Flexible adaptation to an artificial recurrent connection from muscle to peripheral nerve in man

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Kato K, Sasada S, Nishimura Y. Flexible adaptation to an artificial recurrent connection from muscle to peripheral nerve in man. J Neurophysiol 115: 978–991, 2016. First published December 2, 2015; doi:10.1152/jn.00143.2015.—Controlling a neuroprosthesis requires learning a novel input-output transformation; however, how subjects incorporate this into limb control remains obscure. To elucidate the underlying mechanisms, we investigated the motor adaptation process to a novel artificial recurrent connection (ARC) from a muscle to a peripheral nerve in healthy humans. In this paradigm, the ulnar nerve was electrically stimulated in proportion to the activation of the flexor carpi ulnaris (FCU), which is ulnar-innervated and monosynaptically innervated from 1a afferents of the FCU, defined as the “homonymous muscle,” or the palmaris longus (PL), which is not innervated by the ulnar nerve and produces similar movement to the FCU, defined as the “synergist muscle.” The ARC boosted the activity of the homonymous muscle and wrist joint movement during a visually guided reaching task. Participants could control muscle activity to utilize the ARC for the volitional control of wrist joint movement and then readapt to the absence of the ARC to either input muscle. Participants reduced homonymous muscle recruitment with practice, regardless of the input muscle. However, the adaptation process in the synergist muscle was dependent on the input muscle. The activity of the synergist muscle decreased when the input was the homonymous muscle, whereas it increased when it was the synergist muscle. This reorganization of the neuromotor map, which was maintained as an aftereffect of the ARC, was observed only when the input was the synergist muscle. These findings demonstrate that the ARC induced reorganization of neuromotor map in a targeted and sustainable manner.

motor adaptation; artificial neural connection; volitional control; brain-computer interface

INDIVIDUALS WITH STROKE or a spinal cord lesion exhibit a severe motor deficit in their extremities. Although physical rehabilitation can have an impact on functional recovery, even when initiated in the chronic postinjury phase (Dombovy et al. 1998; Jongbloed et al. 1986), the recovery of motor function is often limited (Devivo 2012; Langhorne et al. 2009; Sugiyama et al. 2013). One realistic solution to provide further functional improvement is the use of closed-loop functional electrical stimulation (FES) to reanimate volitional control of paralyzed limbs. Closed-loop FES, which is a kind of activity-dependent stimulation, detects physiological signals, such as cortical (Ethier et al. 2012; Moritz et al. 2008; Nishimura et al. 2013a; Pohlmeyer et al. 2009; Zimmermann and Jackson 2014) or muscle activity (Muraoka 2002; Nishimura et al. 2013a; Peckham et al. 2001; Sasada et al. 2014; Yeom and Chang 2010), and translates it in real time into input-contingent electrical stimulation to muscles, peripheral nerves, or spinal cord. Closed-loop FES creates a novel causal input-output relationship as an “artificial” neural pathway to physiological pathways. From this standpoint, there is a fundamental problem of how subjects incorporate a novel artificial neural connection into volitional limb control with residual pathways. However, the details of this adaptation process remain largely unclear.

To date, adaptability in controlling goal-directed limb movements has been demonstrated using variable error-based experimental paradigms with perturbations that interfere with the execution (Gandolfo et al. 2000; Li et al. 2001; Padoa-Schioppa et al. 2004) or visual feedback (Paz et al. 2003; Wise et al. 1998) of movements. Each experiment has suggested that, with practice, subjects learn to predict and correct the systematic errors of a new environment. Considering these consequences, when we confront a complex situation of controlling movements with a novel artificial neural connection, we also might have the potential to adapt by learning the newly given input-output relationship created by the artificial neural connection.

The purpose of this study was to demonstrate adaptability to an “artificial recurrent connection” (ARC) from a muscle to a peripheral nerve, which is a closed-loop FES. An ARC detects the firing pattern of the motor units (MUs) of the wrist muscle, converts it in real time into a stimulus intensity and frequency that are proportional to its firing rate, and delivers electrical pulses to the peripheral nerve. Electrical stimulation of the peripheral nerve containing motor and afferent nerves is known to induce refractory reactions such as mono- and polysynaptic reflexes through the spinal cord and the direct motor response, i.e., the M-response (Hugon 1973; Jenner and Stephens 1982; Táborská 1973). These responses can be evoked by activity-dependent electrical stimulation to the peripheral nerve so that subjects may volitionally boost ongoing muscle activity. In this study, we evaluated the motor adaptation process using error-based wrist reaching movements during the introduction and removal of an ARC. We have demonstrated that subjects have adequate adaptability to modify descending motor commands and create a new neuromotor map, which is the association between a desired limb movement and the corresponding motor commands.

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MATERIALS AND METHODS

Participants

Twenty-two healthy right-handed volunteers (age range: 25–43 yr, mean ± SD, 32.5 ± 5.6 yr; 1 female) participated in the experiments. The experiments conformed to the Declaration of Helsinki and were approved in advance by the ethics committee of the National Institute for Physiological Sciences of Japan (Approval No. 12B009). Written informed consent was obtained from all subjects before participation.

