BRAIN COMMUNICATIONS

Implantable brain–computer interface for neuroprosthetic-enabled volitional hand grasp restoration in spinal cord injury

Iahn Cajigas,[1] Kevin C. Davis,[2,*] Benyamin Meschede-Krasa,[3,4,5,*] Noeline W. Prins,[2,6] Sebastian Gallo,[2] Jasim Ahmad Naeem,[2] Anne Palermo,[7] Audrey Wilson,[8] Santiago Guerra,[2] Brandon A. Parks,[2] Lauren Zimmerman,[2] Katie Gant,[8] Allan D. Levi,[1,8] W. Dalton Dietrich,[1,2,8] Letitia Fisher,[8] Steven Vanni,[1,8] John Michael Tauber,[3,5] Indie C. Garwood,[3,5] John H. Abel,[3,4,5] Emery N. Brown,[3,4,5] Michael E. Ivan,[1] Abhishek Prasad[2,8] and Jonathan Jagid[1,8]

* These authors contributed equally to this work.

Loss of hand function after cervical spinal cord injury severely impairs functional independence. We describe a method for restoring volitional control of hand grasp in one 21-year-old male subject with complete cervical quadriplegia (C5 American Spinal Injury Association Impairment Scale A) using a portable fully implanted brain–computer interface within the home environment. The brain–computer interface consists of subdural surface electrodes placed over the dominant-hand motor cortex and connects to a transmitter implanted subcutaneously below the clavicle, which allows continuous reading of the electrocorticographic activity. Movement-intent was used to trigger functional electrical stimulation of the dominant hand during an initial 29-weeks laboratory study and subsequently via a mechanical hand orthosis during in-home use. Movement-intent information could be decoded consistently throughout the 29-weeks in-laboratory study with a mean accuracy of 89.0% (range 78–93.3%). Improvements were observed in both the speed and accuracy of various upper extremity tasks, including lifting small objects and transferring objects to specific targets. At-home decoding accuracy during open-loop trials reached an accuracy of 91.3% (range 80–98.95%) and an accuracy of 88.3% (range 77.6–95.5%) during closed-loop trials. Importantly, the temporal stability of both the functional outcomes and decoder metrics were not explored in this study. A fully implanted brain–computer interface can be safely used to reliably decode movement-intent from motor cortex, allowing for accurate volitional control of hand grasp.

1 Department of Neurological Surgery, University of Miami, Miami, FL 33136, USA
2 Department of Biomedical Engineering, University of Miami, Miami, FL 33146, USA
3 Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
4 Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
5 Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
6 Department of Electrical and Information Engineering, Faculty of Engineering, University of Ruhuna, Hapugala, Galle 80000, Sri Lanka
7 Department of Physical Therapy, University of Miami, Miami, FL 33146, USA
8 Miami Project to Cure Paralysis, University of Miami, Miami, FL 33136, USA

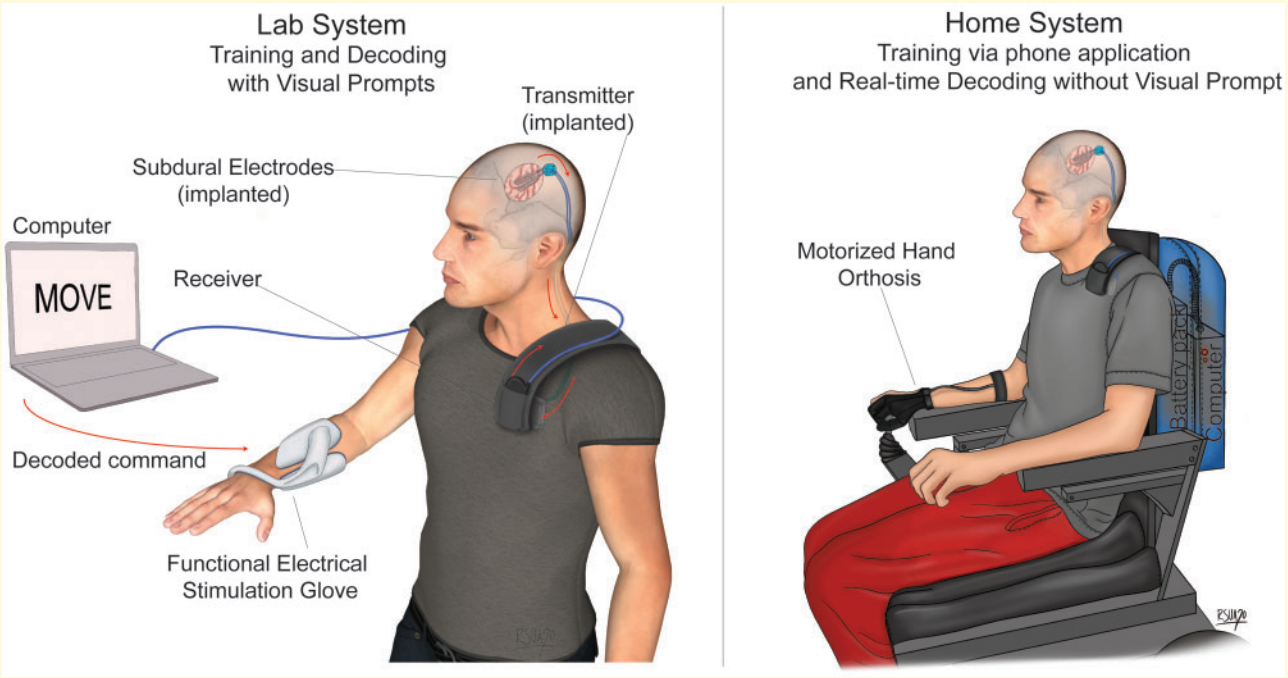
Correspondence to: Jonathan R. Jagid, MD,
Department of Neurological Surgery, University of Miami, 1095 NW 14th Terrace, Miami, FL 33136, USA,
E-mail: jjagid@med.miami.edu

