Self-Support Biofeedback Training for Recovery From Motor Impairment After Stroke

FADY ALNAJJAR 1,2, KEN-ICHI OZAKI 3, MATTI ITKONEN 1, HIROSHI YAMASAKI 1, MASANORI TANIMOTO 3, IKUE UEDA 3, MASAKI KAMIYA 3, MAXIME TOURNIER 1, CHIKARA NAGAI 1, ALVARO COSTA GARCIA 1, KENSUKE OHNO 1,3, AIKO OSAWA 3,IZUMI KONDO 3, AND SHINGO SHIMODA 1, (Member, IEEE)

1Center of Brain Science (CBS), CBS-TOYOTA Collaboration Center (BTCC), Intelligent Behavior Control Unit, RIKEN, Nagoya 463-0003, Japan
2College of Information Technology, UAE University, Abu-Dhabi, United Arab Emirates
3National Center for Geriatrics and Gerontology, Obu 474-8511, Japan
Corresponding author: Shingo Shimoda (shingo.shimoda@riken.jp)
This work was supported by Toyota Motor Corporation, Aichi, Japan.

ABSTRACT Unilateral arm paralysis is a common symptom of stroke. In stroke patients, we observed that self-guided biomechanical support by the nonparetic arm unexpectedly triggered electromyographic activity with normal muscle synergies in the paretic arm. The muscle activities on the paretic arm became similar to the muscle activities on the nonparetic arm with self-supported exercises that were quantified by the similarity index (SI). Electromyogram (EMG) signals and functional near-infrared spectroscopy (fNIRS) of the patients (n=54) showed that self-supported exercise can have an immediate effect of improving the muscle activities by 40-80% according to SI quantification, and the muscle activities became much more similar to the muscle activities of the age-matched healthy subjects. Using this self-supported exercise, we investigated whether the recruitment of a patient’s contralesional nervous system could reactivate their ipsilesional neural circuits and stimulate functional recovery. We proposed biofeedback training with self-supported exercise where the muscle activities were visualized to encourage the appropriate neural pathways for activating the muscles of the paretic arm. We developed the biofeedback system and tested the recovery speed with the patients (n=27) for 2 months. The clinical tests showed that self-support-based biofeedback training improved SI approximately by 40%, Stroke Impairment Assessment Set (SIAS) by 35%, and Functional Independence Measure (FIM) by 20%.

INDEX TERMS Stroke rehabilitation, muscle synergy, brain imagining, biofeedback training.

I. INTRODUCTION
Stroke is the leading cause of long-term disability worldwide. Of more than 750,000 stroke victims in the United States each year [1], approximately two-thirds survive and require immediate rehabilitation to recover lost brain functions [2]. These stroke rehabilitation programs, of which direct and indirect costs were estimated to be 73.7 billion dollars in 2010 [3], aim to help survivors gain physical independence and better quality of life.

Stroke damage typically interrupts blood flow within one brain hemisphere, resulting in unilateral motor deficits, sensory deficits, or both. The preservation of long-term neural and synaptic plasticity is essential for the functional reorganization and recovery of neural pathways disrupted by stroke [4]–[6]. Stroke survivors typically require long-term, intensive rehabilitation training due to the length of time required for these recovery processes [7], [8]. The typical time course for partial recovery of arm movement after mild to moderate unilateral stroke damage is 2 to 6 months, depending on the severity of tissue damage and the latency of treatment initiation [9], [10]; however, patients with severe damage require additional months to years of rehabilitation. Given the economic burden on patients’ families and the medical system, novel rehabilitation methods that promote rapid and complete functional recovery are needed, along with a better understanding of the functional mechanisms and neural circuits that can participate in potential therapeutic processes. The identification of rehabilitation methods that can more effectively recover brain functions in the damaged...
hemisphere by re-engaging dormant motor functions should be a major global objective, from both economic and societal perspectives. Such an objective would require the interface of biology, medical research, and clinical practice [4].

Recently, candidate brain areas that become activated during stroke recovery have been identified in patients and animal models [7]. Brain imaging studies during stroke recovery suggest that the extent of functional motor recovery is associated with an increase in neuronal activity in the sensorimotor cortex of the ipsilesional hemisphere [10]–[12]. Other work has suggested that repetitive sensorimotor tasks may promote cortical reorganization and functional recovery in the ipsilesional area by increasing bilateral cortical activity to enhance neuroplasticity [13]. Activation in the contralesional hemisphere is also observed in the early stages of post-stroke patients. This activation has been explained by the emergence of communication in corticospinal projections that are silent in the healthy state [11], and it may also contribute to movement-related neural activity on the ipsilesional limb [14], [15]. Functional brain imaging studies show that activity of the contralesional hemisphere is increased early after stroke and gradually declines as recovery progresses [16]. The functional relevance of contralesional recruitment remains unclear [17], [18]. Some reported studies have linked high abnormal activity to a high inhibitory signaling drive onto the ipsilesional cortex [19], which may be a major contributor to motor impairment [6], [20]. Recent studies have also investigated the benefits of activating the contralesional and/or ipsilesional hemispheres in functional motor recovery using brain-computer interface (BCI) and transcranial magnetic stimulation (TMS) therapies [21], [22].

Current stroke rehabilitation approaches have largely focused on paretic limb rehabilitation interventions such as muscle strengthening and endurance training [23], forced-use therapy [24], constraint-induced exercise [25], robot therapy with biofeedback [26], nonparetic limb interventions (e.g., mirror-therapy [27], [28]), or bilateral/bimanual training [29], [30]. However, to date, none have clearly investigated how the use of a patient’s unaffected neural circuits in the healthy cortical hemisphere, or in the local peripheral circuit, affect the impaired limb in terms of functional rehabilitation of the bilateral cortical sensorimotor network [31].

In this study, we investigated a motor recovery approach for post-stroke unilateral arm impairment that combined sensory feedback, motor control, and motor intention. While observing a patient cohort with unilateral stroke damage and arm movement impairment, we found that a specific self-guided motion, which we termed self-supported exercise, surprisingly reactivated a healthy muscles pattern in the paretic arm. The key of the self-supported exercise is use of the nonparetic arm as a support to help move the paretic arm. First, we will show the observation of appropriate muscle recruitment and reduction of abnormal muscle synergies for post-stroke patients during the self-supported exercise, which are a common problem in stroke recovery [32]. Then, we conduct the experiments of functional imaging and electromyography recordings and characterized the neurobiology and physiology of this self-supported exercise. Based on this mechanism, we designed a rehabilitation program involving biofeedback-aided self-supported exercises that employ a patients’ self-initiated motor intention. The results of the comparative experiments between the feedback training cohorts and the control cohorts show that this method results in efficient recovery from post-stroke motion paralysis. Finally, we discuss the significance of our findings for the design of biologically-based stroke rehabilitation.

II. METHODS

A. STUDY AND TASK DESIGN

This study was conducted in two phases. The first phase includes testing the immediate effect of self-supported exercises on stroke survivors (n=54; Table 1) and comparing the resulting muscle patterns and sensorimotor brain activity during self-supported exercise with age-matched healthy volunteers (n=25; Table 2). The second phase examined the therapeutic effect of self-supported exercises combined with biofeedback training on a subgroup of the recruited patients from the first phase (n=27). The remaining 27 in the original 54 patients were not able to complete the study due to limited communication and severe cognitive impairment, or were unable to join for the required examination period and were therefore excluded from the second phase of the study (inclusion/exclusion criteria of the patients are in Figure 1). For the age-matched healthy volunteers’ recruitment, volunteers male/female older than 55 years old and with no history of motor impairment were recruited to participate in the study (Age-matched group, Table 2). Most of these healthy volunteers were the spouses of the recruited patients. All experimental sessions took place and were approved by the ethics committees of the National Center for Geriatrics and Gerontology, Aichi-ken, Japan, and the RIKEN Institute, Wako City, Japan. Informed consent was obtained from all participants.