Experimental Setup

The participants sat on a chair while grasping the handle of a robotic manipulandum (Phantom Premium 1.5 High Force; SensAble Technologies, Wilmington, MA) with their right hand (Fig. 1A). The manipulandum measured position and torque in the flexion-extension (F-E) and radial-ulnar (R-U) directions produced about the wrist. A spring force field (0.07 N/cm) was generated in the vertical plane. The right forearm was immobilized in the horizontal plane approximately parallel to the ground by a custom-built fixture. The shoulder was abducted at 45°, the elbow was kept at 110°, and the wrist joint was in a neutral position at 0°, and the subjects could move their wrist joint freely during the task. A monitor was positioned at eye level to display the position of the handle with a blue square cursor (size 8 mm) on a vertical screen.

Recordings

Electromyographic (EMG) activity was recorded with bipolar surface electrodes (NM-512G; Nihon Kohden, Tokyo, Japan) placed on the muscle bellies of the flexor carpi ulnaris (FCU), palmaris longus (PL), flexor carpi radialis (FCR), extensor carpi radialis (ECR), and extensor carpi ulnaris (ECU) of the right arm. EMG signals were amplified (×1,000; MEG-6116; Nihon Kohden, Tokyo, Japan) and bandpass filtered at 50-3,000 Hz. EMG signals were converted into digital data via an analog-to-digital converter system at a sampling rate of 5 kHz for later offline analysis (CED 1401 interface with Spike2 software; CED, Cambridge, UK). The position and torque signals in the F-E and R-U directions from the robotic manipulandum were recorded simultaneously at a sampling rate of 5 kHz and were downsampled to 1 kHz for offline analysis.

Ulnar Nerve Electrical Stimulation

Electrical stimulation was delivered to the ulnar nerve at the elbow level via surface electrodes in trains of 1-ms-duration biphasic square-wave pulses (Bp Isolator; FHC, Bowdoin, ME). A pair of electrodes for ulnar nerve stimulation was placed on the medial surface of the elbow, just proximal to the medial epicondyle of the humerus (Fig. 1A). The ulnar nerve was identified by confirming the evoked responses of the ulnar-innervated muscles, gradually increasing the stimulus current at 1 Hz at rest. The motor threshold (MT) was defined as the minimum current at which the evoked muscle activity was
observed by visual inspection. During stimulation, we confirmed that no participant felt any discomfort with the electrical stimuli.

Experimental Paradigms

Each participant was instructed to perform a visually guided reaching task about the wrist. Visual feedback was provided by a cursor representing the position of the manipulandum handle on the computer screen (Fig. 1A). The cursor (blue square on the screen in Fig. 1A) corresponded to the position of the hand at rest. In the behavioral paradigm, the center target (red square on the screen in Fig. 1A; size 4.2 cm) appeared first, and the participants were relaxed and holding the cursor in the center target for 1 s. A peripheral target (size 3.1 cm) then appeared, and the participants were required to move the cursor into the peripheral target. After holding the cursor in the peripheral target for 1 s, the participants were required to move the cursor back to the center target. Each participant performed this center-out task in three different conditions: without electrical stimulation (experiment 1), with continuous electrical stimulation (experiment 2), and with an ARC from the muscle to the peripheral nerve (experiment 3).

Experiment 1. The participants performed the center-out reaching task to randomly selected targets in eight radial positions (45° apart) without stimulation to confirm the directional tuning of muscle activity. A peripheral target appeared randomly at one of eight locations that were spaced evenly at a distance corresponding to 6 cm of actual distance in the center-out movement. The participants continued to perform the center-out reaching task at least 30 times to each target.

Experiment 2. The participants performed the center-out reaching task to the eight radial positions with continuous electrical stimulation to the ulnar nerve with a current of MT×1.1 and frequency of 3 Hz. This task was used to confirm the direction of the evoked wrist movements and muscle responses that were induced by ulnar nerve electrical stimulation. The participants continued to perform the center-out reaching task at least 30 times to each target.

Experiment 3. The participants performed the center-out reaching task to a peripheral target in three different epochs: “baseline” without the ARC, “ARC” with the ARC, and “washout” without the ARC. Immediately after the baseline epoch of 420 trials (trials 1–420) was completed, the ARC epoch began without any instruction to the participants. The participants performed 420 trials with the ARC (trials 421–840). Immediately after the ARC epoch was completed, the ARC was terminated without any instruction, and the participants then performed 140 movements without the ARC as the washout epoch (trials 841–980). Before the baseline epoch, the location of the target was set at the same location with the end point while continuous electrical stimulation with a frequency of 50 Hz and intensity of MT×1.3 was applied for 2 s under the resting state to the ulnar nerve. The actual distance between the center and peripheral target was set at an average of 5.5–6.0 cm. In addition, we asked the participants whether the electrical stimulation produced any uncomfortable sensation. The intensity was increased gradually in incremental steps of MT×1.3, ×1.4, ×1.5, and ×1.6. Stimulus trains with a current of MT×1.6 and frequency of 50 Hz corresponded to the maximum current and frequency applied by the ARC. After each stimulus train was given, we confirmed that none of the participants felt any discomfort or pain.

Varying subgroups of participants performed the task in three different conditions: “control experiment” (n = 10), “ARC with homonymous experiment” (n = 11), and “ARC with synergist experiment” (n = 10). In the control experiment, the participants performed the same task without the ARC throughout all epochs. Some participants performed more than one experiment. In this case, the interval between successive experimental sessions was at least 8 wk to avoid carryover effects.