Received April 28, 2021. Revised July 27, 2021. Accepted August 19, 2021. Advance Access publication October 21, 2021

Keywords: brain–computer interface; spinal cord injury; functional electrical stimulation; cervical quadriplegia; electrocorticography

Abbreviations: BCI = brain–computer interface; ECoG = electrocorticography; ERD = event-related desynchronization; FES = functional electrical stimulation; HMM = Hidden Markov Model; ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury; JHFT = Jebsen–Taylor Hand Function Test; LDA = Linear Discriminant Analysis; PSD = power spectral density; SCIM = spinal cord independence measure

Graphical Abstract



Introduction

Spinal cord injury (SCI) is a devastating disease, which exerts a disproportionate medical, social and economic toll on those injured and society. Despite many exciting preclinical studies underway, to date, no therapeutic intervention has been demonstrated to definitively improve neurological outcomes or mitigate the effects of secondary neural injury. Neural interface research has been strongly motivated by the need to restore the ability to communicate or improve motor function to the more than 5.4 million individuals in the USA suffering from various neurological disorders and diseases of the central and peripheral nervous system, which result in paralysis, such as stroke (33.7%), SCI (27.3%) and multiple sclerosis (18.6%).[1–6] The long-term use of rehabilitative neuroprosthetics could significantly improve the quality of life of paralyzed individuals with neurotechnology to reanimate non-functional limbs, replace missing limbs with neuroprosthetics, and enable new modes of direct neural communication.[1,4]

Over the last 20 years, there has been a surge in the number of successful applications of brain–computer interfaces (BCIs) for upper extremity control involving reaching and grasping.[7–12] Translating this technology into patients' homes and communities is an important step to enable patients to benefit from this research. However, fully implanted and portable BCIs for reanimating motor movements have yet to be successfully implemented and have never been deployed in an at-home setting. Successful translation of BCIs into a home environment has been possible in some cases; however, these studies have generally relied on signals recorded non-invasively from the scalp via electroencephalography (EEG).[13–16] Scalp EEG recordings suffer from low signal-to-noise ratio, are prone to artefacts, and require assistance from caretakers for setup. Many home implementations of non-invasive BCIs focused on smart home integration[17–22] or communication ability in patients who have lost it, such as those with amyotrophic lateral sclerosis.[23–27] For subjects with SCI, however, restoring hand function is a top priority,[28,29] and a few non-invasive home implementations of motor BCIs have been demonstrated.[30–32] While much progress continues to be made for non-invasive BCIs,[30,33–35] reliable signal acquisition, complex donning and doffing of equipment and lengthy

Table 1 Summary of BCI studies where device used in the home setting

Citation	Input	Output	Patient
Serruya2021	MUA	Orthosis	Stroke
Simeral2021	MUA	Cursor	2 SCI
Zulauf-Czaja2021	EEG	FES	SCI
Oxley2021	ECoG	Cursor	ALS
Dekleva2020	MUA	Cursor	SCI
Sun2020	EEG	Home appliances	
Weiss2019	MUA	Cursor	SCI
Al-Taleb2019	EEG	Pain control	20 SCI (with CNP)
Kober2019	EEG	Cognitive Modulation	7 MS
Pels2019	ECoG	Speller	ALS
Shahriari2019	EEG	Speller	9 ALS
Muller-Putz2019	EEG	FES	SCI
Gao2018	EEG	Speller-like home appliances	8 healthy
Wolpaw2018	EEG	Speller	27 ALS
Martin2018	EEG	Cognitive modulation	
Bundy2017a	EEG	Exoskeleton	10 stroke
Speier2017	EEG	Speller	6 ALS
Kosmyna2016	EEG	Smarthome	
Vansteensel2016	ECoG	Speller	ALS
Brennan2015	EEG	Home appliances	Healthy
Aydin2015	EEG	Smarthome	Healthy
Holz2015	EEG	Speller	ALS
Wang2014	EEG	Smarthome	
Leeb2013	EEG	Robot	ALS/SCI/cerebral palsy/+
Goodrich2015	EEG	Speller	ALS
Vernon2011	EEG	Cursor (phone)	SMA
Sellers2010	EEG	Speller	ALS
Vaughan2006	EEG	Speller	ALS

An extended version of this table can be found in Supplementary Table 7.
ALS = amyotrophic lateral sclerosis; CNP = central neuropathic pain; ECoG = electrocorticography; EEG = electroencephalography; ERD = event-related desynchronization; FES = functional electrical stimulation; MS = multiple sclerosis; MUA = multi-unit activity (e.g. spikes); SMA = spinal muscular atrophy; SCI = spinal cord injury.

