A novel brain-machine interface (BMI) system for motor rehabilitation in a severely impaired chronic stroke participant

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Abstract— People with upper-limb paralysis due to stroke have limited opportunities for rehabilitation. Most stroke survivors, however, still have intact corticospinal tract connectivity and can exhibit voluntary subthreshold muscle activations. Previous studies demonstrated that these people can regain a small but significant amount of recovery following non-invasive brain-machine interface (BMI) therapy that links brain activity patterns to the movement of the paretic limb in real-time [1], [2].

In this study, we sought to improve upon existing BMI therapies in four ways. First, we used an invasive intracortical multi-electrode array placed directly over areas of perilesional motor cortex with intact spinal cord projections, thereby improving the spatial and temporal resolution of the neural signals used for control. Second, we leveraged a seven degree-of-freedom rehabilitation robotic exoskeleton, increasing the complexity of movements that participants could practice. Third, we developed a novel hybrid brain-muscle decoding approach that leveraged a biomimetic model of how functional muscle activations drive movements, and used this to reinforce co-activation of brain and non-pathological muscle patterns [3]. Finally, we performed this rehabilitation over 45 months instead of the typical 6-8 weeks that most rehabilitation protocols use. Here we report methodological and preliminary clinical results from one severely-impaired chronic stroke participant.

***Clinical Relevance*—This is a proof-of-concept (N=1) of a new BMI methodology for rehabilitation.**

I. Introduction

Stroke is the leading cause of disability worldwide with a dramatic increase in the last decade. While there are many therapy options for people with mild-to-moderate upper limb impairment such as physical therapy, options for people with severe impairment are limited. Standard therapeutics typically leverage the first ~6 months following stroke (i.e. acute phase), which is associated with upregulation of neuroplastic mechanisms. Significant recovery following the acute phase (i.e. the "chronic phase") is thought to be limited. Thus, people who remain severely impaired past the acute phase have limited prospects for any recovery.

Recent studies have challenged the view that recovery in the chronic phase is not possible. High-intensity, high-quality therapy (30 hours/week) has demonstrated sustained improvements in arm impairment [4], though how long these benefits last is less clear [5]. Further, people who are chronically and severely impaired have demonstrated small but significant gains in through the use of non-invasive brain-machine interface (BMI) therapies that link brain activity patterns to the movement of a worn orthosis on the paretic limb in real-time [1], [2]. Finally, in many people with chronic and severe paralysis, while their movement is limited, can still voluntarily produce muscle activity [6]. Altogether, these findings led us to hypothesize that an intensive, long-duration, brain-machine interface therapy that leverages brain and residual muscle activations would be able to set a new benchmark for what type of recovery is possible in the severely-impaired, chronic stroke population. Here we present the methods and preliminary results from a proof-of-concept study of this kind (N=1).

II. Approach

A. Hybrid BMI clinical trial rationale

BMI robot therapies decode brain signals to move a wearable orthosis, thereby providing participants with feedback of their brain patterns through the sensation and vision of movement. Both factors, when then coupled with conventional physical therapy, are thought to contribute to improved outcomes possibly because participants learn to attempt movements in a more "movement-potent" state [1]. However, in typical non-invasive BMI therapies, only "move" versus "non-move" can be decoded out from brain signals, limiting the specificity of the feedback that can be given.

Here, we design a novel hybrid brain-muscle invasive BMI therapy. We hypothesize that by recording brain signals invasively, that our decoder can be more specific about not only "move" vs. "non-move", but which direction, speed, and which effectors of the arm should be moved. We can then provide this specific feedback to the participant through a 7 degree-of-freedom exoskeleton robot [7]. Lastly, instead of