Artificial Recurrent Connection

The ARC was generated by using a computer interface that was designed to detect the firing pattern of MUs that showed similar waveforms and converted it into activity-contingent electrical stimulation delivered to the ulnar nerve in real time (Fig. 1). Specific EMG waveforms defined as a putative MU were discriminated from surface EMG of the input muscle according to a template matching algorithm (Alpha Spike Detector; Alpha Omega Engineering, Nazareth Ilitt, Israel) in real time. The algorithm first identified threshold crossing and then discriminated signals that passed through eight template points within a 3.5-ms window. The parameters of the algorithm were determined while the participants were performing the task in experiment 1. We generally selected waveforms with high peak-to-peak voltages, although their parameters were sometimes adjusted depending on the shapes of the recorded EMG signals of each participant.

The firing pattern of a putative MU controlled both stimulation current and frequency in proportion to the moving-averaged firing frequency (250-ms time window) of the putative MU so that subjects could voluntarily alter the stimulation current and frequency dependent on the single source of the putative MU firing rate. If the firing frequencies of the putative MU (X; in Hz) were above the stimulus threshold (Xth; in Hz), stimulus frequency (f; Hz) and current (I; in mA) were modulated by the following equations:

$$f = f_0 + f_g \cdot X \cdot I_0 \leq I \leq I_{Max}$$

where $f_0 = \text{initial stimulus frequency}$ when $X$ was above $X_{th}$, $f_g = \text{gain of stimulus frequency}$, and $I_{Max} = \text{maximum stimulus frequency}$ (in Hz). and

$$I = I_0 + \frac{f}{X_{th}} \cdot X \cdot I_0 \leq I \leq I_{Max}$$

where $I_0 = \text{initial stimulus current}$, $I_g = \text{gain of stimulus current}$, and $I_{Max} = \text{maximum stimulus current}$ (in mA).

Each stimulus parameter was determined in the baseline epoch in experiment 3 using the following criteria: $X_{th}$, less than the firing frequency of the MU while the participant was holding at the center target; $f_0$, stimulus frequency that can induce a smooth movement trajectory; $f_g$, gain that allows $f_{Max}$ to be reached while the participant holds the peripheral target; $I_{Max}$, fixed at 50 Hz; $I_0$, fixed around the MT at rest; $I_{Max}$, gain that allows $I_{Max}$ to be reached while the participant holds at the peripheral target; and $I_{Gain}$, current intensity that can evoke a wrist movement that can hit the peripheral target at rest. Across the subjects, these parameters ranged as follows: $X_{th}$, 0.3–0.5 Hz; $f_0$, 20–30 Hz; $f_g$, 0.3–0.5 Hz; $I_{Max}$, 50 Hz in all subjects; $I_0$, MT×1.0–1.1; $I_0$, 0.05–0.08 mA; and $I_{Max}$, MT×1.4–1.6.

In this study, a muscle was chosen as the input muscle, the activity of which was converted to activity-contingent electrical stimulation. One was the FCU, which is innervated by the ulnar nerve and is monosynaptically innervated by Ia afferents of the FCU, defined as the “homonymous” muscle (Fig. 2A). The PL was tuned in a similar flexor direction to the homonymous muscle; however, it is not innervated by the ulnar nerve, defined as the “synergist” muscle. The ECU is tuned in the extensor direction, defined as the “antagonist” muscle. Therefore, each participant could boost the ongoing muscle activity of the homonymous muscle with ulnar nerve electrical stimulation controlled by the input homonymous or synergist muscle.

Analysis

Evaluation of movement kinematics. We quantified movement performance using the overshoot distance, velocity profile, and deviation of hand trajectory. The overshoot distance was defined as the distance between the peripheral target and the actual end point furthest from the target. The absolute value of overshoot distance was normal-
analyzed the difference in overshot distance between the first 10 and last 10 movements with the ARC using repeated-measures analysis of variation (ANOVA). ANOVA was followed by a Bonferroni-corrected post hoc test. To visualize differences in performance under ARC conditions with the homonymous or synergist muscle, we fitted exponential curves to the data using the curve fitting toolbox in MATLAB. The curves took the discrete form of an exponential function as in Eq. 3:

\[ y = a \cdot e^{-b \cdot x}, \]  

where \( x \) is trial number, \( a \) determines the scale of the change, and \( b \) determines the rate of change. We compared the convergent points between the fitted curve and 5 SD calculated from the baseline epoch. Maximum velocity distance was defined as the distance from the central target and the point at peak velocity of the hand movement. The absolute value of the maximum velocity distance was normalized by the distance between the central and peripheral targets. To quantify