caretaker training continue to impede convenience at-home use.[36–39]

BCI systems using implanted electrodes have shown promise in controlling cursors or robotic arms, though these systems usually require subjects to be constantly tethered to non-portable equipment, such as external power sources and recording hardware, which limit their application to a laboratory setting.[7,9,40,41] Recently, high band-width telemetry enabled a subject with an intracortical BCI to control a computer cursor at home,[42] however, the portability of this system remains limited to the wireless short-range area where the processing equipment is located. Although, current intracortical BCIs provide high resolution neural data, users must have a pedestal mounted to their head yielding an increased risk of infection and a cosmetic concern that user surveys indicate discourage device acceptance.[1] Still, reanimating hand grasp using invasive BCI in the home has yet to be studied. Additionally, BCIs using implanted electrodes generally rely on single-neuron activity,[8,10,12] the recording quality of which is known to decline over time in animals and humans.[43]

Other studies have instead utilized more stable electrocorticographic (ECoG) signals recorded from the brain surface.[15] However, until recent technological developments, these attempts have been limited to temporary implantations due to the nature of the clinical scenarios where ECoG is typically used, that is, seizure localization in epilepsy. Recently, two bilateral wireless epidural implants with 64 channels were shown to allow control of a four-limb neuroprosthetic exoskeleton in a laboratory setting in a subject with tetraplegia with stable decoding function over 24 months.[44] In the home setting, patients with amyotrophic lateral sclerosis have successfully used ECoG BCIs to control a computer cursor[45] or enable communication,[46] but reanimating hand grasp in the home remains an unmet need for those with paralysis. Table 1 summarizes published BCI studies where the device was used in the home setting.[17–27,30–32,42,45–57]

In this study, we sought to evaluate the safety, efficacy and long-term stability of a fully implanted BCI for control of a volitional hand grasp in a subject suffering from cervical quadriplegia via functional electrical stimulation (FES) orthosis in the acute post-operative phase within a laboratory setting and then via a motorized hand orthosis in the home environment. The final system was implemented so that it could be mounted on the subject's wheelchair to provide continuous use outside the laboratory environment without the need for clinician assistance via a patient-controlled smart phone application. This case report has been reported in line with the SCARE criteria.[58]

Materials and methods

Screening protocol

All study procedures were approved by the University of Miami Institutional Review Board and the US FDA (ClinicalTrials.gov: NCT02564419). A total of 21 subjects (4 female) with C5/C6 motor complete SCI, according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNSCI), provided written informed consent for screening with an EEG-based protocol (see Supplementary methods) to test their ability to trigger a FES device based on EEG signals produced while performing motor imagery of dominant hand movement and rest.[59] Subjects had to be 18–50 years old and have a chronic injury (>1-year post-injury) with a C5 or C6 motor level according to the ISNCSCI[60] and had to achieve sufficient hand opening/closing with FES to allow grasping (Supplementary Tables 1 and 2). A total of 17 subjects participated in the EEG screening over 1–10 weeks. One subject, 5 years post-injury, qualified for and consented to the surgical implantation and completed all 16 sessions of EEG screening.

