of training and test data sets from each session. The angular changes at the joints are shown in (B), velocity in (D), and acceleration in (F). FE, flexion/extension; AA, adduction/abduction; PS, pronation/supination; RU, radial/ulnar.

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RECONSTRUCTION OF THE SPIKE TIMING OF DRG NEURONS 799

800 Next, we calculated the spike timing of individual DRG neurons from the decoded firing frequency. Figure 6A shows raster plots 801 for 16 units in a test data set of an actual recording and its pre-802 diction. The overall firing pattern in the prediction was similar 803 to that in the recorded data. To assess the general structure of 804 805 the estimated firing pattern, we compared the total number of spikes between the recorded and predicted data. For 89% of the 806 selected units and 95% of the pruned units, there was no signif-807 icant difference in the total number of spikes. The correlation 808 coefficient for the total number of spikes was 0.998 and 0.999 809



FIGURE 3 | Selection of a subset of DRG neurons of two monkeys by the SLiR model. The proportion of units selected by the SLiR model during the encoding of the angle, velocity, and acceleration of the forelimb joints are shown. The asterisks indicate that there was a significant difference between two groups. The error bars represent the confidence intervals for the proportions

for the selected and pruned units, respectively (Figure 6B). Next, 856 we examined the fine structure of the predicted firing pattern 857 by calculating the cross-correlation for the binned spike number 858 of the recorded and predicted data. A time-lag, which resulted 859 in a maximum cross-correlation value, was less than 10 ms for 860 54% of the selected units and less than 20 ms for 75% of the 861 selected units (Figure 6C). The time-lag for the selected units was 862 smaller than the time-lag derived from a firing pattern decoded 863 by the shuffled kinematics [recorded data, 10 ms (median, n =864 63); shuffled data, 1245 ms; Kolmogorov-Smirnov Test, p < 0.05; 865 Figure 6C], but not for the pruned units [recorded, 2135 ms 866 (median, n = 20); shuffled, 1605 ms; Kolmogorov-Smirnov Test, 867 p = 0.28; Figure 6C]. Thus, the IF model incorporating the SLiR 868 algorithm provided accurate decoding of the spike timing of the 869 DRG neuronal ensembles from the joint kinematics, especially for 870 the selected units. 871

To determine the optimal parameters of afferent electrical 872 stimulation to transmit proprioceptive signals from a neuro-873 prosthesis, the stimulus timing should be able to encode the 874 kinematic information. We applied the SLiR model to the recon-875 struction of kinematic variables from the estimated spike timing. 876 Figure 7A shows the reconstruction of the angle of 4 forelimb 877 joints from the predicted spike timing of a neuronal ensem-878 ble. The prediction performance of all 3 kinematic variables 879 calculated by using the estimated spike timing was much bet-880 ter than that calculated by using the shuffled spike data (paired 881 Student's *t*-test with Bonferroni correction (n = 3), p < 0.0001; 882 Figure 7B). Furthermore, the prediction accuracy of the joint 883 angle calculated by using the estimated neuronal firing pattern 884 was higher than that calculated by using the recorded neu-885 ronal firing (paired Student's t-test with Bonferroni correction 886 (n = 3), p < 0.0001; Figure 7B). Thus, the estimated multiunit activity encoded the joint kinematics, suggesting that the model used to estimate the spike timing of individual units from the joint kinematics can be useful for the design of stimulus



contributed to the encoding of forelimb joint kinematics. (A) Each model W was fitted to DRG neuronal ensemble activity x in a 25-ms time window at various time-lag n relative to the kinematics v. When time-lag n was a positive value, the model W was fitted to DRG neuronal ensemble activity x(t + n),

(correlation coefficient) of each model that was fitted to DRG neuronal ensemble activity at various time-lags relative to joint angle, velocity, and acceleration, respectively. The black lines represent the average results in individual sessions and the red lines represent the average results in all sessions for both monkeys.