In the second phase, the study was designed to test the therapeutic effect of the self-supported exercise combined with biofeedback training. The activation onset of two dominant muscles, were used to examine the accuracy of the desired arm movements, Figure 2. For this particular movement, we noticed that, the simultaneous rather than sequential activation onset of these two muscles indicated an abnormal muscle synergy [37]. We used this feature to develop a muscle-synergy-based biofeedback training protocol to relay brain-state information to the patient as a motivational supplement to our proposed self-supported exercise. The visual feedback consisted of a red ball on a computer screen. The size of the ball changed according to the utilized neural strategy as a way of rewarding or penalizing either normal or abnormal muscle synergies, respectively (Please refer to the flowchart in Figure 4). In addition to the visual feedback, we integrated positive and negative audio feedback to support this process.
### TABLE 1. Demographics of the participating stroke patients. The first phase included the general group (n=54). The second phase included from the general group the FB group (n=13) and the control group (n=14). Stroke Type (S.T.): Ischemia (I), Hemorrhage (H). Lesion/Side (L./S.): Cortical (C), Subcortical (Sc), Right (R), Left (L), Both side (B). Stroke Category: Severe (S), Moderate (M). To form the FB and Control groups, we used stratified sampling. We first divide the patients into severe and moderate paralysis groups. Then we randomly chose the patients into feedback and control groups. We have successfully created the fair two groups in the indices described in Fig. 3 by this method.

| ID | SEX/AGE | TIME SINCE STROKE (M) | S.T. | L./S. | LESION SIZE (CM²) | MOTOR BEFORE | MOTOR AFTER | STROKE CATEGORY |
|----|---------|-----------------------|------|-------|-------------------|--------------|-------------|-----------------|
| 1  | M/72    | 1.5                   | C/R  | 12.1  | 34                | 0            | 71          | 1A              | S               |
| 2  | M/79    | 1.5                   | Sc/R | 6.5   | 39                | 0            | 80          | 1A              | S               |
| 3  | F/64    | 1.5                   | Sc/R | 73.8  | 53                | 1B           | 86          | 3               | M               |
| 4  | M/63    | 1.5                   | Sc/R | 1.5   | 56                | 1            | 73          | 1A              | M               |
| 5  | M/51    | 1.5                   | Sc/L | 0.5   | 65                | 1            | 87          | 1B              | M               |
| 6  | M/55    | 2                     | Sc/R | 6.4   | 49                | 1            | 83          | 1A              | M               |
| 7  | M/49    | 1.5                   | Sc/R | 20    | 35                | 1B           | 83          | 3               | C               |
| 8  | M/75    | 1.5                   | Sc/L | 2.1   | 34                | 1            | 72          | 1              | S               |
| 9  | M/70    | 1.5                   | Sc/L | 91    | 69                | 3            | 81          | 2              | M               |
| 10 | F/76    | 1.5                   | Sc/L | 85.7  | 18                | 0            | 50          | 1B              | S               |
| 11 | M/45    | 1.5                   | Sc/R | 8.5   | 49                | 2            | 87          | 3              | M               |
| 12 | F/93    | 2                     | Sc/L | 0.3   | 26                | 1            | 35          | 1A              | S               |
| 13 | F/74    | 1.5                   | Sc/L | 2.2   | 20                | 0            | 77          | 2              | S               |
| MEAN | 66.4 | 1.58                  | ---  | 23.1  | 41.6              | 75.9         |             |                | S:7/M:6         |
| SD  | 13.7    | 0.19                  | ---  | 34.64 | 16.8              | 10.9         |             |                | ---             |
| 14 | M/88    | 1.5                   | C/R  | 89.8  | 17                | 0            | 20          | 0              | S               |
| 15 | F/78    | 2                     | Sc/L | 5.4   | 14                | 0            | 35          | 1              | S               |
| 16 | F/82    | 1.5                   | Sc/L | 0.5   | 82                | 3            | 86          | 4              | M               |
| 17 | F/82    | 1.5                   | Sc/L | 0.5   | 49                | 2            | 81          | 3              | M               |
| 18 | M/46    | 1.5                   | Sc/R | 62    | 23                | 1            | 35          | 1A             | S               |
| 19 | M/85    | 2                     | Sc/L | 3.1   | 31                | 1            | 41          | 3              | S               |
| 20 | M/90    | 1.5                   | Sc/R | 0.5   | 42                | 2            | 52          | 3              | S               |
| 21 | F/81    | 2                     | Sc/R | 0.5   | 62                | 1            | 80          | 2              | M               |
| 22 | M/80    | 2                     | Sc/L | 0.5   | 42                | 1            | 54          | 1B             | S               |
| 23 | F/76    | 1.5                   | Sc/R | 0.5   | 47                | 2            | 45          | 2              | M               |
| 24 | F/76    | 1.5                   | Sc/R | 8.4   | 14                | 1A           | 35          | 1A             | S               |
| 25 | M/52    | 1.5                   | Sc/R | 3.5   | 58                | 1A           | 87          | 1C             | M               |
| 26 | M/73    | 1.5                   | Sc/L | 0.5   | 50                | 2            | 87          | 2              | M               |
| 27 | F/66    | 1.5                   | Sc/L | 0.7   | 48                | 0            | 67          | 1              | M               |
| MEAN | 73.7 | 1.6                   | ---  | 12.5  | 41.5              | 57.5         |             |                | S:7/M:7         |
| SD  | 12.2    | 0.2                   | ---  | 27.4  | 19.6              | 23.4         |             |                | ---             |
| 28 | M/79    | 1.5                   | Sc/R | 0.5   | 67                | 3            | 3           | M               |
| 29 | F/86    | 1.5                   | Sc/R | 0.5   | 60                | 2            | 3           | M               |
| 30 | M/82    | 2                     | C/R  | 1.9   | 45                | 3            | 1           | M               |
| 31 | F/85/75 | 1.5                   | Sc/R | 5.0   | 73                | 4            | 3           | M               |
| 32 | M/80    | 1.5                   | C    | 2.4   | 36                | 2            | 2           | S               |
| 33 | M/63    | 1.5                   | Sc/L | <0.5  | 48                | 3            | 3           | M               |
| 34 | F/65    | 2                     | Sc/L | 0.5   | 44                | 3            | 2           | S               |
| 35 | F/69    | 1.5                   | Sc/L | 1.0   | 39                | 2            | 3           | S               |
| 36 | M/71    | 1.5                   | Sc/L | 2.9   | 44                | 3            | 3           | S               |
| 37 | F/95    | 1.5                   | ------| ------| 0.5               | 24           | 1B          | M               |
| 38 | F/85    | 1.5                   | Sc/L | 0.5   | --                | --           | --          | --              | S               |
| 39 | F/90    | 1.5                   | Sc/L | 43.1  | 43                | 1C           |            | M               |
| 40 | M/66    | 2                     | Sc/L | 0.5   | 51                | 1            | 1           | M               |
| 41 | F/58    | 1.5                   | Sc/L | 25.8  | 44                | 1            | 3           | S               |
| 42 | M/58    | 1.5                   | Sc/B | 0.6   | 77                | 2            | 2           | M               |
| 43 | M/74    | 1.5                   | Sc/B | 0.5   | 53                | 1            | 3           | M               |
| 44 | M/74    | 1.5                   | Sc/R | 1.13  | 43                | 0            | 2           | S               |
| 45 | M/63    | 1.5                   | Sc/B | 1.9   | 65                | 1            | 1C          | M               |
| 46 | M/69    | 2                     | ------| ------| 0.5               | --           | 4           | S               |
| 47 | F/72    | 1.5                   | Sc/L | <0.5  | 48                | 5            | 3           | M               |
| 48 | M/69    | 1.5                   | ------| ------| 0.5               | 55            | 3           | M               |
| 49 | F/79    | 1.5                   | Sc/L | <0.5  | 78                | 4            | 3           | M               |
| 50 | F/79    | 1.5                   | Sc/R | <0.5  | 42                | 2            | 3           | S               |
| 51 | M/78    | 2                     | Sc/L | <0.5  | 81                | 4            | 3           | M               |
| 52 | M/68    | 1.5                   | ------| ------| 0.5               | 73            | 3           | M               |
| 53 | M/71    | 1.5                   | Sc/R | <0.5  | 60                | 2            | 3           | M               |
| 54 | M/75    | 1.5                   | Sc/R | <0.5  | 57                | 2            | 3           | S               |
We invited patients at 6-8 weeks after stroke onset to participate in brain and muscle measurements during motor exercises. We measured the brain and muscle activity of patients who agreed to join the experiment one time (All stroke patients, 6-8 weeks after stroke onset, residing in the hospital ‘National Center for Geriatrics and Gerontology’, during the study period). Then, in the second phase, patients who agreed to participate in eight weeks of measurements were divided into two groups, feedback training and control cohorts, with respect to the FIM scores, age and damaged region volume, Figure 3.