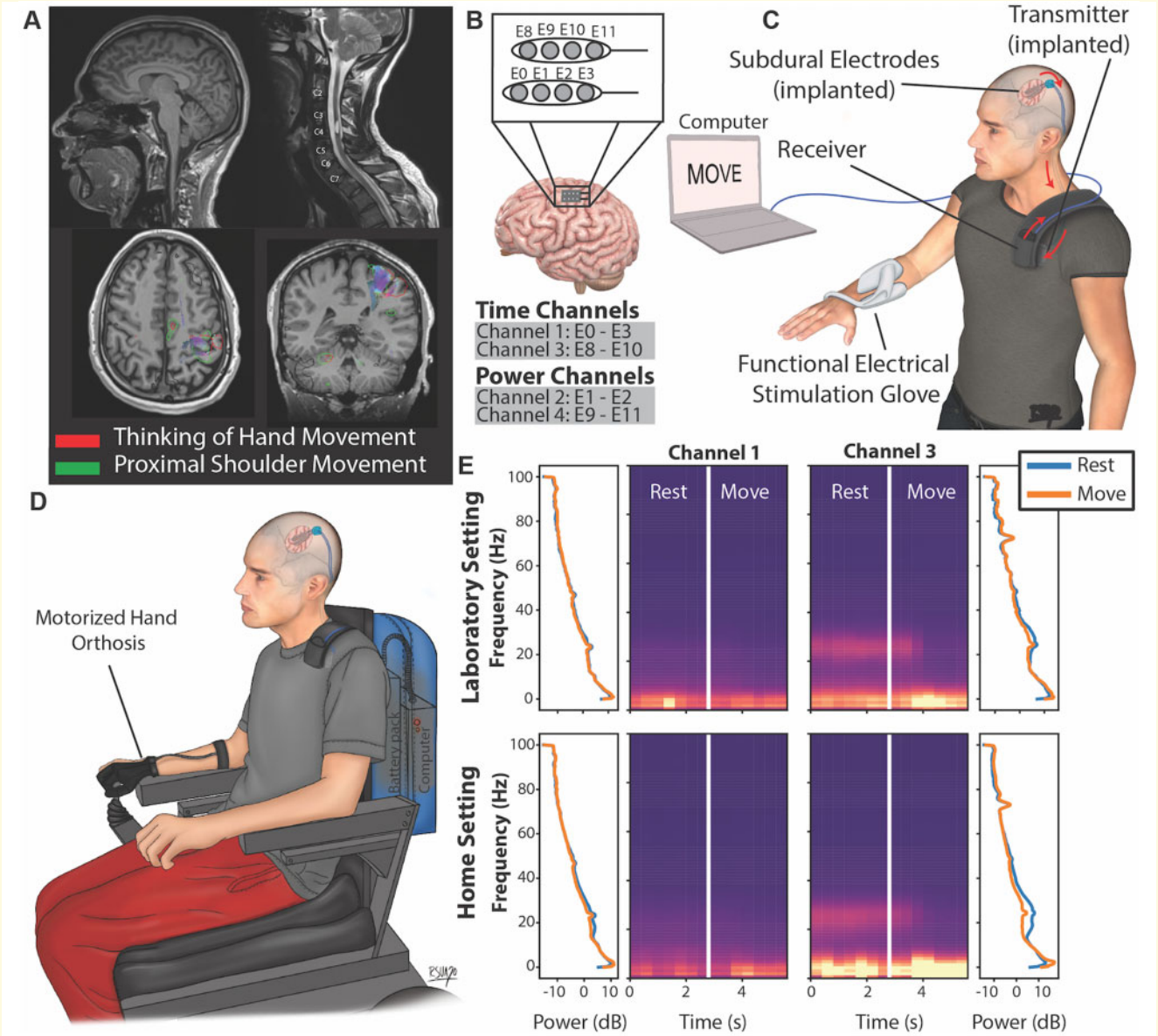


Figure 1 Pre-operative imaging used for electrode placement, laboratory and home system setups and illustration of ECoG ERDs. (**A**) Shows pre-operative sagittal MRI (top) showing post-traumatic cyst centred at C4. Stereotactic navigation was used to plan a small craniotomy over the region of increased fMRI signal during imagined right hand movements, which coincided with the hand/arm area of the precentral gyrus on the left hemisphere. (**B**) Shows relative location of electrodes on brain surface and configuration of data channels with respect to surface electrode contacts. (**C**) Shows the upper extremity laboratory setup. Real-time ECoG recordings from hand motor cortex are obtained via an antenna placed over the implanted transmitter. The antenna is connected to a receiver that then connects to laptop computer. The subject is prompted to think about resting or moving his right hand during a computer task and the signals recorded from the channels shown in **B** are processed to build classifiers that can be used to classify when the subject is thinking about move or rest. When a move state is correctly decoded, FES of the right hand is applied to the subject using a FES orthosis. (**D**) Shows the portable BCI system setup. Note that the FES orthosis has been replaced by a motorized hand orthosis. (**E**) Centre shows the average spectrogram for the continuous time channels (1 and 3) over all upper extremity task along with corresponding average power as well as the average PSD for move and rest states for each channel. All PSDs have confidence intervals calculated by the standard error of the mean. As can be clearly seen by the central spectrogram, motor imagery causes a decrease in the power in the beta and low gamma frequencies of the ECoG.

Surgical protocol

Pre-operative evaluation with functional magnetic resonance imaging was used to map the site of cortical activation during imagined dominant (right) hand movements and actual shoulder movements. Diffusion tensor imaging was used to identify the location of the corticospinal tract fibres that had previously controlled the dominant hand movement in the subject. The merged pre-operative

Video 1 Laboratory decoding of motor imagery. The subject is presented with prompts to think about moving their hand or relaxing. When a move signal is correctly decoded, the FES sleeve is triggered to initiate extension of the patient's digits.

Video 2 BCI setup and use at home. The BCI equipment is easily setup and configured by the subject and a family member or caregiver, this includes donning the mechanical glove and external telemeter. Using the mobile phone application enables data collection at home. Upon deployment, the subject was able to use the BCI to pick up common objects at home.

imaging, as shown in Fig. 1A, was used to plan a small craniotomy over the left motor cortex with the assistance of frameless stereotaxy (Stealth S7, Medtronic, Minneapolis, MN). Intraoperative electrical stimulation via the Nicolet® Cortical Stimulator (Natus Neuro, Middleton, WI) and electromyogram (EMG) monitoring was used to definitively identify motor cortex by evoking EMG activity in muscles proximal to the level of SCI. As determined from the pre-operative imaging and intraoperative stimulation, two four-contact electrodes (Resume II leads, Medtronic, Minneapolis, MN) were approximately centred on the hand/arm area on the left hemisphere with the long-axis of the leads oriented in the anterior–posterior direction. The leads were tunnelled subcutaneously to the left subclavicular region where they were connected to the implanted transmitter (Activa PC+S, Medtronic, Minneapolis, MN). Surgical implantation occurred on 30 November 2018 at the University of Miami Hospital, and consistent with deep-brain stimulation implantation reports of low infection and adverse event rates,[61,62] no complications occurred and the patient was discharged home on post-operative day 2.