Fig. 2. Directional tuning and evoked responses of the wrist muscles. A: relative locations of the recorded wrist muscles (FCU, flexor carpi ulnaris; PL, palmaris longus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; and FCR, flexor carpi radialis) and the ulnar nerve. The ulnar nerve (cyan) innervates the FCU, defined as the “homonymous muscle” (blue). PL is a synergist of the FCU as the wrist flexor, defined as the “synergist muscle” (red). ECU is an antagonist of the FCU as the wrist extensor, defined as the “antagonist muscle” (black). The described bones and muscles were illustrated on the basis of BodyParts3D (Database Center for Life Science, licensed under Creative Commons Attribution-ShareAlike 2.1 Japan). B: example of muscle tuning obtained by averaged EMGs from 30 trials per target in the center-out task toward the 8 radial targets. The polar plot shows hold-period muscle activity and the preferred direction calculated by vector summation. The summation of the vectors of muscle tuning of the homonymous (FCU, blue line), synergist (PL, red line), antagonist (ECU, black line), ECR (green line), and FCR (orange line) muscles is also represented. The direction of the evoked movement by ulnar nerve stimulation is represented (cyan). The dotted circles show the averaged muscle activity while the subjects were holding the center target. C: the averaged directions of the evoked force by ulnar nerve stimulation (cyan) and the preferred directions of the homonymous (FCU, blue), synergist (PL, red), antagonist (ECU, black), ECR (green), and FCR (orange) muscles. Horizontal bars indicate \( P \leq 0.01 \) with paired \( t \)-test. D: example of evoked muscle responses and wrist movements. The stimulus-triggered averages of the rectified EMGs of the homonymous (FCU, blue), synergist (PL, red), antagonist (ECU, black), ECR (green), and FCR (orange) muscles (top panels) and the evoked positions (cyan) during rest (bottom panels) in the center target (left), the moving state from the center to the peripheral target (middle), and the holding state inside the peripheral target (right) are shown. In only the homonymous muscle, the evoked responses of \( M \) and \( H \) waves could be observed that were beyond the 5SD level calculated from the baseline period (gray dotted line) during the resting, moving, and holding phases. Evoked movements also occurred after stimulation in all phases.
the curvature of hand trajectory, we measured the deviation of hand trajectory at its peak relative to a line connecting the start and target positions. The absolute value of deviation was normalized by its mean value during the baseline epoch.

**Evaluation of muscle activity.** To investigate the descending motor commands to motoneuron pools, we measured the firing rates in the putative MU of the input muscle and the rectified EMG of the recorded muscles during the holding phase at the peripheral target in each trial. However, stimulation artifacts were superimposed on the raw EMG signals during the ARC epoch. Therefore, we set “catch trials” during the late ARC epoch, in which the ARC was terminated suddenly while the participants were holding the cursor in the peripheral target. The 10 catch trials were set randomly without any instruction to the participants during the late ARC epoch (trials 741–840). The recorded muscle activity from 50 to 150 ms just after the ARC was terminated was used to measure the EMGs. EMGs were normalized based on the average EMG of the last 10 trials of the baseline epoch and compared with those in the control experiment. The difference of the EMGs between the ARC and control experiments was evaluated by an unpaired \( t \)-test.

**RESULTS**

**Relationship Between Muscle Tuning and Output Effect of Ulnar Nerve Stimulation**

The muscles were characterized by investigating their preferred direction of activity. Figure 2B shows a typical example of the preferred direction of each muscle and the direction of the evoked movement. Homonymous (FCU, blue) and synergist muscles (PL, red) were tuned in the flexion direction, whereas the antagonist muscle (ECU, black) was tuned in the extension direction. The direction of the evoked movement (cyan) and preferred direction of the homonymous muscle were identical. The other recorded muscles, i.e., the FCR (orange) and ECR (green), were tuned in the F-R and E-R directions, respectively. This result was supported by the pooled data shown in Fig. 2C. The averaged preferred directions of the homonymous, synergist, antagonist, ECR, and FCR muscles and the direction of the evoked movements were 250.5 ± 20.5°, 189.1 ± 25.9°, 308.1 ± 17.7°, 41.9 ± 18.7°, 156.0 ± 18.6°, and 234.2 ± 14.1°, respectively. There was no significant difference between the direction of the evoked movements and the preferred direction of the homonymous muscle (\( P = 0.353 \), paired \( t \)-test). The differences between the direction of the evoked movements and the preferred directions of the homonymous, synergist, antagonist, ECR, and FCR muscles were −11.5 ± 5.9°, 52.7 ± 26.4°, −79.7 ± 25.9°, 191.8 ± 25.8°, and 78.4 ± 27.1°, respectively.

The stimulus-triggered average of the rectified EMGs was calculated while the participants were resting in the center target, moving toward the FU target (225°), and holding the FU target under continuous stimulation (Fig. 2D). The two main components of the muscle responses were observed in the homonymous (FCU) muscle with the first peak with an onset of 8 ms and the second peak with an onset of ~20 ms. We identified the first component as the M wave, which was induced by direct activation of motor axons, and the second component as the H reflex, which was induced by monosynaptic Ia afferent fibers (Hugon 1973; Marchand-Pauvert et al. 2000). Clear M and H responses could only be observed in the homonymous muscle in all phases, whereas no obvious response was observed in the other muscles. The H response was modulated depending on the task phase due to the excitability of the motoneuron pool (Fig. 2D, top). These responses led towitches in the homonymous muscle and boosted the ongoing voluntary movement in the F-U direction (positions X and Y in Fig. 2D, bottom).

**ARC from Muscle to Peripheral Nerve**

To establish an ARC that boosts an ongoing wrist movement, a homonymous (Fig. 3Aa) or synergist muscle (Fig. 3Ba) was chosen as the input muscle to the ARC. Because the surface EMG signal contains contributions from a greater number of MUs (Hu et al. 2013), the template matching method was employed to discriminate the specific waveform of a putative MU in real time. We set the criteria for selecting a putative MU with a relatively high peak-to-peak amplitude by visual inspection. The average firing frequencies of the input putative MU of the homonymous and synergist muscles were 0.7 ± 0.6 and 0.9 ± 0.7 Hz for the center target and 17.6 ± 8.6 and 16.7 ± 8.7 Hz for the peripheral target, respectively. The minimum time between spikes of MUs was within 10 ms for both homonymous (Fig. 3Ab) and synergist muscles (Fig. 3Bb), which seemed too fast for the firing rate of a single MU. The detected MUs contained a few different waveforms (insets in Fig. 3, Ab and Bb). Thus waveforms of the detected MUs contained multiple MUs, rather than a single MU. In this situation, the stimulus artifacts did not contaminate the detected waveforms of a putative MU, as shown in the insets of Fig. 3, Ab and Bb, in Fig. 3, Ad and Bd, and in the peristimulus time histograms (PSTH) of the MU in Fig. 3, Ac and Be, suggesting that the risk of a positive reverberating loop caused by the stimulus artifacts could be eliminated.