combination of the SLiR algorithm and a fire model. (B) Examples of recorded temporal changes of the firing frequency of 6 neurons in Monkey C (black line) and their prediction using the SLiR model (red line). The correlation coefficient (R) between the recorded and predicted firing frequency is shown in the insets. (C) Histograms of the correlation coefficient between the observed firing frequency and the prediction by the SLiR. The histograms are shown for the units selected in the encoding of forelimb joint kinematics by the SLiR model (red bar) and the pruned units (blue bar). The light red and blue bars represent the histogram for the selected and pruned units in the shuffled

parameters that provide proprioceptive information from the periphery.

DISCUSSION

An ideal proprioceptive neural interface should enable individuals to perceive proprioception that is driven by electrical stimula-tion of the nervous system as if it comes from their own body. Vibratory or electrical stimulus of a tendon excites muscle spin-dles or cutaneous receptors to produce the illusion of movement in humans (Goodwin et al., 1972; Craske, 1977; McCloskey et al., 1983; Gandevia, 1985; Collins and Prochazka, 1996; Dhillon and Horch, 2005; Roll et al., 2009; Thyrion and Roll, 2010). Simulated patterns of vibration to a couple of tendons have been shown to induce illusory multi-joint movements (Thyrion and Roll, 2010). Thus, it is important to optimize the parameters of peripheral

kinematic data, respectively. The total number of selected and pruned units were 63 and 20, respectively. (D) Selection of a subset of kinematic variables from both monkeys by the SLiR model. The proportion of kinematic variables selected by the SLiR model in the encoding of firing frequency of DRG neurons is shown. The asterisks indicate significance. The error bars represent the confidence intervals for the proportions. (E) Contribution of angle, velocity, and acceleration components of kinematics to the reconstruction of the firing frequency. Reconstruction was conducted from each kinematic component and weighted values determined by the SLiR model with population data. Graphs are shown for the selected (red) and pruned units (blue). The indicated values are the average results in 6 sessions. The asterisks indicate significance. The error bars represent the standard deviation of the mean.

electrical stimulation that produces kinesthetic illusion as a part of a somatosensory BMI. One strategy for the design of optimal stimulation patterns to afferents is to mimic the neuronal rep-resentation of limb positions and kinematics. At an early stage of the development of BMI, a decoder was designed based on experi-mental evidence for the causal relationship between the activity of neurons in the primary motor cortex and kinematic parameters of limb movements or muscle activity (Chapin et al., 1999; Wessberg et al., 2000; Serruya et al., 2002; Morrow and Miller, 2003). As an analogous strategy, understanding decoding rules in which limb movements are transformed into the activity of sensory neurons is an important first step toward a proprioceptive neural interface. We showed that an IF model incorporating the SLiR algorithm accurately predicted the electrical activity patterns of DRG neu-ronal ensembles from forelimb joint kinematics. The predicted



1075 MULTICHANNEL RECORDING FROM THE CERVICAL DRGs OF 1076 BEHAVING PRIMATES

production of artificial kinesthetic sensation.

The activity of peripheral afferents has been recorded by single fiber recordings from humans and awake animals. These
studies were able to identify the response properties of single
afferent fibers to various external mechanical stimulation or both
passive and voluntary movements (Hagbarth and Vallbo, 1967,
1968, 1969; Matthews, 1972; Gandevia and McCloskey, 1976;
McCloskey, 1978; Loeb and Duysens, 1979; Schieber and Thach,

ing studies demonstrated difficulty in describing decoding rules at the population level. In the present study, we recorded the 1130 population activity of peripheral afferents simultaneously from 1131 voluntarily behaving monkeys using multi-electrode arrays. The 1132 results demonstrate that temporal changes in the angle, velocity, 1133 and acceleration of various forelimb joints can be reconstructed 1134 from the activity of DRG neuronal ensembles, suggesting that the 1135 population activity of peripheral afferents encodes forelimb joint 1136 kinematics. 1137