Device

The Activa PC+S (Medtronic, Minneapolis, MN) is a deep-brain stimulation system that allows for real-time sensing and recording of brain activity. In this study, two four-contact electrodes were used for real-time sensing of the ECoG. The eight contacts were configured in bipolar mode (Fig. 1B) resulting in a total of four EcoG channels. Channels 1 and 3 output the real-time EcoG at a sample frequency of 200 Hz whereas channels 2 and 4 output the average power between 4 and 36 Hz computed on-board the transmitter at sample frequency of 5 Hz (Supplementary Table 3). Packets of data were transmitted every 0.4 s.

Data collection

Laboratory

The subject came to the laboratory 2–3 times per week for 1–2 h at a time. A timeline of the 29-weeks laboratory trial is included in the Supplementary methods (Supplementary Fig. 1). From study weeks 9–19, 'closed-loop' upper extremity experiments were conducted where the decoded motor imagery state from the online classifier was used to drive FES of the right upper extremity via an external orthosis (Bioness H200, Bioness, Valencia, CA) (Video 1). The details of the in-laboratory testing including development of initial decoders are included in the Supplementary methods. Figure 1C summarizes the laboratory setup.

To assess the ability of ECoG to discriminate between move and rest motor states, the subject was asked to think about rest for 3 s, followed by thinking about dominant hand movement for 3 s. Synchronization between the displayed message (Fig. 1C) and the recorded ECoG was achieved by application of a small pulse to the subject's scalp (below sensation threshold) that would cause an artefact in the recorded ECoG. The recorded data were segmented using transition pulse and labelled according to the displayed desired motor state to create dataset for classifier training.

Home

Beginning in July 2020, the continuous decoding system was deployed in the subject's home with the ability to control and calibrate the system via a custom smartphone-based application (Video 2 and Supplementary Fig. 5). The at-home system was constructed using an external battery (50 000 mAh power bank, Krisdonia, China), a nano computer (m90n Nano, Lenovo, China) and housed in a custom 3D-printed case. This casing was mounted to the back of the subject's wheelchair as shown in

Video 3 Functional task to transfer light object. The subject successfully used the BCI to trigger FES allowing the subject to grasp and transfer a cup between targets placed in front of the subject.

Fig. 1D. Hand grasp was actuated by a Bluetooth-enabled battery powered mechanical hand orthosis (Neomano, Neofect, South Korea) instead of FES.

In-home training data were collected in 5-min trials where epochs of 'move' (close hand) and 'rest' (open hand) instructions were delivered to the subject via the subject's smartphone while ECoG data were recorded. Motor instructions were randomly chosen to last between 6 and 10 s (in 0.4-s intervals corresponding to packet transmission frequency) before transitioning to the other motor state in order to capture the random transition between motor states that would occur during real-time use. A total of 33 trials performed in this manner were collected for at-home decoding algorithm training. Held-out open-loop validation data were collected in the same fashion, without actuating the mechanical glove, and was not used for training. Finally, held-out closed-loop validation data were collected in the same fashion, but the decoded motor state was used to control the mechanical glove online, giving the subject visual feedback of the decoder output.

Feature extraction

For operation of the decoder in both laboratory and home settings, we sought to map the power spectral density (PSD) of the EcoG recording to the binary move/rest state of the hand. In the laboratory, the power spectrum of the signals was estimated based on 2.8 s (7 packets) worth of data for the continuous time channels (Channels 1 and 3). Spectral frequencies from Channels 1 and 3 from each window of 2.8 s were binned into eight pre-specified segments (Supplementary Fig. 3). For Channels 2 and 4, the average spectral power was calculated. The averages from each channel and each bin were made up the feature vector for that window.

In the home, data from each channel were divided into overlapping windows and the PSD was computed for each window. A window size of 3.2 s was selected with a window step of 0.4 (Supplementary Fig. 6). For each window, spectral estimates from Channels 1 and 3 were obtained from frequency bands ranging from 0 to 100 Hz, computed using a multitaper method (Supplementary methods). For Channels 2 and 4, the median spectral estimate was calculated and included in the feature vector for that window.

Decoding model architecture

In-lab decoding

Five commonly applied machine-learning classifiers were tested: bagged trees, *k*-nearest neighbours, linear discriminant, linear support vector machine and an artificial neural network. All in-laboratory classifiers were trained in Matlab 2018*b*, and online experiments were conducted in Matlab 2015*a*. Offline classifiers were selected as outlined in Supplementary Table 4.

At-home decoder

In order to build a robust decoder used in the home, using training data with random transitions between move and rest instruction, we revised the decoder architecture to model the temporal dynamics of switching between states. A two-step decoder architecture first used linear discriminant analysis for supervised learning and a Hidden Markov Model to capture patterns in the time domain.