| GROUP | N | SEX | AGE (YEARS) | DOMINANT ARM |
|-------|---|-----|-------------|---------------|
| AGE-MATCHED | 25 | Male (8) | Male (77.1±6) | Right |
| Female (17) | Female (65.7±12) | All (69.4±10.3) | |
| YOUNGER | 8 | Male (8) | 36.4±6.2 | Right |

**B. SURFACE ELECTROMYOGRAPHY (EMG)**

We used electromyography (EMG) to measure the activity of four major muscles for each of the four exercises. EMG data was acquired using wireless electrodes (BTS FREEEMG 300; BTS Bioengineering Corp., Milan, Italy). The electrodes were placed on the pectoralis-major muscles (PMM), biceps-brachii (BM), brachioradialis (BRM), and anterior deltoid (AD), on both the paretic and non-paretic arms, in accordance with the guidelines of the Surface Electromyography for the Non-Invasive Assessment of Muscles Project [38]. These muscles were selected experimentally to accommodate the nature of the selected motion, which mainly involve elbow motion and a little of shoulder motion. EMG signals were recorded at a sampling frequency of 1 kHz. For muscle synergy computations, the entire time-series EMG data was rectified and processed with a low-pass filter with a cutoff frequency of 32 Hz. EMGs were normalized by their maximum mean measured during the experiment [39].

**C. MUSCLE SYNERGIES, SYNERGY SIMILARITY INDEX, AND THE LATERALITY INDEX**

An analysis of muscle synergy was introduced to estimate the control signals of redundant musculoskeletal systems projecting muscle activity into lower-dimension space [40]. Several studies have shown that behavioral analysis based on muscle synergies can uncover hidden features that are unobservable by direct measurement of muscle activity [39]–[42]. In this study, muscle synergies were used to quantify the quality of the paretic arm motion compared to the nonparetic arm motion using a Similarity Index (SI). Muscle synergy is described as follows:

\[ M = WC, \]
\[ M \in \mathbb{R}^{m \times t}, W \in \mathbb{R}^{m \times n}, C \in \mathbb{R}^{n \times t}, \]

\[ M \] is the matrix representing \( m \) muscle activities for time \( t \). \( W \) is a vector to express the muscle synergy (muscle pattern) that can reduce the number of \( m \) signals into the number of \( n \) signals. \( C \) represents the \( n \)-dimensional signals for \( t \) to control the number of \( m \) muscles. \( W \) and \( C \) are estimated using non-negative matrix factorization (NMF) (more details about muscle synergies computation can be found in [39]).
We measured the same muscles on the paretic and non-paretic arms and computed the muscle synergies of the paretic and nonparetic arms independently. Here we assume $W_p$ describes the muscle synergy of the paretic arm and $W_i$ describes the muscle synergy of the nonparetic arm. To quantify the quality of the paretic arm motions, we compared $W_p$ and $W_i$ based on the fact that the right and left arm synergies are highly similar, while the synergies are different between individuals [39]. The similarity index $SI$, therefore, is computed by the following equation [39]:

$$SI = \frac{1}{n} \sum_{x=1}^{n} \left( r \left( W_p(x), W_i(x) \right) \right)$$  \hspace{1cm} (3)

From Eq. 3, SI has the range $[0, 1]$. A high SI value indicates that both synergies $W_p$ and $W_i$ are similar muscle synergies. In the healthy subjects, the paretic and nonparetic arms were replaced with the non-dominant and dominant arms, respectively.

D. BRAIN IMAGING: FUNCTIONAL NEAR-INFRARED SPECTROSCOPY (fNIRS)

Brain hemodynamic changes in stroke patients were monitored using a continuous wave fNIRS system (OMM-3000; Shimadzu Corp., Kyoto, Japan) consisting of three semiconductor laser diodes producing wavelengths of 780, 805, and 830 nm. Changes in oxyhemoglobin (oxy-Hb), deoxyhemoglobin, and total hemoglobin levels as a function of light absorbance and path length were calculated in 48 channels (we have used the NIRS standard cap, 8-source/8-detector, 24 channels each hemisphere). We used a fixed task cycle (resting-state, task-state, and resting-state) for each motion type (20s each), Table 2. Initially, each task cycle contained 10~12 trials, and each cycle was performed four times. The order of motion types was randomized to reduce possible processing artifacts. The final evaluation was determined by the load average of the four cycles.

We performed a multiple comparisons analysis of oxy-Hb change for the resting-state and task-state. The LABNIRS package (Shimadzu Corp., Kyoto, Japan) was used to filter and process the data. A common autoregressive (AR) model was used to prevent the temporal correlation caused by physiological noise in the NIRS time series. A Gaussian response function was applied to model the data (oxy-Hb = 4 s), and significance was set at p < 0.05.

With NIRS, we have investigated the contralateral and ipsilateral hemodynamic response of the primary sensorimotor cortex M1/S1, our region of interest (ROI), during the designed tasks. M1/S1 is located anterior and posterior to the central sulcus [43]–[45], figure 7a. The M1/S1 includes the primary motor cortex (MI) and the primary sensory cortex (SI). We confirmed experimentally increased activity in both ipsilateral and contralateral M1/S1 cortex during voluntary arms movements [46].

The Laterality Index (LI) is a measure to compare the neural activity of two ROIs between hemispheres [47]. LI can quantify left and right hemisphere contributions and connectivity depending on conditions [48]. LI values can be computed using the following formula:

$$LI = \frac{I - C}{I + C}$$  \hspace{1cm} (4)

where I and C represent the number of activated voxels (p < 0.05) in the ipsilesional and contralesional ROIs, respectively. LI values range from +1, indicating that all activation occurred in the ipsilesional hemisphere, to −1, indicating that all activation occurred in the contralesional hemisphere. 0 indicates that balanced activation occurred in both the ipsilesional and contralesional hemispheres. In this study, we focused only on the absolute value of LI, as we were interested to determine if there was a balance in both hemisphere activations, which should be natural when performing bimanual task (value distributed closer to 0) or if activation was imbalanced, which is unnormal when performing bimanual task.

E. BRAIN IMAGING: FUNCTIONAL MAGNETIC RESONANCE IMAGING (fMRI)

Partly separated from the above study with stroke patients, we have conducted an fMRI study on a total of 8 healthy adults to have more insight at brain activities during the self-supported exercise (details are in Table 2). All of the subjects were right-handed and neurologically normal. Each subject provided written informed consent in accordance with procedures approved by the RIKEN Brain Science Institute Ethics Committee and Functional MRI Safety and Ethics Committee in RIKEN. Data obtained from two additional subjects were excluded from the analysis due the termination of the experiment at the subject’s request.

Two sessions, a passive session and an active session, were included. During the passive session, 5-meter-long non-metallic cables were used to pull the participants arms inside the scanner (review experimental setup in Figure 5a). The cables were connected such that the participants could perform the elbow flexion task if the experimenter pulled the cables. This session was an equivalent to the externally supported motion conducted with the stroke patients. Thus, participants were instructed to relax and to not perform any active movement. Three tasks were performed in the scanner in one session: externally supported right hand motion (EaR), external-support left hand motion (EL), and externally supported bimanual motion exercise (ES). In the active session, participants were instructed to perform the elbow flexion task without the experimenter’s support. To instruct the participants’ task flow in the scanner, stimuli were displayed via a back projection screen located at the head of the scanner bore and viewed via a mirror to the participant (Avotec Inc., Stuart, FL, USA; 800 × 600: 60 Hz). In this session, participants were instructed to perform the following elbow flexion tasks: right hand motion (AR), left hand motion (AL), bimanual exercise (BI), self-supported exercise (SS), and self-touch (ST). In both the passive and active session, motions were
presented to the participants in a randomized order to avoid sequential repetition of the stimulus and to reduce possible processing/task-sequence-related artifacts. Each motion was presented three times to each participant and lasted for 20 seconds, followed by a 30-second rest. The experimenters monitored the participants online through a video camera while participants performed the tasks to be sure that all requested tasks were completed.