Since a moving average of a 250-ms window of the input MU firing rate was used to control stimulation frequency, the temporal relationship between the input MU firing rate and stimulation varied depending on its firing rate. A high probability of stimulus occurred at around 200–300 ms after input MU firing (Fig. 3, Ac and Bc).

For the ARC with the homonymous muscle, a high probability of the putative MU firing was observed around the latency of the...
H response (as shown in the PSTH in Fig. 3Ae). Therefore, some M and H responses might be detected as the putative MU.

**Behavioral Adaptation to an ARC**

Figure 4 illustrates a typical example of the position and velocity profiles of hand trajectories on a two-dimensional plane for 30 s in each epoch. In the baseline epoch, the hand trajectories hit the target with bell-shaped velocity profiles (trials 411–420 in Fig. 4, A and B). After 420 trials in the baseline epoch, the ARC with the homonymous muscle was applied suddenly without any instruction. The ARC boosted the ongoing wrist movement, as shown by the hand trajectories that overshot the target in the early ARC epoch (trials 421–424 in Fig. 4A). The velocity profiles also showed discrete peaks (trials 421–424 in Fig. 4B). The number of successful trials was reduced in the early ARC epoch (n = 4) compared with the baseline epoch (n = 10). However, as practice progressed with the ARC, the hand trajectories hit the target in the late ARC epoch and performance was significantly improved in this epoch (n = 10), up to the same level as in the baseline epoch (trials 831–840 in Fig. 4A). The velocity profiles were again concentrated into a single bell-shaped distribution (trials 831–840 in Fig. 4B). These findings indicate that the participants could learn to control the ARC. Conversely, when the ARC was terminated suddenly after 420 trials with the ARC, the hand undershot the target. Trial by trial, the participants...

Fig. 4. Adaptation process of the ARC with the homonymous muscle. Typical examples of position (A) and velocity profiles (B) on a 2D plane are shown for each 30-s period in the late phase of the baseline epoch, early and late phases of the ARC with the homonymous muscle epoch, and early and late phases of the washout epoch. The trial numbers and numbers of successful tasks during each 30-s period are shown in each epoch. Orange horizontal lines in the position profile indicate the target range, and gray vertical lines in the position and velocity profiles indicate the time the cursor entered the peripheral target. a.u., arbitrary units.
returned gradually to a kinematic pattern that was similar to that observed in the baseline epoch (trials 841–849 in Fig. 4, A and B). In the late washout epoch, performance was completely identical to that of the baseline epoch (trials 971–980 in Fig. 4, A and B).

Figure 5 shows a typical example of hand trajectories over the adaptation process. For both ARCs with the homonymous and synergist muscles, overshooting the target was observed commonly during the early ARC epoch. However, the hand trajectories hit the target during the late ARC epoch in both cases. Regardless of whether the ARC was applied or not, the hand trajectories were approximately straight for the ARC with the homonymous muscle (Fig. 5A). Conversely, for the ARC with the synergist muscle, the hand trajectory curved in the ARC epoch. This curved trajectory became prominent in the late phase of the ARC epoch and was sustained briefly during the washout epoch (Fig. 5B).

To quantify this adaptation process to the ARC across all participants, we measured the overshoot distance in each trial. The average overshoot distances across all participants are shown in Fig. 6, Aa and Ba. The overshoot distance under both conditions was approximately zero in the baseline epoch. It was at its largest in the first trial of the ARC epoch. However, the overshoot distance diminished gradually trial by trial in both conditions, which was evidenced by the clear learning curve of overshoot distance over the course of practice with the ARC. Repeated-measures ANOVA found that the reduction in the overshoot distance was reliable for both ARC patterns (P < 0.005 in each case), suggesting that the participants could adapt to the ARC in both conditions so that they could incorporate it into the volitional control of their wrist movements. Fitted curves were also plotted for each connection pattern. The parameters \( a \) and \( b \) were determined as follows: \( a = 5.82 \) and \( b = 0.0274 \) for the ARC with the homonymous muscle, and \( a = 6.70 \) and \( b = 0.0080 \) for the ARC with the synergist muscle. Thus the convergence point of the overshoot distance was longer for the ARC with the synergist muscle than for the ARC with the homonymous muscle, suggesting that adaptation to the ARC with the synergist muscle was more difficult than for the ARC with the homonymous muscle.

We also measured the maximum velocity distance for the distance from the center target and the point at peak velocity of the hand movement (Fig. 6, Ab and Bb). The maximum velocity distance was relatively stable throughout the baseline and ARC epochs, but it was lowest in the first trial of the washout epoch, which indicated that the cursor undershot the target just after disconnecting the ARC (see also the early phase of the washout epoch in Fig. 4B). However, it returned quickly to the values in the baseline epoch, suggesting that the participants readapted quickly to the absence of the ARC.