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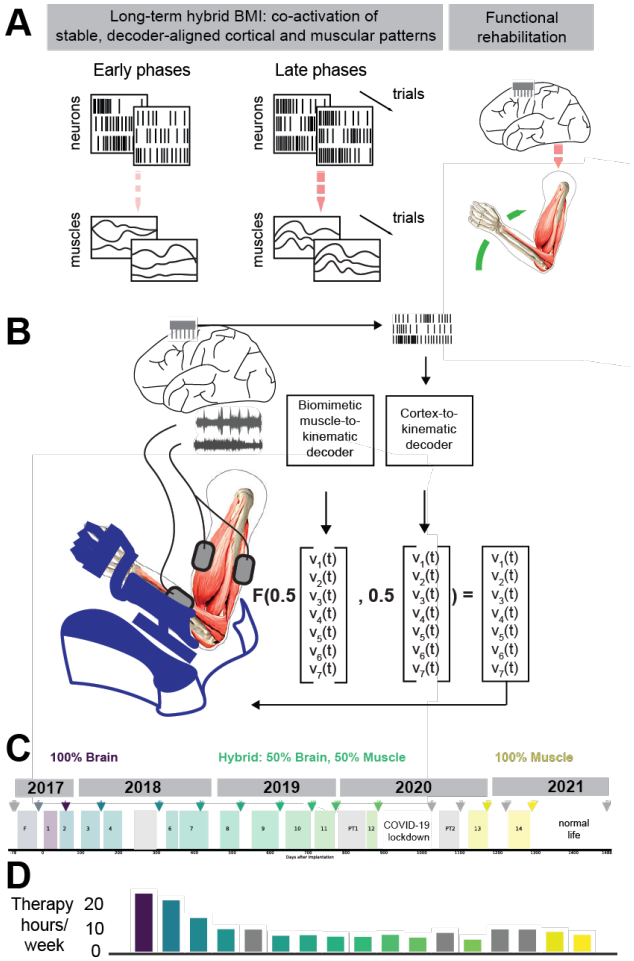

Figure 1. A) Rationale of long-duration hybrid BMI therapy, **B)** hybrid brain-muscle BMI decoder architecture **C)** Overview of invasive therapy including transition from brain-only decoding (purple), to hybrid brain and muscle decoding (blue/green), to muscle-only decoding (yellow). In some phases only neurophysical therapy was given (gray). **D)** Therapy intensity by phase.

just brain activity contributing to the decoded output of the BMI, we also leverage subthreshold muscle activations through multi-electrode surface electromyography (sEMG) recordings. sEMG activity is decoded using a biomimetic sEMG-to-kinematics decoder that has been trained from the participants' healthy arm [3], [7]. Together we term the brain decoder and sEMG decoders running in parallel as the "hybrid brain-muscle decoder". Brain and muscle contribute approximately equally to the decoded output (**Fig. 1B).**

We hypothesized that extensive practice with this novel hybrid BMI decoder along with neurophysical therapy will serve to 1) reinforce stable, movement-specific brain patterns in a part of the brain with intact spinal cord connectivity, 2) reinforce stable, albeit subthreshold, biomimetic muscle patterns, 3) reinforce cortico-muscular correlations resulting in potentiated cortico-muscular connectivity, and finally 4) result in rehabilitation of the participant's upper limb during movements outside the hybrid BMI setting (**Fig. 1A**).

B. Hybrid BMI clinical trial overview

This work was conducted as part of the ISMORE clinical trial approved by AEMPS (Spanish Agency of Medicine and Sanitary Products) registered online (link here). The trial recruits severely-impaired chronic stroke participants (>9 months post-stroke) with paralysis of one hand (no residual active finger extension) and a Medical Research Council score of < 2 for upper limb movement. Participants undergo a non-invasive familiarization phase of ~2 months in which they practice exoskeleton brain-control using EEG patterns. At the end of this phase, they then undergo an invasive microelectrode array brain implant localized to a section of perilesional motor cortex that still has intact connectivity to the spinal cord (measured through diffusion tensor images, DTI). Using this implant, the participants then control the exoskeleton using just brain activity (100% brain), then hybrid brain and muscle activity (hybrid: 50% brain, 50% muscle), and then just muscle activity (100% muscle) (**Fig. 1C**). Throughout all phases of the trial, participants receive exercise therapy based on central and spinal neurophysiological circuitry, mirror therapy, and biomechanical and soft tissue interventions. Here, we report the results from one participant who underwent the clinical trial from 2017 through 2021 (45-month duration).

III. Methodology

A. Hybrid BMI system architecture

Key components of the BMI system architecture include the 1) 7 degree-of-freedom robotic exoskeleton, 2) invasive microelectrode array and acquisition hardware, 3) sEMG recording electrodes and hardware, 4) BMI machine that aggregated data, was used to train decoders, and send commands to a visual feedback screen and the exoskeleton robot, 5) Decoding algorithms and approaches themselves. Below we review each of these components:

1) Exoskeleton robot

The robotic exoskeleton (Tecnalia, San Sebastian, Spain) was attached to the participant's paretic upper limb as schematized in **Fig. 1B**. The robot allowed the patient to perform planar arm movements (2 DOFs) and rotations (1 DOF), wrist pronation and supination (1DOF), and thumb, index, and middle/ring/pinky finger flexion and extension (3 DOFs).