The functional imaging was conducted using an Agilent 4-Tesla whole-body MRI system (Agilent Inc., Santa Clara, CA, USA) with a circularly polarized quadrature birdcage radio-frequency coil as a transmitter and 16 array coils as receivers (Nova Medical Inc., Wilmington, MA, USA). A total of 36 axial slices (20.8 cm FOV, 64 × 64 matrix, 4 mm thickness, 0 mm gap) with 30° forward rotation from the AC-PC plane were acquired using a four-shot Echo Planar Imaging (EPI) pulse sequence (volume TR 4.68 s, TE 20 ms, flip angle 65.3°) for the three functional runs, each consisting of 228 volumes. After temporal sensitivity encoding TSENSE reconstruction (acceleration factor 4), the sampling frequency was quadruplicated and the effective volume TR became 1.17 s. Before functional runs, a whole-brain anatomical image (voxel size = 1 × 1 × 1 mm³) was acquired using a 3D MPRAGE pulse sequence.

For the first phase, the patients were subacute stroke survivors recruited 6 weeks after stroke onset (patients with severe stroke impairment, n=25; patients with moderate impairment, n=29), details are in Table 1. Motor impairment level was determined as severe or moderate based on clinical assessments of motor functional independence measure (FIM-motor) at admission (severe: FIM motor score < 45; moderate: FIM motor score 45 to 80) [33], [34]. More details on the patients’ demographics, including stroke type and stroke lesion size, can be reviewed in Table 1. The data collected from age-matched healthy volunteers (Table 2) performing similar tasks, however, were used as a healthy control cohort for the results of this stage.

At the first phase, we asked the patients to perform a point-to-point reaching task with a range of elbow flexion, using four types of motion (Figure 2; see also Movie 1): single paretic arm exercise, bimanual exercise, externally supported exercise, and self-supported exercise. Single paretic arm exercise required moving the paretic arm only. Bimanual exercise required motion using both the paretic and nonparetic arm. Externally supported exercise involved a motion of the paretic arm supported by a therapist. Self-supported exercise required support to the paretic arm using the nonparetic arm of the patient. Patients with severe impairment who could not move their paretic arm were asked to produce motor intention. Both paretic and nonparetic arm exercises were included to compare the brain and muscle activity patterns for the same participant. In this experimental stage, motion trials were performed in three randomized sets, with each set consisting of ten trials per motion (each trial duration was approximately 2 seconds). For this phase, the study was designed to test the immediate effects of the self-supported exercise on the muscle patterns and sensorimotor cortex activities of the stroke-affected side and compare these to the results of the bimanual and the externally supported exercises.

Of the 54 stroke survivors of the first phase, 27 patients could continue and completed the second phase (intervention period of 8 weeks). The patients were randomized to receive either the self-supported exercise combined with a biofeedback training (feedback cohort; n=13) or standardized therapeutic exercises combined with the self-supported exercise and no biofeedback training (control cohort; n=14). We ensured that our randomized separation procedure fairly distributed individuals across the two cohorts. Figure 3 shows the resulting baseline data of the clinical FIM-motor and FIM-cognitive scores, time after stroke, and the patients’ age and stroke lesion size. Clinical assessments of FIM-motor and Stroke Impairment Assessment Set (SIAS) [35], [36] to assess upper limb function were conducted before and after the intervention for both groups. SIAS contains a detailed assessment of motor impairment, including dystonia, distal and proximal muscle weakness, ataxia, sensory deficits, and higher cortical function. It correlates with other outcome scales (Fugl-Meyer Assessment) and indicates responsiveness to change, so that a three-point change in the scale is similar to a two-point increase in NIHs [36]. The feedback group engaged in the self-supported exercise with biofeedback training, including standardized therapeutic exercises (conducted 1.5 h/day, 5 days/week, for 8 weeks). The control group engaged in the self-supported exercise with standardized therapeutic exercises and no biofeedback training, conducted for the same amount of time.

All data processing was done by in-house software written in C/C++ with the exception of the motion correction [49]. The motion correction was done by AFNI’s 3dvolreg. After EPI image reconstruction, respiratory and
cardiac signals measured from the participant during the experiment were used to remove physiological fluctuations from the functional images by a retrospective estimation and correction method [50]. EPI data were then preprocessed for slice-timing and motion correction. Since our task required arm movements inside the scanner, participants were requested to wear a customized mouthpiece to limit their jaw movements. A 3D motion correction technique was used to detect and correct for small head movements [51]. The EPIs were spatially smoothed using a Gaussian kernel with a full width at half maximum of 10 mm. We applied a General Linear model (GLM) analysis to each ROI for each subject to extract the contrast-enhanced subject’s blood oxygen level-dependent (BOLD) signal and obtain beta map of voxels that were significantly correlated with the task, Figure 5b.

For each voxel in ROI, neuronal activation amplitude (percent signal change) was tested in M1+S1 ROI among multiple arm-motion task conditions for individual brain data. ROIs were selected based on the activation from the functional localizer experiment for the individual subjects. We used the false discovery rate (FDR) for selecting the thresholds (P < 0.05).

In addition to the activation amplitude of ROI, we also measured the lateralization index (LI) using the total number of activated voxels for each M1/S1, Eq.4., where C was contra-dominant, and I was ipsi-dominant. LI is +1/−1 for unilateral activation pattern, and values close to 0 reflect more bilateral activation patterns.

F. STATISTICAL ANALYSIS

For the first phase, we used two-tailed t-tests to examine differences in means across groups, exercises, or different time-points of recovery to test for differences between summary statistics. All data presented in the manuscript are represented as mean± standard error. We implemented non-parametric tests in the form of Wilcoxon signed-rank and rank-sum tests to determine significant outputs across participants. To control for multiple comparisons, as in Figure 6d and Figure 7c, we report the Bonferroni–Holm corrected p values [52].

To evaluate the training effect, we used FIM motor scores, as well as, the SIAS to focus on the recovery of motor function. We conducted a nonparametric bootstrap test [53] in which we mixed the FIM motor scores of the two cohorts to test for differences. The analytical results showed that both FIM motor and SIAS scores of the feedback training patient cohort were significantly improved after training. Statistical power analysis are in Table 3.

III. RESULTS

A. SELF-SUPPORT STIMULATES DORMANT MUSCLE ACTIVITY IN THE PARETIC ARM

To examine the immediate effect of self-supported exercise compared to other forms of motor rehabilitation, we recruited 54 patients with stroke (25 and 29 with severe and moderate stroke, respectively; see Table 1 for patient characteristics) for a motor study with concurrent electromyographic (EMG) muscle recordings. We measured EMG activity from the dominant muscles in stroke-paretic and nonparetic arms while the patients performed a point-to-point reaching exercise with a range of elbow flexions. Four types of reaching motions were studied: single paretic arm exercise, bimanual exercise, externally supported exercise, and self-supported exercise.
The statistical power between the cohorts showing significant differences in SI, LI and FIM motor analysis was above 0.8. The cohort sample size was large enough to statistically support Figures 1-3.