Since hand trajectory showed a curve for the ARC with the synergist muscle (see Fig. 4B), we quantified the curvature of hand trajectory as the deviation of hand trajectory at its peak relative to a line connecting the start and target positions (Fig. 6, Ac and Bc). We found that the deviation of hand trajectory increased significantly as the participants adapted to the ARC only in the case of the ARC with the synergist muscle. This increased deviation was still present in the first few trials of the washout epoch. The hand trajectory of the ARC with the homonymous muscle was a straight line.

**Neuronal Mechanism of Adaptation to an ARC**

To investigate further the underlying neuronal mechanism of motor adaptation to an ARC, we measured the firing rate of the putative MU and EMGs of each muscle during the hold phase (Fig. 7). The firing rate of the MUs was stable over the baseline epoch for both the ARC with the homonymous (Fig. 7Aa) and synergist muscles (Fig. 7Ab). The firing rate of the putative MU for the ARC with the homonymous muscle decreased significantly compared with that in the control experiment (gray plots) and continued to decrease over the course of the ARC epoch (Fig. 7Aa). During the washout epoch, the firing rate returned to the same level as in the baseline epoch. Conversely, for the ARC with the synergist muscle, the firing rate of the putative MU increased gradually over the ARC epoch (Fig. 7Ab). In the last 80 trials of the ARC epoch, the firing rate of the putative MU was significantly higher than in the control epoch (P < 0.05). This tendency remained for 20 trials, even in the washout epoch. Thus the adaptation process was different.

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Fig. 5. Hand trajectory for a representative participant with the ARC from the homonymous and synergist muscles to the ulnar nerve. Typical examples of hand trajectories for the ARC with the homonymous (A) or synergist (B) muscle are shown for each 30-s period in the late baseline epoch, early and late phases of the ARC epoch, and early and late phases of the washout epoch. Orange squares show the target ranges. The trial numbers and numbers of successful tasks during each 30-s period are shown in each epoch.
between the ARC with the homonymous and synergist muscles, suggesting that input muscle-specific reorganization was induced by the ARC.

To investigate the descending motor commands to the motoneuron pools of each muscle, we analyzed the rectified EMGs of the homonymous, synergist, and antagonist muscles (Fig. 7, Ab–Ad and Bb–Bd). The activity of the homonymous muscle increased gradually (Fig. 7, Ab and Bb), whereas the synergist muscle decreased gradually (Fig. 7, Ac and Bc), in the baseline epoch. These changes plateaued after 300 trials. Thus we verified that the participants adapted sufficiently to the task in the baseline epoch, and then we turned on the ARC at trial 421 without any instruction. In the ARC epoch, since the artifacts of the electrical stimulation interfered with the evaluation of muscle activity, we set catch trials during the late ARC epoch. For the ARC with the homonymous muscle, the resultant EMGs of both homonymous (Fig. 7Ab; P < 0.01) and synergist muscles (Fig. 7Ac; P < 0.05) in the catch trials decreased significantly compared with those in the control trials. We could not find any aftereffect in the EMGs of any muscle in the washout epoch (Fig. 7, Ab–Ad). Conversely, for the ARC with the synergist muscle, the EMG of the synergist muscle increased (Fig. 7Bc, P < 0.01), whereas that of the homonymous muscle decreased (Fig. 7Bb, P < 0.005). This aftereffect was observed for the homonymous and synergist muscles, but not for the antagonist muscle (Fig. 7, Bb–Bd). During the washout epoch, the activity of the homonymous muscle decreased substantially over 40 trials compared with that in the control experiment (1st–10th: P < 0.00001; 11th–20th: P < 0.005; 21st–40th: P < 0.05) and returned to the same level as in the control experiment after 40 trials. The activity of the synergist muscle remained high until after 80 trials in the washout epoch (1st–40th: P < 0.005; 41st–80th: P < 0.05). These results suggested that the input-output relationship was recalibrated and reorganized in a sustainable manner through the ARC. EMGs of the FCR and ECR, which are antagonists of the homonymous muscle, were mostly silent throughout all epochs.
DISCUSSION

Our results showed the adaptation process to an ARC that was designed to detect the firing pattern of a putative MU and convert it to activity-contingent electrical stimulation delivered to a peripheral nerve. We found that the participants had adequate adaptability to consolidate a newly embedded ARC with their physiological pathways into volitional limb control by selectively recalibrating or reorganizing their neuromotor map.

Muscle-Controlled FES to a Peripheral Nerve

We demonstrated a novel closed-loop FES controlled by the firing rate of an MU, which was detected via the template matching method from surface EMG signals. In typical FES systems, the patient uses switches (Brandell 1982, Burridge et al. 1997) or muscle activity (Frigo et al. 2000; Muraoka 2002; O’Keeffe and Lyons 2002; Peckham et al. 2001; Popovic et al. 2001) to trigger preprogrammed patterned stimulation of paralyzed muscles to produce stereotyped movements. These produce an all-or-none triggering of FES and are not adaptable for making online adjustments. Conversely, our system resolved problems of uncontrollable behaviors induced by non-volitional, preprogrammed stimulation and demonstrated clearly that the subjects controlled the closed-loop FES.