2) Intracortical electrode array & acquisition hardware

A Blackrock Utah array (NeuroPort, 1.5mm electrode length, 4x4 mm size, 96 channels) was inserted into perilesional premotor cortex of the participant in the hand and arm area. The specific implantation site was determined through tractography performed on DTI, where the tract seeds were placed in the pons and traced up to cortex to identify sections of cortex with intact corticospinal tract connectivity. Once the implantation procedure was completed and following 3 days of recovery from surgery, the array was connected to the Neural Signal Processor system (Blackrock Microsystems), and signals were acquired at 30kHz and processed in the Cerebus software. Single and multi-unit action potentials were isolated by first bandpass filtering signals between 250-6kHz and either manually spike sorting or setting a threshold of -5 RMS. For the first year of the trial, units were identified via manual spike sorting at the start of each session. Following the first year, once recordings stabilized, an automatic threshold crossing approach was used for

expediency. Spike sorted or unsorted threshold data was streamed to the BMI computer over ethernet. In this paper we refer to single-units, multi-units, or threshold crossings generally as "neural units".

3) sEMG recording electrodes & acquisition hardware

At the start of each session, 14 pairs of surface Ag/AgCl bipolar electrodes (Norotrode 20, Myotronics) were placed on the following upper limb muscles: First dorsal interosseous, Abductor pollicis longus, Extensor carpi ulnaris, Extensor carpi radialis, Extensor digitorum, Flexor digitorum superficialis, Flexor carpi radialis, Pronator teres, Biceps, Triceps, Deltoid anterior, Deltoid medialis, Teres major, and Pectoralis major. Electrode positions were marked using permanent marker on the skin to reduce session-to-session drift in electrode placement. A ground electrode was placed on the clavicle. Data was acquired at 1000 Hz by a BrainAmp system (BrainVision) and streamed into the BMI computer over ethernet. EMG features were computed on the BMI computer and included mean absolute value, variance, waveform length, root mean square, and Willison amplitude.

4) BMI computer

Data from the intracortical array and sEMG sensors was aggregated on the BMI machine running a custom python interface. Data streams were acquired in parallel processes, pre-processed, ported to their respective decoders, and finally combined (if hybrid). Prior to sending the velocity commands to the exoskeleton, a previously-defined user-specific safety boundary was consulted to ensure that the exoskeleton would not move into a position or at a velocity that was uncomfortable for the participant. The exoskeleton velocities were updated at a rate of 20 Hz.

The BMI machine also ran the task logic for the exoskeleton training paradigm. The task was typically a target acquisition task in which the target consisted of a specific location/angle of all 7 DOFs, and a subset of DOFs were required to enter the target with certain tolerance to be considered a successful acquisition. As the participant grew more proficient and comfortable in the exoskeleton, target locations/angles were made further and further from the consistent "home" location.

The BMI machine also rendered a visual graphic of the target exoskeleton and the current position/orientation of the exoskeleton that the participant was controlling. This visualization updated in real-time, giving the participant clear feedback about which DOFs were in vs. out of the target.

5) Brain, muscle, and hybrid decoding algorithms

The brain decoder was a velocity Kalman filter decoder designed to predict exoskeleton position and velocity (hidden state) based on population spike counts binned in 100ms bins (observations). As in [8], both position and velocity were included in the hidden state to account for the influence of both on brain activity, but the participant directly controls velocity with measured neural signals. The decoder was trained and adapted using existing methods [9], [10]. Specifically, to train the decoder, once spike sorting or thresholding was completed at the beginning of each session, the participant was asked to attend to and actively try to generate appropriate muscle activity as the exoskeleton played through a series of pre-programmed movements involving all degrees of freedom. We refer to this type of block as "compliant movements". Once the decoder was trained, a block of closed-loop decoder adaptation with a linearly decreasing assist was run. Once control was acceptable (similar to previous sessions), the decoder was fixed for that session. In early phases (e.g. 2, 3, 4) decoder seeding and adaptation were run daily. In later sessions when neural unit recordings had stabilized, daily decoder re-seeding and adaptation were stopped. The same decoder was then used day-to-day.