Previous multichannel recording studies of DRGs have 1138 been performed in anesthetized animals. These studies used 1139 multi-electrode arrays on cervical (Umeda et al., 2012) or lumbar 1140



FIGURE 7 | Performance of the SLiR model in predicting joint kinematics from the predicted DRG neuronal ensemble activity. (A) Examples of recorded kinematics from the shoulder, elbow, wrist, and finger (digit 2 MCP) joints (black) and their prediction from DRG activity using the ordinary linear regression model (red). The correlation coefficient (R) between the recorded and predicted kinematics is shown in the upper right corner of each graph.



(B) Test performance [correlation coefficient (R)] of the SLiR model in predicting the kinematics of the forelimb joints from the recorded (black), predicted (red), and shuffled (white) activity. The indicated values are the average results from 6 sessions and the error bars represent the standard deviation (n = 274 data sets). The asterisks indicate significance [paired Student's *t*-test with Bonferroni correction (n = 3), p < 0.0001].

(Stein et al., 2004; Weber et al., 2011) DRGs and detected neu-1164 ral signals from approximately 100 sensory neurons. Here, for 1165 the first time, we recorded simultaneously the activity of DRG 1166 1167 neuronal ensembles using multi-electrode arrays from behaving 1168 non-human primates. The number of detected units in this study 1169 was fewer than in the previous recordings from anesthetized ani-1170 mals. Although the prediction accuracy for the encoding of joint kinematics from DRG population activity was lower than the 1171 1172 previous experiments using anesthetized animals (Umeda et al., 2012), this study showed that joint kinematics could be recon-1173 structed successfully from the activity of a fewer number of units 1174 at a certain level of accuracy (Figures 2, 3). Since muscle spindle 1175 discharge is affected by fusimotor drive, active movements may 1176 differ from the pattern of peripheral proprioceptive inputs that 1177 are merely generated by passive movements (Hunt and Kuffler, 1178 1951; Matthews, 1972). The arm position is perceived more accu-1179 rately during active movements than passive movements (Paillard 1180 and Brouchon, 1968; Bairstow and Laszlo, 1979; Gritsenko et al., 1181 2007). Therefore, it is important to study the kinesthetic mech-1182 anism by analyzing neuronal activity in awake subjects rather 1183 1184 than in anesthetized subjects, and proprioceptive signals arising from self-initiated movements rather than externally imposed 1185 movements. 1186

1187 Microneurography is a powerful technique and has provided much data concerning the physiological properties of primary 1188 afferents. However, microneurography is technically difficult to 1189 perform on subjects performing multi-joint movements, such as 1190 reaching and grasping movements, because an isolated afferent 1191 nerve is recorded by inserting a single fine electrode into the 1192 peripheral nerve of the moving limb (Vallbo et al., 2004). The 1193 activity of single DRG neurons has been recorded in awake mon-1194 keys (Schieber and Thach, 1985; Flament et al., 1992); however, 1195 they were only able to analyze the movement of the wrist in 1196 one direction. We were able to record afferent discharges during 1197

reaching movements of the entire forelimb for 10 min. Although the recording of individual units was stable during only 1 session, the shape of the units was not affected by movement of the forelimb. The amount of data was sufficient to assess the relationship between population activity in DRG neurons and joint kinematics. Recording stability requires further improvement of the chronic implantation of electrode arrays for a BMI with sensory feedback.