| Target                                           | Groups (Sample Size)                        | Effect size | Power | P value  |
|--------------------------------------------------|---------------------------------------------|-------------|-------|----------|
| SI in Bimanual exercise                          | Healthy vs. Severe (25)                     | 3.60        | 1.00  | $0.62 \times 10^{-5}$ |
| SI in Bimanual exercise                          | Healthy vs. Moderate (25)                   | 1.89        | 0.99  | $0.38 \times 10^{-3}$ |
| SI in Bimanual exercise                          | Severe vs. Moderate (29)                    | 1.38        | 0.99  | $0.73 \times 10^{-3}$ |
| SI between BI and SS                             | Severe vs. Severe (25)                      | 3.15        | 1.00  | $0.55 \times 10^{-4}$ |
| SI between BI and SS                             | Moderate vs. Moderate (29)                  | 1.64        | 0.99  | $0.22 \times 10^{2}$  |
| SI in Self-support                               | Healthy vs. Severe (25)                     | 1.44        | 0.99  | $0.13 \times 10^{-1}$ |
| LI in Bimanual exercise                          | Healthy vs. Severe (25)                     | 1.28        | 0.99  | $0.45 \times 10^{-3}$ |
| LI in Bimanual exercise                          | Healthy vs. Moderate (29)                   | 0.86        | 0.88  | $0.75 \times 10^{-2}$ |
| LI in Bimanual exercise                          | Severe vs. Moderate (29)                    | 0.96        | 0.92  | $0.83 \times 10^{-2}$ |
| LI between BI and SS                             | Severe vs. Severe (25)                      | 2.83        | 1.00  | $0.49 \times 10^{-4}$ |
| LI between BI and SS                             | Moderate vs. Moderate (29)                  | 1.12        | 0.99  | $0.75 \times 10^{-2}$ |
| FIM after training                               | Feedback vs. Control (13)                   | 1.14        | 0.81  | $0.22 \times 10^{-2}$ |
| SIAS after training                              | Feedback vs. Control (13)                   | 1.38        | 0.86  | $0.51 \times 10^{-2}$ |
| Difference of SI after training                  | Feedback vs. Control (13)                   | 2.38        | 0.94  | $0.32 \times 10^{-3}$ |
| LI after training                                | Feedback vs. Control (13)                   | 1.84        | 0.91  | $0.40 \times 10^{-2}$ |
| fMRI tests                                       | Self-support vs. Bimanual (8)               | 2.55        | 0.99  | $0.14 \times 10^{-1}$ |
| fMRI tests                                       | Self-support vs. Left hand (8)              | 4.38        | 0.99  | $0.25 \times 10^{-2}$ |
FIGURE 6. Self-supported exercise activates paretic arm musculature and enhances the recruitment of normal muscle patterns. a. EMG of biceps (BM) in the paretic (PA) and nonparetic arms (NPA) of a representative post-stroke patient with severe impairment. BM activity in the paretic arm was observed only during self-supported exercise. b. EMG of pectoralis-major (PMM) and BM in the PA and NPA for a patient with moderate impairment during the elbow flexion task. PMM activity in the paretic arm was found only during the self-supported exercise. The plot shows that muscle usage combinations were more natural, with fewer abnormal synergies during self-supported exercise than during other exercises. c. The estimated muscle synergies from a representative age-matched healthy subject (H1) and stroke patient (P4) while performing bimanual and self-supported exercises. Two synergy-vectors $W(1)$ and $W(2)$ were estimated from the EMG signal. The resulting muscle synergies from the dominant and non-dominant arms of H1 were almost identical in both motions (Similarity Index (SI) > 80%). In P4, self-support showed higher similarities of the estimated synergies between the paretic and nonparetic arms. d. Summary plot that illustrates the average SI across 25 age-matched healthy subjects and 54 patients with severe and moderate stroke while performing the bimanual motion or self-supported exercise. P values to show the significant differences in this graph are summarized in Table 3.

Patients with severe impairments that performed the self-supported exercise, but not other types of motions, showed marked BM activation in the paretic arm (PA) similar to that for the nonparetic arm (NPA), despite weaker muscle contractions on the affected side (Figure 6a, representative data of a patient with severe stroke). To exclude possible EMG electrode artifacts, we also placed insulating material between the patient’s hands to prevent electrical flow from the nonparetic arm to the paretic arm through direct skin contact; we observed that self-support driven muscle activity remained robust. These findings show that self-support is unique among physical therapies for EMG activation and effectively normalizes activity in the peripheral damaged side during arm motion.

Motor rehabilitation therapies are often associated with abnormal muscle synergies, which may introduce pain or limit smooth and efficient arm motions and result in a poor quality of recovery. We examined whether self-supported...
FIGURE 7. Self-supported exercise normalizes bilateral sensori-motor cortical activity in patients after stroke. a. Visualization of fNIRS and EMG data representing the brain activity of the patients with severe impairment during the elbow flexion task. Little to no activity was observed in bimanual and externally supported exercises in the damaged hemisphere, resulting in no muscle activity. During the self-supported exercise, the damaged hemisphere was activated to a similar level with the intact hemisphere. b. Visualization of fNIRS and EMG data representing the brain activity of patients with moderate impairment during the elbow flexion task. Changes in LI depending on the exercise demonstrate the features of brain activity in the different exercises. c. Summary plot that illustrates the average LI across 25 age-matched healthy subjects and 54 patients with severe and moderate stroke while performing the bimanual motion or the self-supported exercise. The results show that activity in both hemispheres were balanced during the self-supported exercise. P values to show the significant differences in this graph are summarized in Table 3. d. Normalized brain activity for 25 age-matched healthy subjects during bimanual and self-supported exercises. Brain activity was normalized to 100% during the self-supported exercise.

exercises enabled the development of normal muscle synergies for patients with moderate impairments. An analysis of the pattern of muscle recruitment in each patient revealed that self-supported exercises correlated with a reduction of abnormal muscle synergies. For example, one patient (P4) showed that self-support, but not other form of exercises,
triggered EMG activation of both the BM and PMM of the paretic arm. The pattern of activity in these two muscles was similar to that of the nonparetic arm, Figure 6b. From the Figure (see also Movie 1), patient with moderate impairment shows that the weak movement of the paretic arm during the bimanual motion was associated with concurrent activation of the BM but not the PMM in the paretic arm. Activation of the PMM was required to stabilize the shoulder joint in the flexion task to ensure smooth movement; this has been observed from data of the nonparetic arm [54].

When performing simple motions, healthy subjects showed similar muscle patterns, termed muscle synergies and defined in Eq.1, for controlling the dominant and non-dominant arms (Figure 6c). [39], [41] Therefore, we used the similarity between muscle synergies, the SI (Eq.3), between the paretic and nonparetic arm to quantify the changes of muscle activities by self-supported exercise. Figure 6e illustrates muscle synergies of P4 while performing the bimanual (BI) and self-supported (SS) exercises. The SI shows a similarity change from 46% to 80% when the motion was changed from bimanual to self-support. This result indicates that at the time of self-support the nonparetic arm not only passively controlled the motion of the paretic arm but, interestingly, pushed it to recruit similar muscle patterns. Figure 6d shows that all 54 recruited patients with stroke who had severe or moderate impairment presented a notable immediate effect in their paretic arm muscle activity after self-supported exercise (p < 0.01 after applying a Bonferroni–Holm correction [52]) and that the SI during self-support was closer to the healthy range estimated from the 25 age-matched healthy subjects performing the bimanual or self-supported exercises in a similar task.

B. SELF-SUPPORT ENHANCES CONTRA- AND IPSILESIONAL SENSORIMOTOR COMMUNICATION

We investigated the brain neural circuit mechanisms of the self-support effect with functional near-infrared spectroscopy (fNIRS) in all the 54 patients. The patients performed self-supported, externally supported, and bimanual exercises while sensorimotor cortical activity was measured by fNIRS to identify patterns that may correlate with exercise-dependent recovery. Patients with severe impairment performing bimanual and externally supported exercises had weak ipsilesional sensorimotor cortex activity compared with the contralesional sensorimotor cortex (Figure 7a). In contrast, in patients with severe impairment performing the self-supported exercise, ipsilesional sensorimotor cortex activity was increased to a relatively similar level to the contralesional sensorimotor cortex activity. In patients with moderate impairments, sensorimotor cortex activity with the self-supported exercise also showed a similarity in activation profiles between ipsilesional and contralesional hemispheres compared to bimanual and externally supported exercises, Figure 7b.

In the imaging study, the ROI focused on activity in the sensorimotor cortex (Figure 7a). An LI between ipsilesional and contralesional hemispheres was computed based on the ROIs (Eq.4), Figure 7c. In patients with severe/moderate impairment, the LI for bimanual exercise was relatively large, indicating an imbalance of brain activity on the affected side compared to the unaffected side. On the other hand, the LI during the self-supported exercise was closer to 0, demonstrating that both hemispheres were equally activated. For the age-matched healthy subjects, both bimanual and self-supported exercises showed LI values closer to 0, suggesting that both hemispheres should be equally activated in healthy case.

Together, these results show that the LI of patients performing self-supported exercises were within the same range of that of age-matched healthy subjects’ movements regardless of the degree of impairment, Figure 7c. This indicates that self-supported exercise may able to activate dormant cortical neural circuits for self-repair, as measured by the concordant increased EMG signals and appropriate muscle synergies in the paretic arm.

C. SELF-SUPPORT-COUPLED BIOFEEDBACK FACILITATES STROKE REHABILITATION THERAPY

Based on the above observation, we believe that the combination of self-supported exercise with customized stroke rehabilitation therapies has the potential to accelerate functional motor recovery by enhancing activity in the M1/S1 network, inducing muscle activity in the paretic arm. We hypothesized that the concurrent activation of self-support-driven neural circuits coupled with top-down engagement of motor intention signals from higher executive areas could restore the function of sensorimotor pathways and lead to functional motor recovery, as defined by the patient’s ability to move the paretic arm solely by motor intention [55]. For this self-support-based rehabilitation method, we constructed a biofeedback system to relay real-time muscle-synergy-state information to the patient, who in turn could generate top-down motor intention signals in conjunction with ongoing self-supported exercises and create a closed-loop self-motivation-driven rehabilitation system. The visual sensory feedback in the closed loop consisted of a red ball on a computer monitor that changed its size in accordance with muscle-synergy state activity during the self-supported arm exercises (Movie 3). Instead of using a single muscle biofeedback system, we used a muscle synergy feedback system since muscle synergy can be used to evaluate the improvement in muscle activity by self-supported exercise, as represented in Figure 6d.