The sEMG decoder was a linear regression model that predicted kinematic velocities to send to the exoskeleton every 50ms from sEMG features. Two different variants of the sEMG decoder were devised: 1) prediction of kinematic velocities directly from sEMG features, 2) prediction of kinematic state (e.g. open vs. close hand) that was then mapped onto kinematic velocities. Both decoders were trained from sEMG signals recorded from the participant's unaffected (left) arm while they were wearing a left-armed exoskeleton and performing blocks of "compliant movements". Notably, when the decoders were trained the sEMG features were z-scored. Thus, even though the participant could not generate the same levels of amplitude or modulation with their paretic limb as they could with their unaffected limb, the decoders would successfully predict kinematics if the relative activities of the muscles were correct (e.g. agonists activating, antagonists inhibiting). If the participant had developed muscle synergy patterns that were not typical of healthy muscle patterns (e.g. agonist antagonist co-activation), the robot would not move, encouraging the participant to try to generate more biomimetic muscle patterns. Generally, the first type of decoder (directly predict kinematics) performed well for kinematics of the upper arm DOFs (planar arm translation and rotation, pronation/supination) whereas the second type of decoder (predict states) performed better for kinematics of the hand DOFs (finger extension/flexion).

The hybrid decoder initially linearly combined predicted velocities from the brain and muscle decoders' outputs (equation 1). After sufficient practice though, it became apparent that the participant could just rely on one type of signal (brain or muscle) to advance the exoskeleton towards the target location. To encourage co-activation, a new multiplicative rule was introduced mid-way through the trial that required the brain and muscle signals to both be advancing towards the target for the exoskeleton to move (equation 2).

$$vel_{hybrid} = 0.5 * vel_{brain} + 0.5 * vel_{muscle} \quad (1)$$

$$\begin{aligned} &if\ sign(vel_{brain}) == sign(vel_{muscle}): \quad (2)\\ &\quad vel_{hybrid} = 0.5 * vel_{brain} + 0.5 * vel_{muscle}\\ &else:\\ &\quad vel_{hybrid} = 0 \end{aligned}$$

B. Adjuvant neurophysical therapy

Prior to and following hybrid BMI sessions, four trained physiotherapists and one osteopath provided customized, complementary therapy that targeted stretching the soft tissues and tendons, practicing active movements outside of