The evoked movement was controlled by both the electrical current and frequency, which were proportional to the MU firing rate. The control of force output is accomplished by both

Fig. 7. Population data of firing rates of input motor units and muscle activity for the ARC with the homonymous (A) and synergist muscles (B). The data were averaged across all participants, and error bars represent ±SD. Each plot represents averaged muscle activity among each 10 trials. The averaged firing rates of input motor units (a) and muscle activity (b–d) in the control experiment in which the subjects performed the task without an ARC are shown as gray lines. *P < 0.05; **P < 0.01 (unpaired t-test).
the recruitment of MUs and their firing rate in a physiological situation (De Luca et al. 1973; Goldberg and Derfler 1977; Tanji and Kato 1973). It has been shown that MUs are controlled in unison, rather than individually, indicating that they receive a common drive (De Luca et al. 1982; De Luca and Erim 1994). The common drive received by all MUs in a pool is translated into individual firing patterns for each motoneuron by the input/output characteristics of the motoneuron (Erim et al. 1996). Therefore, modulating both the stimulus intensity and frequency may enable participants to control their movements more naturally and precisely. From these findings, we believe that modulating both current intensity and frequency is a physiologically appropriate way to activate the nervous system, and the firing rate of MUs is an appropriate signal for controlling an ARC. Since the activity of the motor cortex is consistently related to EMG signals over a wide range of motor tasks (Holdefer and Miller 2002; Jackson et al. 2007; Pohl Meyer et al. 2007; Shin et al. 2012), muscle activity contains rich information of cortical activity and thus can be used as a surrogate for cortical activity. Furthermore, the employment of a muscle offers the advantage of a robust signal-to-noise ratio. Therefore, the sources of control signals for closed brain-computer interfaces with wide clinical applications can be expanded substantially (Nishimura et al. 2013a).

Some of the evoked muscle responses, such as M or H responses, were detected as the input signals when the input muscle was the homonymous muscle (Fig. 3Ae), indicating a high risk of a positive feedback loop created by the ARC. However, the subjects could control the boosted wrist movement via the ARC (Figs. 4–6), suggesting that the risk of positive loop feedback by detecting H or M responses did not influence the controllability of the ARC to a significant degree.

Muscle-controlled FES to a peripheral nerve activates both efferent and afferent nerves. Ulnar nerve stimulation evoked M- and H-responses that led to twitches in the homonymous muscle and boosted the ongoing voluntary movement in the flexion-ulnar direction (Fig. 2D). The ulnar nerve contains various afferents that include muscle and cutaneous afferents. Thus FES to a peripheral nerve has the strong advantage that it not only boosts motor output but also boosts somatosensory sensation. If subjects can utilize the artificial sensation induced by an ARC, this protocol may be developed as a potential neuroprosthetic treatment toward the bidirectional restoration of motor and somatosensory functions.

Flexible Adaptation to an ARC

In this study, we have shown that the participants adapted to a newly given ARC to boost ulnar-innervated muscle activity, irrespective of the input muscles. The participants gradually learned to predict evoked output and recalibrate their descending commands to the homonymous muscle, as evidenced by a decrease in homonymous muscle activity during the catch trials (Fig. 7, Ab and Bb). These results were common with the input muscles (i.e., homonymous and synergist muscles), suggesting that the participants could utilize the ARC by recalibrating the descending motor commands to the ulnar-innervated homonymous muscle in a targeted manner. Furthermore, irrespective of the input muscle, hand trajectory undershot during the early phase of the washout epoch, indicating the participants reduced their total output (Fig. 4A). This could be achieved in an optimal way to minimize energetic cost, which can be explained by the computational framework of optimal control theory (Diedrichsen et al. 2010; Pedotti et al. 1978; Scott 2004).

We also found differences in adaptation strategy depending on the input muscle: 1) behavioral adaptation to the ARC with the synergist muscle required greater practice than for the ARC with the homonymous muscle (Fig. 6, Aa and Ba); 2) deviation of hand trajectories emerged only for the ARC with the synergist muscle (Figs. 5B and 6Bc); and 3) the activity of the synergist muscle decreased during adaptation to the ARC with the homonymous muscle, whereas it increased for the ARC with the synergist muscle (Fig. 7, Ab and Bb). These different consequences between input muscles might be plausible in light of each causal input-output relationship of the ARC. The preferred direction of the input homonymous muscle was almost the same as the direction of the output force evoked by ulnar nerve stimulation (Fig. 2, B and C). Thus, for the ARC with the homonymous muscle, recalibration of the gain from the input descending command to the evoked force output was required to maintain total force output. The results showed that the participants took a strategy to reduce the descending commands to both the homonymous and synergist muscles (Fig. 7, Aa–Ac) to compensate for the evoked movements created by the ARC. As for the ARC with the synergist muscle, the overshoot distance decreased during the ARC epoch (Fig. 6Ba), suggesting that the task performance improved over time. However, the increased curvatures in the trajectories to the flexion side after learning (Figs. 5B and 6Bc) indicate that the learning strategy for the ARC might not have been optimal. The preferred direction of the PL (synergist) muscle was different from the direction of the evoked movement by ulnar nerve stimulation (Fig. 2C). Considering this difference in direction, the learned strategy might have been that the participants firstly moved their hand toward the flexion side by volitionally activating the synergist muscle. Indeed, the activity of putative MU (Fig. 7Bc) and global activity (Fig. 7Bc) of the synergist muscle during the ARC epoch were substantially greater than those during the control experiment (gray lines in Fig. 7, Ba and Bc). This activity then triggered activation of the FCU (homonymous) muscle via the ARC, causing a pull toward the ulnar direction. As it turned out, volitional activation of the homonymous muscle was reduced (Fig. 7Bb) during the ARC epoch. This strategy appears to be suboptimal but might actually minimize the cost to perform the task.