The biofeedback training system was tested by 13 stroke patients (see Figure 1 for the detailed process of patient recruitment). It was incorporated it into their daily rehabilitation program, and we measured changes in EMG patterns and fNIRS brain imaging. Figure 8a illustrates the SI time history of patient 1 (P1) with biofeedback training. Before the training program, P1 could not move his arm at all (SIAS=0,
F. Alnajjar et al.: Self-Support Biofeedback Training for Recovery From Motor Impairment After Stroke

FIGURE 8. Stroke patient rehabilitation of arm motion using biofeedback-based self-supported exercise.

a. Similarity index (SI) of a representative patient P1 performing biofeedback rehabilitation during 10 weeks after stroke onset (and extra 2 weeks follow-up after detached from the hospital). Arm motion recovery is represented by the increase in bimanual exercise. Clinical scores before/after, for these patients, show significant motor recovery, (SIAS shows also recovery from 0 to 1A). b. Oxy-Hb (t-values) for P1 before and after neurofeedback rehabilitation during the affected arm motion. Almost no brain activity and EMG signal were observed before the training program. These observations suggest that his motion intention did not reach M1. In the 2-month rehabilitation period, he recovered the ability to activate M1 by his own motion intention for arm motion, suggesting that neural pathways for motor intention and for muscle activation by self-support were functionally connected by concurrent activation in the biofeedback training program.

c. FIM motor scores after feedback training (mean and standard error for the feedback group). FIM motor scores in the feedback training cohort were significantly improved compared with the control cohort even though the baseline was the same in the two cohorts at admission. A P value was computed by a non-parametric bootstrapping test with blind analysis [56]. These results suggest that the proposed training can provide a significant improvement in functional recovery.

d. Improvement of SIAS scores after feedback training. SIAS score 1A, 1B and 1C were computed as 1.25, 1.5 and 1.75 respectively. This result implies that motion paralysis of feedback training cohort improved more than control cohort.

e. Difference of SI between SS and BI in the feedback training cohort and the control patient cohort. The difference of SI between SS and BI was significantly smaller than that of control cohort.

FIM motor=34), and almost no brain activity was observed on the ipsilesional side when the patient tried to move his arm (Figure 8b). After 8 weeks of rehabilitation, he recovered his arm movement (SIAS=1a, FIM motor=71), and M1/S1 in the ipsilesional hemisphere was activated even in relation to rehabilitated arm motions.
**FIGURE 8.** (Continued.) Stroke patient rehabilitation of arm motion using biofeedback-based self-supported exercise. **g.** FIM motor score vs. Similarity Index (SI). During bimanual exercise, there was a positive correlation between SI and FIM motor score. In contrast, during the self-supported exercise the SI was more flat than the FIM motor score (the p-value is 1.8 $10^{-2}$ in Self-Support and 5.4 $10^{-6}$ in Bimanual Exercise). These values imply that the linear regressions are significant. **h.** FIM motor score vs. Laterality Index (LI). During bimanual motion the LI values of patients with severe impairment were all negative; however, during the self-supported exercise they were increased, implying that the activity of the affected hemisphere was also increased. Some patients with moderate impairment showed the same tendency as the changes noted in the patients with severe impairment, where LI changed from negative values to values around 0. However, the majority of patients with moderate impairment who showed an increased hemispheric activation in ipsilesional sensorimotor cortex with larger positive values of LI than the healthy elderly during bimanual exercise instead showed a reduction in brain activity during self-supported exercise.

Figures 8c, d, e and f show the statistical analysis results of the changes of FIM, SIAS, SI and LI of the feedback training and the control cohorts after the 8-week training period. These results showed a significant difference in brain activities by LI, motion paralysis recovery indicated by SI and SIAS and functional recovery indicated by FIM.

**D. FUNCTIONAL BRAIN IMAGING REVEALS SELF-SUPPORT MECHANISMS IN HEALTHY SUBJECTS**

We investigated the neural circuit mechanisms underlying the self-supported exercise effect with an fMRI study in healthy subjects ($n=8$, Table 2). Although it would be ideal to study stroke patients by fMRI to examine the self-support effect, this experiment is not currently possible due to technical issues with patient communication and stability in the scanner during arm exercises, as well as considerations of clinical safety, comfort, and protocol in our study. In the study group of healthy young participants, the ROI was defined as the sensorimotor cortex M1/S1 (Figure 5b). We examined brain activation patterns for three physical dimensions of the self-supported exercise: the self-touch effect, the bimanual exercise effect, and the external-support effect, and evaluated the roles of these diverse sensory or motor inputs on the laterality index (LI) and sensorimotor M1/S1 cortex activities during the self-supported exercises to evaluate changes in brain activity, including possible alterations in interhemispheric communication.

The fMRI results in Figure 9a show that self-touch (ST) increased the blood oxygenation level dependent (BOLD) activity in S1 of the contra dominant hemisphere (here it could be equivalent to the ipsilesional hemisphere) although external (passive) touch did not activate the same area [56], [57]. The S1 activation resulted from an increase in interhemispheric S1-S1 communication [58]. Furthermore, we observed a significant increase of activity in the M1/S1 region when hand motions were synchronized both in active motion BI and externally- supported bimanual exercises ES. Similar to the self-touch findings, the increased brain activity during motion synchronization can also be attributed to interhemispheric M1-M1 communication [59], [60]. Overall, the higher sensorimotor cortical activity observed for the self-support effect appears to represent the summed activity of the two independent increases in activity of the M1/S1 region from self-touch and bimanual motion. Figure 7a also shows that self-support compared to other arm motions elicited higher BOLD activity in the contra dominant M1/S1 region, although the laterality index LI was still distributed around 0.

Figure 9b describes the LI during bimanual and self-supported exercise in the fMRI experiments. The results demonstrate that the activity balance between hemispheres was maintained in both exercises while BOLD activity during the self-supported exercise was significantly stronger than that during the bimanual exercise, suggesting concurrent stimulation of the M1/S1 sensorimotor region by two inputs (first, motion synchronization movements of both arms involving M1-M1 communication, and second, self-touch sensory feedback involving S1-S1 communication) resulted in a robust enhancement of BOLD activity in the M1/S1 region [61]. A healthy elderly cohort
FIGURE 9. Brain mechanisms of self-supported exercise involve the activity summation from two pathways. a. The BOLD activity of M1/S1 in the non-dominant hemisphere of a representative healthy participant while performing the task. Self-touch activated parts of M1 and S1 and self-support enhanced activity in both areas. Brain activity for the externally supported exercise was weaker than that for the self-supported exercise even though the supported side motion was the same. The bar graph represents normalized BOLD activity in M1/S1 across the eight participants. BOLD activity was normalized to 100% during the self-supported exercise. BOLD activity during the self-supported exercise was larger than for the self-touch and externally supported exercises, suggesting that the simultaneous activation of self-touch and bimanual motion increased brain activity in the ROIs. b. Laterality index (LI) during bimanual and self-supported exercise. There was no significant difference between the laterality indices during bimanual and self-supported exercise, although the activity level during the self-supported exercise was significantly higher than that during the bimanual exercise.

showed also similar changes in LI and activity level during both exercises in the fNIRS analysis described in Figure 7c.

Above results suggest that concurrent stimulation of the M1/S1 region in the damaged hemisphere of stroke patients by self-supported exercise correlates well with the observed increase in the EMG activity of motor units.