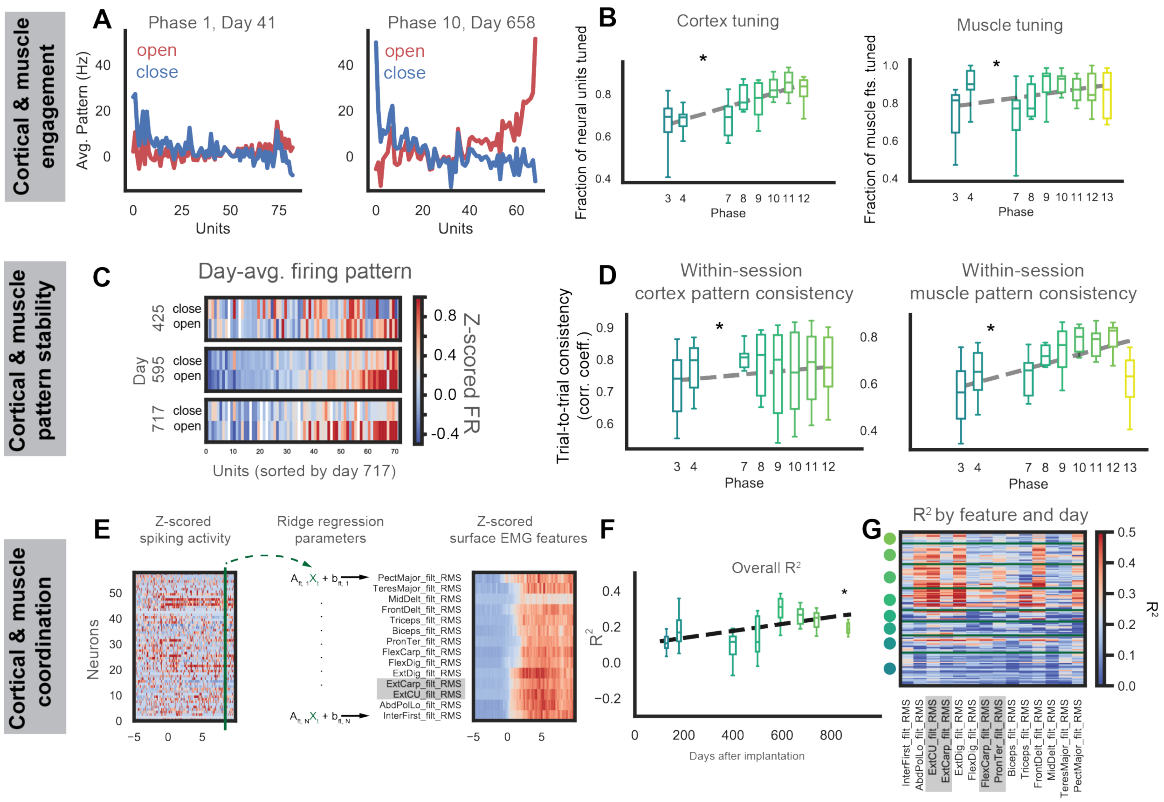

Figure 2. A) Average firing pattern for open (red) vs. close (blue) for units recorded on Day 41 (phase 1) vs. Day 658 (Phase 10). B) Fraction of units and muscle features that are have significantly different patterns for open vs. close significantly increases over hBMI training (t-test for significant slope: left: N=234 sessions, $p < 0.001$, right, N = 254, $p < 0.001$) C) Within-session average firing pattern for open vs. close for units recorded after change from manual spike sorting to threshold crossing. Same units recorded, same unit ordering. D) Within-session pattern consistency is measured by using a trial-average template to predict held-out trial patterns. The correlation coefficient of the prediction significantly increases over recovery for single-unit brain patterns and sEMG features (t-test for significant slope: left: N = 234 sessions, $p < 0.001$, right: N = 254, $p < 0.001$). E) Using ridge regression to quantify the predictability of sEMG features from brain single-unit activity. F) Predictability of sEMG features significantly increased over the hBMI trial (t-test for significant slope: N = 134, $p < 0.001$) G) Many muscle features become more predictable.

the exoskeleton, mirror therapy, and focusing on functional movements that could not be trained in the robotic exoskeleton. As previous studies have hypothesized that BMI therapies serve as a 'priming' of the sensorimotor system for improved learning and rehabilitation from physical therapy [1], it was important to our study to have high-quality, high-dosage, neuro-biomechanical therapy along with the BMI.

C. *Participant 1*

Participant #1 was a woman who suffered an ischemic stroke at the age of 55. The stroke affected cortico-subcortical structures in the left fronto-posterior and parietal areas resulting in severe hemiplegia of her right upper limb. She had a NIHSS score of 5, spasticity in her hand, and preserved somatosensation, as confirmed by a neurologist. After discharge from the stroke unit, the patient received a series of inpatient and outpatient rehabilitation therapies over the following 7 months, which ended with a stable severe upper limb paresis. At the time of enrollment in the clinical trial, the patient was 59 years old, had not received any rehabilitative treatment during the previous 39 months and remained chronically impaired (46 months since stroke). She presented an averaged baseline upper-limb modified Fugl-Meyer assessment (mFMA-UE) motor score of 9, MRC < 2 for upper limb movement, an ARAT score of 0, and a Wolf Motor Function Test (WMFT) score (excluding weigh to box and grip strength) score of 13.5. The participant presented no residual finger extension nor movement of the hand, almost zero elbow and shoulder flexion/extension ability and severe spasticity of the upper arm that impeded the use of the paretic upper limb and hand in functional unimanual or bimanual tasks.

D. *Data analysis*

Since the participant was very focused on improving hand opening and closing, there are many hBMI sessions dedicated to training that movement. In **Fig. 2,** neural units and muscle features were analyzed during hand-open and hand-close hBMI blocks.

Neural units were summed in bins of 100ms (same update rate as the brain decoder). Muscle features were calculated in bins of 50ms and were z-scored based on the mean and standard deviations computed from a block of the same compliant movements performed at the beginning of each session.