In-home training data were collected in 5-min trials where epochs of 'move' (close hand) and 'rest' (open hand) instructions were delivered to the subject via the subject's smartphone while ECoG data were recorded. Motor instructions were randomly chosen to last between 6 and 10 s (in 0.4 s intervals corresponding to packet transmission frequency) before transitioning to the other motor state in order to capture the random transition between motor states that would occur during real-time use. A total of 33 trials performed in this manner were collected for at-home decoding algorithm training. Held-out open-loop validation data were collected in the same fashion, without actuating the mechanical glove, and was not used for training. Finally, held-out closed-loop validation data were collected in the same fashion, but the decoded motor state was used to control the mechanical glove online, giving the subject visual feedback of the decoder output. A detailed description of the at-home decoder architecture and other architectures that were explored in cross-validation are found in the Supplementary methods.

Functional tasks

From study weeks 11–19, during the in-laboratory testing, several tasks were performed alongside the upper extremity trials to quantify any improvements in upper extremity function. Starting on Week 11, whenever a correct move state was decoded and the subject was receiving FES to open and close the hand, he was asked to

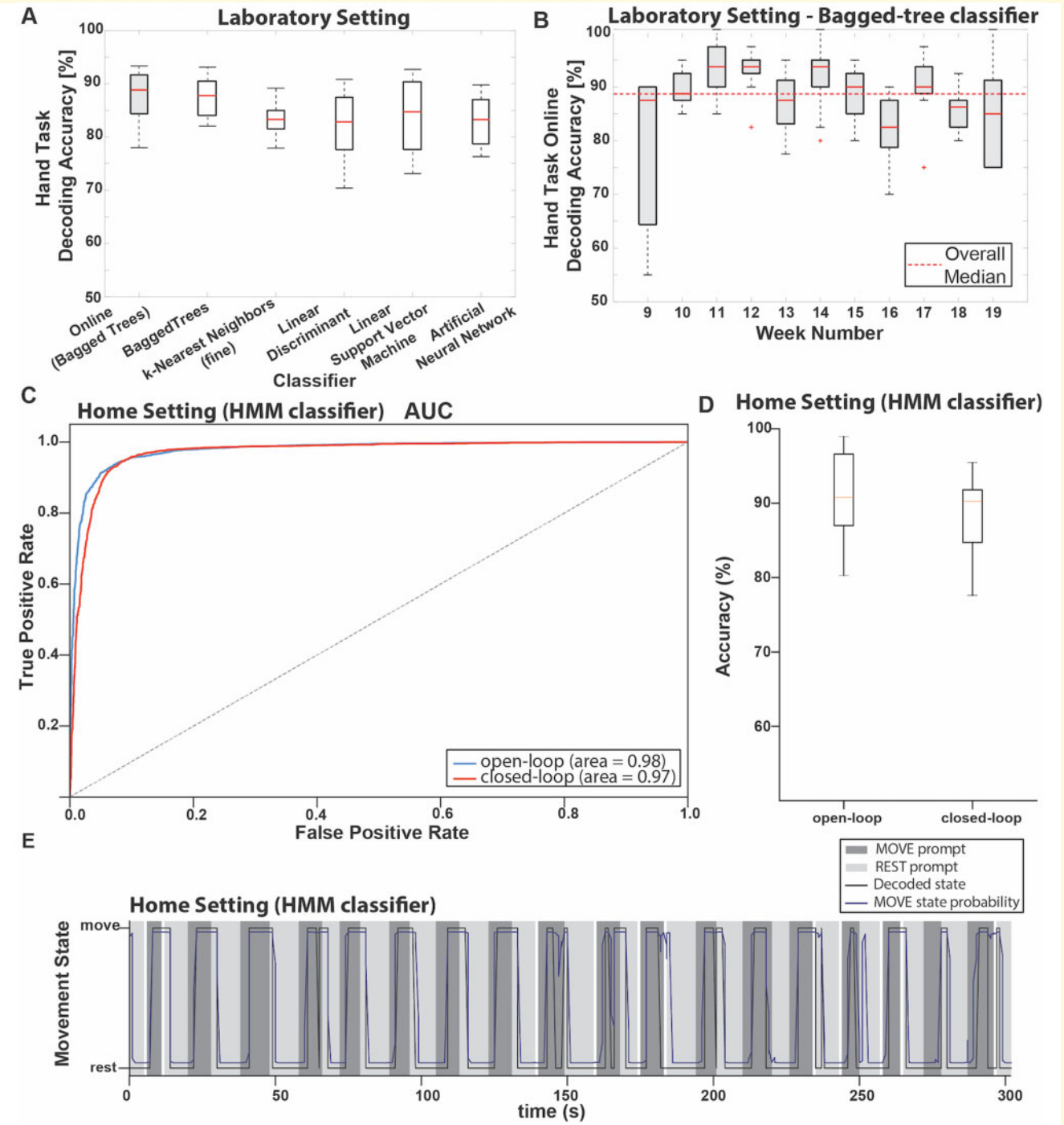


Figure 2 Upper extremity decoding performance. (**A**) Shows the accuracy of different types of classifiers to decode rest/move states during the hand task in the laboratory. Best online and offline in-laboratory performance was seen with bagged-tree classifier—89.0% (median 88.75%, range 78–93.3%). (**B**) Shows that the decoding accuracy remained relatively stable over the 10 weeks of upper extremity tasks. (**C**) Shows the performance of the at-home decoder under open-loop and closed-loop settings. (**D**) Shows the distribution of at-home decoding accuracies under open-loop ($N = 13$) and closed-loop ($N = 12$) settings. (**E**) Shows a sample at-home time series during an accuracy assessment demonstrating the movement state being displayed to the subject, the decoder movement state probability, and the decoded state.