IV. DISCUSSION
This study describes a biological mechanism that can improve the efficiency of recovery time from stroke-based unilateral motor paralysis. Our main finding is based on the observation that self-supported arm movements triggered an unexpected and immediate upsurge of EMG muscle activity in the post-stroke paretic arm as described Figure 6. The muscle
FIGURE 10. Schematic model of functional neural pathways engaged in self-support-based arm movement rehabilitation. a. Existing neural pathways for arm movement control. b. Neural pathways activated during self-support biofeedback training. The neural pathways for the paretic arm muscles are activated by interhemispheric M1/S1 communication even though motion intention does not activate the pathway directly due to the stroke. We encourage the motion intention during the training by the visual feedback, resulting in the simultaneous activations of the neural pathways for the paretic arm control and the motion intention. c. Neural pathways activated during paretic-arm movement before and after training. The neural pathways for motion intention and paretic arm control are reconnected by the simultaneous activation of these pathways established by the self-support-based biofeedback training.
activities of the paretic arm were equivalent to the activities in the nonparetic arm during self-supported exercise. The brain pathways activated by self-supported exercises were characterized as a mid-level reflex loop responding to the synergistic inputs of self-touch sensory-feedback [56] and bilateral motion synchronization [29], [30]. The fMRI results during the self-supported exercise performed by healthy subjects in Figure 9 suggested the convergence of these synergistic inputs, due to enhanced activation of the neural pathways controlling arm motion, which appeared to be a summation of bilateral motion synchronization and self-touch.

Brain imaging results in Figures 7 and 9 demonstrated that the simultaneous stimulation of the M1/S1 sensorimotor cortex in the ipsilesional hemisphere involves putative interhemispheric M1-M1 communication with the contralateral hemisphere, through arm motion synchronization and self-touch involving S1-S1 communication. Moreover, together, these increase the M1/S1 activity in the ipsilesional hemisphere and correlate with an observed increase in EMG motor activity in the paretic arm. The increase in interhemispheric communication during self-supported exercise is suggested by an increase in M1/S1 activity, as measured by fMRI, during self-supported exercise compared with that during bimanual exercise in healthy subjects even though the activity balance of the regions was the same during both exercises. We speculate that an alteration of inhibitory signals may facilitate the activation of neural pathways, and that this may explain the immediate upsurge of muscle activity in the paretic arm [62]. The feedback training results described in Figure 8 showed that the brain activity changes by self-supported exercises encourage the recovery of motor paralysis and improve the motor functions.

Based on these findings, we propose a schematic working model for the brain pathways activated by a self-supported exercise after unilateral stroke damage (Figure 10). The self-support effect is driven by the combined effect of two neural pathways. The first pathway is initiated by self-touch of the paretic arm by the nonparetic arm that triggers a local sensory feedback signal, which activates S1-S1 communication for the return of putative inhibitory signals to ipsilesional S1. We propose that this pathway may assist in the reconnection of sensory feedback with motor output centers, closing the impaired sensorimotor loop for motor control of the paretic arm via peripheral stimulation and aided by concurrent sensory feedback from the paretic arm to the nonparetic arm. The second pathway is activated by bimanual arm motion that increases M1-M1 communication to train appropriate patterns of muscle recruitment. The simultaneous activation of these two pathways by self-supported exercises distinguishes the proposed rehabilitation training from conventional bimanual training. The synchrony may also help to coordinate motor intention signals between the two hemispheres, resulting in the restoration of motor intention pathways to the paretic arm. Based on our brain imaging results, the two pathways appear to enhance ipsilesional M1/S1 activity. We hypothesize that the enhanced activity via synaptic plasticity gradually restores M1 muscle control signals to elicit appropriate muscle activity and synergistic recruitment patterns in the impaired limb, and that this may account for the normalization of EMG muscle activity that we observed during the self-supported exercise.

In our feedback system, closed-loop biofeedback from visual input was implemented to overcome the motivational difficulties of patients as they attempted to initiate top-down motor intention while self-supported exercise concurrently activated local sensorimotor control circuits. The combined activation of motor intention and self-support in convergent neural pathways may enable the concurrent engagement of repair circuits responsive to this dual activation. The brain activity of patients after biofeedback rehabilitation suggests that motor intention may be weakly connected to selective neural pathways to activate the muscles in the paretic arm and highlights the synergy of intention with self-supported exercise.

V. CONCLUSION

In this paper, we proposed a biofeedback training system for post-stroke patients based on the observation that self-supported arm movements triggered an unexpected and immediate upsurge of EMG muscle activity in the paretic arm. The proposed system enhances reconnection of the neural pathways by concurrent Hebbian-type. Our results showed that self-supported exercise significantly improved the speed, extent, and accuracy of stroke recovery, suggesting promising utility in stroke therapy for damaged neural pathways when guided by appropriate contralateral circuits.

Brain imaging by fNIRS and fMRI shows that the combination of self-touch and motion synchronization encourage S1-S1 and M1-M1 communications and the local control loop for activating the muscle activities was eventually stimulated by the self-supported exercises. The key to effective self-support therapy is the simultaneous activation of local neural circuits for target muscle stimulation and top-down sensorimotor intention pathways.

Furthermore, the self-support paradigm has the potential to be generalized beyond arm movement to other stroke-affected areas. For example, in gait rehabilitation of impaired lower limbs, the restoration of local neural circuits in the impaired leg with self-supported supervision from the healthy leg may be an effective approach to restore primitive walking patterns. Traditional treatments by well-trained therapists [63], [64] that stimulate sensory receptors such as muscle spindles could share the same recovery mechanism as self-support training, because such therapies tend to increase the activation levels of local neural pathways. A detailed analysis of mirror movements after stroke [65] suggests that the activation of subcortical circuits must be compatible with the mid-level reflex loop during self-supported exercise, as an important common factor for recovery after stroke. Further investigation is required to find suitable self-support combinations for recovery from various types of motion paralysis.
F. Alnajjar et al.: Self-Support Biofeedback Training for Recovery From Motor Impairment After Stroke

[33] J. Ancheta, M. Husband, D. Law, and M. Reding, “Initial functional independence measure score and interval post stroke help assess outcome, length of hospitalization, and quality of care,” *Neurorehabilitation Neural Repair*, vol. 14, no. 2, pp. 127–134, Jun. 2000, doi: 10.1177/1549683001402005.

[34] K. S. Hayward, S. S. Keys, R. N. Barker, and S. G. Brauer, “Clinically important improvements in motor function are achievable during inpatient rehabilitation by stroke patients with severe motor disability: A prospective observational study,” *NeuroRehabilitation*, vol. 34, no. 4, pp. 773–779, Jun. 2014, doi: 10.3233/NRE-141076.

[35] N. Chino, S. Sonoda, K. Domem, E. Saitoh, and A. Kimura, “Stroke impairment assessment set (SIAS),” in *Functional Evaluation of Stroke Patients*, N. Chino and J. L. Melvin, Eds. Tokyo, Japan: Springer-Verlag, 1996, pp. 19–31.

[36] M. Liu, N. Chino, T. Fujii, Y. Masakado, K. Hase, and A. Kimura, “Psychometric properties of the stroke impairment assessment set (SIAS),” *Neurorehabilitation Neural Repair*, vol. 16, no. 4, pp. 339–351, Dec. 2002, doi: 10.1177/15496838002239279.

[37] F. S. Alnajjar, J. C. Moreno, K.-I. Ozaki, I. Kondo, and S. Shimoda, “Motor control system for adaptation of healthy individuals and recovery of post-stroke patients: A case study on muscle synergies,” *Neural Plasticity*, vol. 2019, Mar. 2019, Art. no. 8586416, doi: 10.1155/2019/8586416.

[38] R. Merletti and H. Hermens, “Introduction to the special issue on the SENIAM European concerted action,” *J. Electromyogr. Kinesiol.*, vol. 10, no. 5, pp. 283–286, Oct. 2000.

[39] F. Alnajjar, T. Wojtara, and S. Shimoda, “Muscle synergy space: Learning model to create an optimal muscle synergy,” *Front Comput Neurosci.*, vol. 7, pp. 136, Oct. 2013, doi: 10.3389/fncom.2013.00136.

[40] G. Torres-Oviedo and L. H. Ting, “Muscle synergies characterizing human postural responses,” *J. Neurophysiol.*, vol. 98, no. 4, pp. 2144–2156, Oct. 2007, doi: 10.1152/jn.00360.2006.

[41] F. Alnajjar, M. Itkonen, V. Berenz, M. Tournier, G. M. Perera, and X.-F. Huang, “Muscles within muscles: Coordination of 19 muscle segments within three shoulder muscles during isometric motor tasks,” *J. Electromyogr. Kinesiol.*, vol. 17, no. 1, pp. 57–73, Feb. 2007, doi: 10.1016/j.jelekin.2005.10.007.