Neural units or sEMG features were averaged across the first 5 seconds of an open or close trial and were aggregated over all trials on a particular session. In **Fig. 2B,** units or features were considered "tuned" if they showed significantly (measured by $p < 0.05$ on a Mann-Whitney U test) different patterns between hand-open and hand-close. In **Fig. 2D**, neural units and sEMG trials were subsampled and averaged

to create an open and close trial-averaged template. The correlation between this template and held-out trials was computed. This process was repeated 50 times with different subselections of trials, and averaged to yield a single correlation coefficient value for each session. A similar approach was taken in **Fig. 2F** but instead of a template, a set of Ridge regression models were fit from population brain activity (z-scored, according to means/standard deviations derived from a compliant block) to predict individual sEMG features (**Fig. 2E**). Held out data was predicted with the Ridge models and variance explained (R^2) aggregated over sEMG features (**Fig. 2F)** and displayed for each sEMG feature (**Fig. 2G)** is shown.

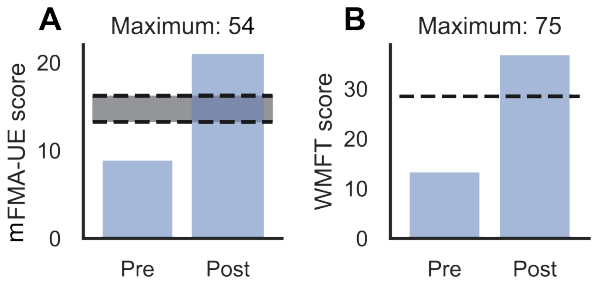

Figure 3. A) Changes in modified Fugl-Meyer Assessment for the Upper extremity (mFMA-UE) and B) Wolf motor function test (WMFT) gains from beginning to end of the hBMI trial. Dashed lines plot range or threshold indicating minimal clinically important difference.

IV. Results

A. Trial duration

The clinical trial was run in participant #1 for 45 months (July 2017 – March 2021). The initial months included a battery of clinical scales, neuroimaging, and a non-invasive BMI familiarization phase. After array implantation in Sept 2017, **Fig 1D** shows the average number of hours per week that the participant underwent therapy interventions. Though initially very intense with a peak of 25 hrs/week, the therapy plateaued to become more sustainable at ~8 hrs / week for most of the months. To our knowledge this is the **longest therapeutic intervention ever attempted in a stroke patient.**

B. Significant modulation of brain and muscle patterns with long-term hBMI therapy

Since the hBMI therapy required both brain and muscle patterns to modulate to enable the exoskeleton to reach targets, we first tested how the number of recorded neural units and muscle features changed in their modulation over the course of the trial. **Fig. 2A** shows an example of the average firing pattern for the population of neural units during open (red) vs. close (blue) trials early in the trial (left, Day 41, Phase 1) and late in the trial (right, Day 658, Phase 10). While the population consists of different units, more units show different firing during open vs. close later in the trial. We quantified this effect for brain units and muscle features (**Fig. 2B**) and found that over the course of the trial both brain and muscle activity become significantly more tuned.

C. Brain + muscle patterns stabilize with hBMI therapy

We hypothesized that long-term training with the hBMI system would result in relatively consistent brain and muscle patterns (**Fig. 1A**) since the hBMI gives the participant direct feedback about these signals. To assess this, we analyzed a subset of sessions in which the simple grasping movement "hand open" and "hand closed" that only involved the thumb, index, and middle/rink/pinky DOF were required to move to achieve the target. **Fig 2C** shows population pattern for "hand open" vs. "hand close" for the same population of neural units with the same sorting. Patterns on day 425 look different than those on 595, but stabilize by day 717. This observation is quantified by characterizing how well trial-average templates for hand-open and hand-close can predict held-out single-trials. Prediction accuracy significantly increases over the clinical trial (**Fig. 2D**), illustrating that long-term practice of the hBMI paradigm does help reinforce consistent brain and muscle patterns.

D. Brain-muscle correlations significantly increase with long-term hBMI therapy

We also hypothesized that long-term training with the hBMI would reinforce brain-muscle correlations that might result in potentiated cortico-muscular connectivity and rehabilitation. We quantified the predictability of sEMG features from the brain's population neural unit activity using a ridge regression model (**Fig. 2E**) to predict held-out trials of sEMG. The R^2 of the ridge models significantly increased over the hBMI trial (**Fig. 2F**). This increase was not just driven by a single sEMG muscle but occurred over many muscles (**Fig. 2G**).