ENCODING OF JOINT KINEMATICS BY THE ACTIVITY OF DRG NEURONAL ENSEMBLES

We showed that the SLiR algorithm accurately predicted the kine-1232 matics of various forelimb joints, including not only proximal 1233 joints, but also distal joints using the same data set. The coding 1234 of positions and movements of the ankle joint by a population 1235 of peripheral afferents was examined by collecting a number of 1236 separate microneurographic recordings during repeated move-1237 ments (Bergenheim et al., 2000; Roll et al., 2000; Jones et al., 1238 2001; Aimonetti et al., 2007). However, these studies demon-1239 strated that movement directions in two-dimensional space at a 1240 single joint of a leg could be estimated using the collected record-1241 ing data. Although a reach-to-grasp movement seems to be a 1242 simple motion, it is a movement with multiple degrees of free-1243 dom. PCA of joint kinematics showed that 90% of the overall 1244 variability was accounted for by the first 12 principal components 1245 among a total of 30 principal components for Monkey C, and was 1246 accounted for by the first 7 principal components among a total of 1247 12 principal components for Monkey T. The SLiR analysis in this 1248 study showed that the simultaneously recorded activity of DRG 1249 neuronal ensembles represents kinematic information of multiple 1250 joints of the forearm at multiple degrees of freedom. 1251

The activity of the DRG neuronal ensembles encoded 1252 joint angle with higher correlations compared to velocity 1253 and acceleration (**Figure 2**). According to recent reports of 1254

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microneurographic recordings from a single afferent in volun-1255 1256 tarily moving human subjects, the activity of a single group Ia afferent from the muscle spindle encodes velocity and accelera-1257 tion and that of a group II afferent conveys velocity information 1258 (Dimitriou and Edin, 2008a,b). In the present study, we recorded 1259 population activity containing the activity of cutaneous recep-1260 tors that also contributed to the kinesthetic sense in addition to 1261 that of muscle spindles (Collins and Prochazka, 1996; Collins 1262 et al., 2005; Cordo et al., 2011). Hence, the summation of pop-1263 ulation activity from variable peripheral receptors may indicate 1264 that the best encoded kinematics is the joint angle. Population 1265 activity encoded angle information at 180 ms before spike dis-1266 charge, and velocity and acceleration information at 75 ms before 1267 the spike discharge (Figure 4B). These results suggest that the 1268 kinematic information preceding to the movement is useful for 1269 accurate estimation of spike timing. This finding implies that 1270 a model that calculates stimulus timing from kinematic infor-1271 mation of forelimb joints is practical for an online feedback 1272 system. 1273

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1275 AN IF MODEL INCORPORATING THE SLIR ALGORITHM

1276 The IF model has proven to be useful in addressing the question 1277 of how joint kinematics are encoded in the response of neurons. The leaky version of the IF model accurately predicted the spike 1278 1279 timing of a peripheral sensory neuron in response to an external 1280 stimulus and succeeded in describing the functional properties 1281 of the receptor to this stimulus (Pillow et al., 2005; Kim et al., 2010; Dong et al., 2013). The model has been used to predict the 1282 1283 responsiveness of single neurons. In the present study, we divided 1284 the model into two steps and fitted a model in the first step to data from a neuronal population that was recorded simultane-1285 ously from the DRGs. Through a fire process, the model provided 1286 1287 an accurate prediction of spike timing at the population level.

1288 During the integration of inputs, we used the SLiR algorithm. 1289 The SLiR algorithm automatically and effectively selected relevant 1290 feature sets from many parameters to attain a higher generalized performance than that obtained from other ordinary linear 1291 regression models (Figueiredo and Nowak, 2003; Ganesh et al., 1292 2008). Its superior generalized performance was indicated previ-1293 1294 ously using population recordings from the DRGs of anesthetized monkeys (Umeda et al., 2012). By selecting the optimal ensemble 1295 1296 from joint kinematic variables for the decoding of the firing rate, 1297 the analysis revealed that joint angle contributed the most to the 1298 decoding of spike frequency. The results are consistent with those in the encoding analysis; the population activity of DRG neurons 1299 encoded the joint angle at the highest prediction accuracy. 1300

1301 In a somatosensory BMI, proprioceptive feedback should be applied to the nervous system in real time. For the model to be 1302 available practically for rapid proprioceptive feedback, the com-1303 puter load should be reduced so as to conduct the calculations in 1304 1305 real time. The reduction of input parameters without any deterioration of prediction performance may prove to be useful in 1306 BMI systems that limited hardware speed. The SLiR algorithm 1307 selected important kinematic information automatically from 1308 the entire recorded data without affecting model performance 1309 through machine learning. Therefore, the IF model incorporat-1310 1311 ing the SLiR algorithm is a practical method for the application

of rapid proprioceptive feedback to the brain in a bidirectional 1312 sensory-motor BMI.