[42] R. Pfurtscheller and A. Berghold, “Patterns of cortical activation during planning of voluntary movement,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 72, no. 3, pp. 250–258, Mar. 1989, doi: 10.1016/0013-4694(89)90250-2.

[43] R. Ackerley, E. Hassan, A. Curran, J. Wessberg, H. Olausson, and F. McGeown, “An fMRI study on cortical responses during active self-touch and passive touch,” *Frontiers Behav. Neurosci.*, vol. 6, p. 51, Aug. 2012, doi: 10.3389/fnbeh.2012.00051.

[44] S. Guest, J. M. Dessirier, A. Mehrabayan, F. McGeown, G. Essick, G. Gescheider, A. Fontana, R. Xiong, R. Ackerley, and K. Blot, “The development and validation of sensory and emotional scales of touch perception,” *Attention, Perception, Psychophys.*, vol. 73, no. 3, pp. 531–550, Feb. 2011, doi: 10.3754/154596830014000205.

[45] S. M. Brodie, A. Villamayor, M. R. Borich, and L. A. Boyd, “Exploring the specific time course of interhemispheric inhibition between the human primary sensory corticities,” *J. Neurophysiol.*, vol. 112, no. 6, pp. 1470–1476, Sep. 2014, doi: 10.1152/jn.00744.2014.

[46] Y. Aramaki, M. Honda, T. Okada, and N. Sadato, “Neural correlates of the spontaneous phase transition during bimanual coordination,” *Cerebral Cortex*, vol. 16, no. 9, pp. 1338–1348, Sep. 2006, doi: 10.1093/cercor/hbj075.

[47] K. McGregor, K. Heilman, J. Nocera, C. Patten, T. Manini, B. Crosson, and D. K. Stevenson, “Noninvasive functional imaging of human brain imagery related cortical activation,” *PLoS ONE*, vol. 7, no. 3, Mar. 2012, doi: 10.1371/journal.pone.0032324.

[48] M. S. Brodie, A. Villamayor, M. R. Borich, and L. A. Boyd, “Exploring the specific time course of interhemispheric inhibition between the human primary sensory corticities,” *J. Neurophysiol.*, vol. 112, no. 6, pp. 1470–1476, Sep. 2014, doi: 10.1152/jn.00744.2014.

[49] N. S. Ward, M. M. Brown, A. J. Thompson, and R. S. J. Frackowiak, “Neural correlates of outcome after stroke: A cross-sectional fMRI study,” *Brain*, vol. 126, no. 6, pp. 1430–1448, Jun. 2003, doi: 10.1093/brain/awg145.

[50] K. Kawahara, M. Shimodzozen, S. Etoh, K. Kamada, T. Noma, and N. Tanaka, “Effects of intensive repetition of a new facilitation technique on motor functional recovery of the hemiplegic upper limb and hand,” *Brain Injury*, vol. 24, no. 10, pp. 1202–1213, 2010, doi: 10.3109/02699052.2010.506855.

[51] H. Kagami, M. Itkonen, F. Shibata-Alnajjar, N. Hattori, M. Kinimoto, K. Takahashi, T. Fuji, H. Ootomne, I. Miyai, Q. An, N. Yang, H. Yamakawa, Y. Tamura, A. Yamashita, H. Asama, S. Shimoda, and H. Yamasaki, “Effect of physical therapy on muscle synergy structure during standing-up motion of hemiplegic patients,” *IEEE Robot. Autom. Lett.*, vol. 3, no. 3, pp. 2229–2236, Jul. 2018.

[52] N. Ejaz, J. Xu, M. Branscheidt, B. Hertler, H. Schambra, M. Widmer, A. V. Faria, M. Harran, J. C. Cortes, N. Kim, T. Kitago, P. A. Celnik, A. Luft, J. W. Krakauer, and J. Diedrichs, “Finger recruitment patterns during mirror movements suggest two systems for hand recovery after stroke,” *Biorxiv*, Jan. 2017, Art. no. 129510, doi: 10.1101/129510.

**Fady Alnajjar** received the M.Sc. degree in artificial intelligence and the Ph.D. degree in system design engineering from the University of Fukui, Japan, in 2007 and 2010, respectively. Since 2010, he has been a Research Scientist with the Brain Science Institute (BSI), RIKEN, Japan. He conducted neuro-robotics study to understand the underlying mechanisms for embodied cognition and mind. In 2012, he started an interest in exploring the neural mechanisms of motor learning, adaptation, and recovery after brain injury from the sensory- and muscle-synergies perspectives. His research target is to propose an advanced neuro-rehabilitation application for patients with brain injuries.
KEN-ICHI OZAKI is currently pursuing the M.D. degree with the Department of Rehabilitation Medicine, National Center for Geriatrics Gerontologyn.

MATTI ITKONEN received the M.S. degree in computer science from the University of Kuopio, in 1997. He has been a Technical Staff with the RIKEN Intelligent Behavior Control Unit, since 2014.

HIROSHI YAMASAKI graduated from the Department of Physical Therapy, College of Medical Technology, Hokkaido University, in 1997. He received the Ph.D. degree in computational intelligence and system sciences from the Tokyo Institute of Technology, in 2011. He has experience as a Lecturer with the Department of Physical Therapeutics, Showa University up to 2014. His research interests include computational human motion study, exploring optimality underlying coordination of multijoint movements, and its application to movement education and physical rehabilitation.

MASANORI TANIMOTO received the M.S. degree from Nagoya City University, in 2014. He is recognition Physiotherapist in the Department of Rehabilitation Medicine, National Center for Geriatrics Gerontologyn.

IKUE UEDA is currently an Occupational Therapist with the Department of Rehabilitation Medicine, National Center for Geriatrics Gerontologyn.

MASAKI KAMIYA received the M.S. degree from Fujita Health University, in 2013. He is recognition Occupational therapist in Department of Rehabilitation, National Center for Geriatrics Gerontologyn.

MAXIME TOURNIER received the M.S. degree in image, vision and robotics from the Institut National Polytechnique de Grenoble, in 2007, and the Ph.D. degree in computer graphics in 2011. He has been a Research Scientist with the RIKEN Intelligent Behavior Control Unit, since 2011.

CHIKARA NAGAI received the B.S., M.S., and Ph.D. degrees from Akita University, in 1999, 2001, and 2005, respectively. He has been a Research Scientist with the RIKEN Intelligent Behavior Control Unit, since 2013.

ALVARO COSTA GARCIA received the M.S. degree in telecommunications engineering from the Systems Engineering and Automation Department, Miguel Hernández University of Elche, Spain, in 2013, and the Ph.D. degree in the Program on Industrial and Telecommunications Technology from the Miguel Hernández University of Elche, in 2016. He is currently a Research Scientist with the Intelligent Behavior Control Unit, BSI, RIKEN. During the Ph.D., his research was focussed on lower limb rehabilitation methods and the study of cognitive mechanisms related to gait through the evaluation of electroencephalographic signals. Recently, he has started studying cortico-muscular coherences in order to develop more efficient neuro rehabilitation techniques.

KENSUKE OHNO received the B.S. degree from the TOYOTA Technological Institute, in 2012, and the M.S. degree in health science from Fujita Health University, in 2014. He has been a Visiting Technical Staff with the RIKEN Intelligent Behavior Control Unit, since 2014, and has also been a Technical Staff with the Kanagawa Institute, since 2019.

AIKO OSAWA is currently pursuing the M.D. degree with the Department of Rehabilitation Medicine, National Center for Geriatrics Gerontologyn.
IZUMI KONDO is currently a Physiatrist and is also working as the Vice-Director of Hospital, National Center for Geriatrics and Gerontology (NCGG) and he also manages the Department of Rehabilitation Medicine and the Center of Assistive Robotics, NCGG. He is developing a number of robots for the support of daily life of older adults.

SHINGO SHIMODA (Member, IEEE) received the B.S., M.S., and Ph.D. degrees in mechanical and electronic from the University of Tokyo, Tokyo, Japan, in 1999, 2001, and 2005, respectively. He spent as a Visiting Student at MIT, from 2003 to 2004. He was a Research Scientist with the Biomimetic Control Research Center, RIKEN, Japan, in 2005. In 2008, he became a Unit Leader at the RIKEN Brain Research Institute-TOYOTA Collaboration Center, Intelligent Behavior Control Collaboration Unit, Nagoya, Japan. He is also a principle Chair of Technical Committee on Cognitive Robotics in IEEE Robotics and Automation Society.