pick up and move a small cup (or a checker introduced from Week 13) from one side of the table to the other at the centre of a target. The placement accuracy was measured as a function of the distance of the cup/checker to the target (Video 3). Additionally, during Weeks 8–29 a modified version of the Jebsen–Taylor Hand Function Test (JHFT)[63] was performed once per week to quantify functional improvement. Passive and active range of

motion was also measured each week. Pinch force between the index finger and thumb during FES was measured each week using a digital pinch gauge (Baseline digital pinch gauge, Fabrication Enterprises, USA). Due to the Covid19 pandemic, functional assessments were unable to be performed during the at-home testing.

Clinical assessments

During the in-laboratory portion of the study, the subject underwent weekly interviews to assess for adverse events and was also surveyed for changes in self-perceived functional independence. Changes in health status were assessed with the MOS 36-item short-form health survey (SF-36).[64] Perceived changes in functional independence were assessed with the spinal cord independence measure (SCIM)[65] version III, which ranges from 0 to 100 and higher score indicates increased independence. Detailed neurological evaluation for documentation of level and severity of SCI was conducted monthly according to the ISNCSCI.[60] During home use, the SCIM and SF-36 were administered once per week.

Statistical analysis

Data were tested for normality using the Lilliefors test. Where multiple groups where involved, Levene's test for equal variance was used to evaluate homoscedasticity across. In case of single comparisons, the Student's *t*-test was used for data that was normally distributed otherwise the ranked sum test was used. For testing differences between multiple groups, we used One-way ANOVA or Kruskal–Wallis tests.

Data availability

Individual participant data that underlies the results reported in this article after de-identification, study protocol, statistical analysis plan and analytic code will be made available upon request to researchers who provide a methodologically sound proposal. Requests should be made to corresponding author.

Results

Decoder performance

Figure 2A summarizes decoding performance across all in-laboratory upper extremity sessions (open loop and closed loop) for Weeks 9–19 for different classifier types. For offline analysis of the closed-loop experiments, a total of 80–240 trials were used with half of the data set used for training and the other half for testing. The accuracies presented represent the average of 100 random split cross-validation iterations. Mean online decoding accuracy per week was 89.0% (median 88.75%, range 78–93.3%), which was not significantly different from offline performance across the 5 types of classifiers tested (Kruskall–Wallis test with Tukey–Kramer adjustment for multiple comparisons, $P > 0.06$). Online decoding during Weeks 9–19 remained relatively stable for upper extremity tasks across weeks as shown in Fig. 2B.

The decoder trained for the at-home setting performed very well on non-ambiguous windows of data, i.e. those that did not contain mixed move/rest signals, in both open-loop and closed-loop trials (Fig. 2C and D). Using the decoded probability of motor intent, the area under

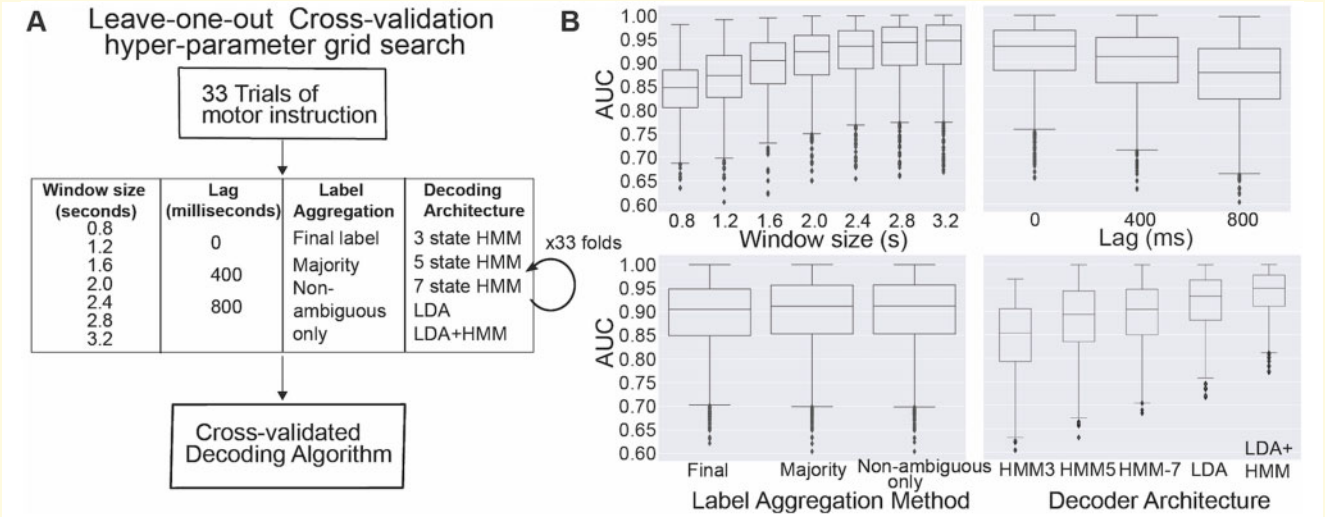


Figure 3 Cross-validation overview. (**A**) Summarizes the structure of the grid search for leave-one-trial-out cross-validation depicted for 33 trials of motor instruction. Selected hyper-parameters are summarized in Table 2. (**B**) Shows the impact of each hyper-parameter plotted over all other hyper-parameterizations. Window size, lag and decoder architecture had large impacts on performance, but label aggregation method had a similar distribution of performance over all other hyper-parameterizations.