However, it might be possible that coactivation of the muscles around the wrist joint increased joint impedance, which might have caused the deviated hand trajectory and increased the muscle activity of the synergist muscle. The present results indicated that the activation level of the antagonist muscles (see Fig. 7, Ad and Bd, and results) did not change across the session with the ARC (Fig. 7, Ad and Bd), suggesting that the effect of joint impedance would be low. However, the activity of the synergist muscle increased and the activity of muscles that were not recorded might also have increased. Since the number of recorded muscles was limited in the present study to prevent cross talk by contamination with the activity of neighboring muscles, the present results could not rule out this possibility. Further studies with exhaustive recordings including other small muscles might be needed to...
characterize the specificity of the muscle responses caused by the ARC in detail.

A reasonable hypothesis is that the adaptation process to the ARC may also involve modified processing in the motor-related cortical areas. Previous studies have shown that the motor areas in the frontal lobe play an important role in motor skill acquisition and online control of a novel motor skill, as evidenced by neural discharge patterns that adapt after training with novel forces (Gandolfi et al. 2000; Li et al. 2001; Padova-Schioppa et al. 2002, 2004; Sanes and Donoghue 2000; Xiao et al. 2006). It has been documented in biofeedback experiments in which animals were trained to modulate cell activity volitionally (Fetz and Finocchio 1975) that M1 cells and upper limb muscles that were coactivated normally could be dissociated readily. For M1 neurons, even those with relatively direct connections to spinal motoneurons, their synaptic efficacy at corticospinal connections can be changed dramatically (Davidson et al. 2007; Nishimura et al. 2013b), indicating that M1 neurons are not always effective at driving their target motoneurons. These observations may explain the flexible muscle activation patterns induced by the ARC. An alternative explanation is that the adaptation of forward models leads to corresponding changes in the neuromotor map (Kawato 1999; Shadmehr et al. 2010; Wolpert et al. 1998). The cerebellum may be involved in feedback corrections given that it is richly interconnected with M1 (Evarts and Thach 1969; Middleton and Strick 2001) and is involved in motor skill learning (Doya 1999; Miall et al. 1993; Miall and King 2008). In each case, further research is required to elucidate the contribution of higher order brain structures in the adaptation process to an ARC.

Plastic Change of the Neuromotor Map

The behavioral aftereffect returned rapidly to the baseline level within 10 trials (Fig. 6Bc), regardless of the input muscle to the ARC, although the reorganization of the activation pattern of muscles was maintained for more than 70 trials for the ARC with the synergist muscle (Fig. 7Bc). The reason for this discrepancy between behavior and muscle activation patterns remains unclear. It has been shown that plastic changes at both the spinal and supraspinal levels are necessary for the acquisition of a motor skill or functional recovery after neural damage (Liu et al. 2013; Wolpaw and Tennesen 2001), which are related to these changes in the synergistic muscle group (Cheung et al. 2012). Paradigms similar to those used in the current study, such as activity-dependent stimulation, also showed plastic changes in the neuromotor map (Jackson et al. 2006; Lucas and Fetz 2013) and modifications of the synaptic strength of corticospinal connections (Nishimura et al. 2013b). Similar mechanisms are thought to underlie use-dependent plasticity after learning and functional recovery. It has been shown, by the acquisition of a novel motor skill, that M1 can alter the somatotopic map (Kleim et al. 1998; Pascual-Leone 1995). Remarkable plastic changes in the neuromotor map of monkeys have been demonstrated by the functional recovery that follows surgical crossing of forelimb motor nerves (Brinkman et al. 1983) and spinal cord injury (Nishimura et al. 2007). Therapeutic open-loop FES has been documented to promote functional recovery after stroke (Popovic et al. 2004). Long-term exposure to an ARC could sustain the reorganization of cortical and spinal circuitry (Jackson et al. 2006; Lucas and Fetz 2013; Nishimura et al. 2013b) and facilitate functional recovery (Guggenmos et al. 2013). Since the reorganization of the neuromotor map observed in the present study lasted for only 80 trials, clinical application for a more prolonged effect would probably require the use of a chronic ARC with a portable (Muraoka 2002) or implantable bidirectional neural interface (Gan et al. 2012; Mavoori et al. 2005) during free behavior and lead to more permanent changes.

Clinical Application of ARCs

The ARC was required to modulate the firing patterns of MUs so that it could volitionally boost ongoing muscle activity. Considering the clinical application of ARCs, our target patients would be those with motor deficits who still retain residual descending pathways and some ability to modulate their muscle activity volitionally. However, following stroke, the ability to control limb movements volitionally is sometimes severely crippled and replaced by involuntary hypertonic grouped movement patterns (Dewald et al. 1995; Miller and Dewald 2012). In this case, it might be difficult to detect reliably the controllable MUs in the affected limb. Indeed, a previous study demonstrated the ineffectiveness of peripheral closed-loop FES in hypertonia (Chae and Hart 2003). Further improvements, such as the combination of a decoding technique using activity from multiple muscles (Ramos-Murguiaday et al. 2015) or cortically controlled FES (Ethier et al. 2012; Moritz et al. 2008; Nishimura et al. 2013a; Pohlmeyer et al. 2009; Zimmermann and Jackson 2014), might be needed for the clinical application of ARCs.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

K.K., S.S., and Y.N. conceived design of research; K.K., S.S., and Y.N. performed experiments; K.K. analyzed data; K.K., S.S., and Y.N. interpreted results of experiments; K.K. prepared figures; K.K. drafted manuscript; K.K., S.S., and Y.N. edited and revised manuscript; K.K., S.S., and Y.N. approved final version of manuscript.

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