E. Clinical improvement

Here we report the substantial increase in clinical outcome observed over the long-term hBMI trial. Pre-measurements were taken before the start of the clinical trial, and post-measurements were taken a few days after the end of the last phase of therapy. Follow-up measurements were taken 6 months after post-measurements. **Fig. 3A** shows changes in the modified Fugl Meyer-Upper Extremity (mFMA-UE: scores related to the coordination/speed and reflexes not included) impairment clinical scale. The participant shows a maximum gain of 15/54 points, and a 12-point stable increase at follow-up. **Fig. 3B** shows changes in the function-based tasks of the Wolf Motor Function Test (WMFT) [11]. We exclude the two strength-based tasks (weigh to box and grip strength measurements). This participant exhibited a maximum increase of 31/75 points in the WMFT scale, and a 24-point stable increase at follow-up. Both the FMA-UE and WMFT increases are well above the minimal clinically import difference [12], [13].

V. Discussion

Overall, we have demonstrated the first-ever invasive BMI therapy for stroke rehabilitation. Others have developed invasive BMIs for stroke patients for the purpose of designing assistive devices [14], [15], [16], but not for rehabilitation. We have also demonstrated, to the best of our knowledge, the longest-ever clinical trial totaling a duration of 45 months. Generally clinical trials run their interventions for a duration of 3-4 months at most, making this trial longer by more than an order of magnitude. Most notably, we have demonstrated

substantial recovery of a severely-impaired chronic stroke patient greater than that previously seen in prior BMI therapies [1], [2], [17], or any therapy including neuromuscular stimulation [18], robot therapy [19], or invasive neuromodulation [20], [21], [22]. These results show that substantial recovery still may be possible in the chronic phase, particularly if a person still has intact corticospinal tracts and voluntary subthreshold muscle activation patterns. We also note that this level of recovery has had substantial implications for this participant – she is now able to use her affected hand to help the unaffected hand in activities of daily living. Further, her regained movement now qualifies her for therapies that were previously inaccessible, including traditional physical therapy.

The overall hypothesis of this therapy was that jointly reinforcing co-activation of brain patterns in perilesional cortex and biomimetic muscle patterns over a long duration could trigger the potentiation of cortical-muscular connectivity. Of course, muscle patterns themselves originate from the coordinated activity of distributed cortical and subcortical motor control structures, so more accurately, the therapy was designed to reinforce supraspinal neural activity patterns that both produced biomimetic muscle activations and involved perilesional cortex areas that still had remaining projections down the corticospinal tract. Prior work emphasizes the role of perilesional premotor and supplementary motor cortex in recovery from brain injury [23], [24]. By using the hBMI to reinforce coordination amongst supraspinal networks controlling the musculature, we think stronger descending commands became possible resulting in better control of movement. Unfortunately, directly testing this using transcranial magnetic stimulation motor-evoked potentials is not practical as the participant still has parts of the intracortical array implanted.

The main limitation is that this is an N-of-1 study, and so the exact characteristics of people that may be able to recover to this extent are unknown. We are also unable to determine exactly how/to what extent each factor contributed to our participant's recovery given that they received the hBMI therapy, as well as a variety of adjuvant neurophysical therapies in parallel. Specifically, we cannot say whether the invasive implant or the high DOF exoskeleton was truly critical or if long-term training in a non-invasive regime with a simpler orthosis would have accomplished the same endpoints. We hypothesize, based on existing randomized-control BMI interventions [6], that exoskeleton feedback matching the intention to move was a key factor in the participants' experienced benefit. Future work will study the brain and muscle patterns from this intervention to see how broadly the brain-muscle interactions generalized to movements attempted outside of the exoskeleton.

Overall, we view this work as very promising in the broader landscape of post-stroke rehabilitation: we have demonstrated unprecedented recovery of a severely impaired chronic stroke patient using a novel brain-machine interface therapy over a long duration. Despite the participant's multi-modality and severity of symptoms (spasticity, muscular co-contractions, complete upper-limb paralysis), this clinical intervention was still effective. However, there are many therapeutics that are very effective for individual participants but fail to show success at a broader population level [25]. Indeed, reproducing this effort across the number of participants required to demonstrate statistical significance of the therapy and identify the components that specifically drove therapeutic improvement will be difficult. Instead, we propose using the outcome from this trial to support efforts in neurofeedback-based and/or myoelectric-based closed-loop therapeutics that can be employed by patients in the clinic or even in their own home so that they can continue their rehabilitation for long durations even in the chronic phase. For example, comfortable sEMG sensors designed for long-term wear could stream data to a soft, wearable orthosis [26] to enable myoelectric control. Minimally invasive brain implants could also be coupled to such a system enabling brain control and/or hybrid control.

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