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LIMITATIONS OF THE IF MODEL INCORPORATING THE SLIR ALGORITHM

Our results showed that the IF model incorporating the SLiR 1317 algorithm successfully reconstructed the temporal firing pattern 1318 of DRG neuronal ensembles from forelimb joint kinematics. 1319 However, the reconstruction deviated from the original firing pat-1320 tern, which may have arisen from a smoothing effect introduced 1321 by the linear regression analysis that was used during the inte-1322 gration step. In the linear regression analysis, the output was 1323 obtained from a weighted sum of the inputs. This procedure 1324 potentially has a smoothing effect on the output. As shown in 1325 Figure 5B, the rapid increase of firing frequency could not be 1326 reconstructed by the SLiR algorithm, suggesting that the lin-1327 ear regression analysis failed to reproduce correctly the dynamic 1328 property of DRG neuronal activity. Second, it is difficult for the 1329 linear regression analysis to reproduce a flat baseline near zero 1330 when units do not fire (Figure 5B, unit6). Small constant values 1331 in the baseline can yield some spikes through the IF procedure 1332 where there was no firing in the original data. This phenomenon 1333 led to an increase of background activity in some units. If these 1334 deviations could be reduced, spike timing can be reproduced 1335 from the kinematics more accurately. In spite of the limitations 1336 of the model, its simplicity is a strong advantage for its use for 1337 generation of stimulus parameters in a proprioceptive interface. 1338

APPLICATION OF A PROPRIOCEPTIVE INTERFACE TO A BMI

Peripheral electrical stimulation can activate various modalities 1341 of peripheral afferents including muscle spindle afferents, Golgi 1342 tendon organs, joint receptors, cutaneous receptors, and pain 1343 receptors. Information about limb position and movement is 1344 conveyed to the central nervous system via the activity of cuta-1345 neous receptors (Clark et al., 1979; Edin and Johansson, 1995; 1346 Edin, 2001; Cordo et al., 2011) as well as muscle spindles and joint 1347 receptors (Goodwin et al., 1972; Gandevia and McCloskey, 1976; 1348 Craske, 1977; McCloskey et al., 1983; Gandevia, 1985; Ferrell 1349 et al., 1987; Collins and Prochazka, 1996). Our previous study 1350 indicated that adding the neuronal activity of cutaneous receptor 1351 ensembles to that of muscle receptors including muscle spindles 1352 and joint receptors significantly improved the decoding accu-1353 racy of forelimb kinematics provided by the activity of muscle 1354 receptors only in anesthetized monkeys (Umeda et al., 2012). 1355 The recorded units in the present study included muscle spin-1356 dles, cutaneous receptors, and a Golgi tendon organ in Monkey 1357 C, which encoded the forelimb joint kinematics. Thus, stimu-1358 lation of a combination of muscle spindles, joint receptors, and 1359 cutaneous receptors may induce more realistic perception of limb 1360 sensation than stimulation of a single modality of peripheral 1361 afferents. Conversely, there is a possibility that peripheral stimula-1362 tion can activate pain receptors and generate noxious sensations 1363 to subjects. Since the stimulation threshold of pain receptors is 1364 higher than that of muscle spindle afferents, joint receptors, and 1365 the majority of cutaneous receptors (Lloyd, 1943; Marchettini 1366 et al., 1990), control of stimulation strength can allow one to avoid 1367 generation of noxious sensation. 1368

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