Table 2 Final at-home decoder hyper-parameters selected via leave-one-out cross-validation

Hyper-parameter	Selected value
Window size, w (s)	3.2
Label scheme, *y*	$y^{(3)}$
Decoder architecture	LDA-HMM
Lag *l* (s)	0.0

the receiver-operator characteristic curve (AUC) was calculated for each window of non-ambiguous data. Open-loop and closed-loop trials had similar decoding performance with AUC of 0.98 and 0.97, and accuracy with a mean of 91.3% (median 90.8%) and 88.3% (median 90.3%), respectively. During state transitions, in which windows contained changes in motor intent, there was an average delay of 2.3 s to transition to the intended motor state. These delays in time to motor intent are seen in a time series data sample (Fig. 2E) where the change in the decoded state lags changes in the prompt. This delay contributes to a slightly decreased accuracy (0.69) when analysing data across windows where motor intent changes for both open-loop (AUC = 0.78) and closed-loop (AUC = 0.77) trials.

Cross-validation

The cross-validation results for the at-home decoder are summarized in Fig. 3. Selected hyper-parameters are summarized in Table 2. Window size, lag and decoder architecture had large impacts on performance, but label aggregation method had a similar distribution of performance over all other hyper-parameterizations.

Functional improvement

The subject showed improvement in the accuracy of placing a small cup, 60.1% ± 7.8% (mean ± SD) at Week 11 versus 82.8% ± 4.7% at week 19 (two-tailed *t*-test, $P = 0.03$) or a checker (64.5% ± 7.3% at week 13 versus 88.8% ± 4.8% at Week 19, two-tailed *t*-test, $P = 0.03$) at the centre of a target as summarized in Fig. 4A and B.

Functional improvement was quantified as the reduction in the average time taken to perform specific components of the JHFT (Fig. 4C). Significant improvements were observed in lifting small objects, lifting light cans and lifting heavy cans through orthotic-assisted tasks. Along with a trend towards improvement in writing speed (32.3–26.4 s, two-tailed *t*-test, $P = 0.15$), clarity of the handwriting also improved throughout the course of the study (Fig. 4D). Further, pinch force increased from 1 to 3 lb within 10 weeks.

Clinical assessments

While there was no change in ISNCSCI American Spinal Injury Association impairment scale from a C5 motor level, there was an unexpected slight increase in the motor zone of partial preservation (defined as the myotomes below the level of injury with residual innervation) on the left from C6 to C8. Additionally, after study week 23, the subject began to be able to extend his right thumb volitionally with motor strength 2/5 in the absence of the FES orthosis (Video 4). During the laboratory portion of the study, there was no change in the SCIM from a baseline score of 26. The SF-36 indicated a 32.5% improvement in pain, a 5% increase in energy and an 8% decrease in emotional well-being. Interestingly, during the in-home portion of the study, there was a 22.5% increase in pain (from 100% down to 77.5% in the setting of a newly diagnosed and treated urinary tract infection) and a one-point increase in the SCIM [from 26 to 27 due to improvement in self-care (see Supplementary Tables 5 and 6 for a breakdown of scores)].

Discussion

Successive continuous movement of the hands were first noticed by Jasper and Penfield in 1949 to produce a blocking of the beta rhythm in the pre- and post-central hand area as measured in ECoG.[66] Interestingly, the reductions in the beta power band observed in the ECoG, called event-related desynchronizations (ERDs), are also observed during imagined movements of the limb. Therefore, it is not surprising that ERDs and other changes in the frequency characteristics of the EEG and ECoG have been investigated by numerous researchers as potential control signals to trigger stimulation of paralyzed muscles[59] or to control the position of a cursor on a computer screen.[16] A fully implanted ECoG-based BCI using ERDs within the ECoG signals, has been developed to allow typing in a fully locked-in patient with amyotrophic lateral sclerosis.[46] However, to our knowledge, no prior fully implanted and portable motor BCI has been successfully deployed in a home environment to allow volitional restoration of hand grasp.

Our results demonstrate that a fully implanted BCI can be safely and reliably used to decode movement-intent from motor cortex allowing for volitional control of hand grasp by a patient with SCI in laboratory and home environment. In closed-loop experiments, movement-intent was decoded from real-time ECoG recordings obtained from electrodes placed on the hand/arm motor cortex and the output of the classifier was used to trigger an external assistive device with a high degree of accuracy. The performance of the decoder has remained stable for the 22 months since initial device implantation with median accuracy around 90%. Additionally, there was significant improvement in both the accuracy and speed of several functional hand tasks, though stability of these improvements overtime was not experimentally assessed. We also observed improvements in self-perceived pain and energy scores during the initial laboratory testing

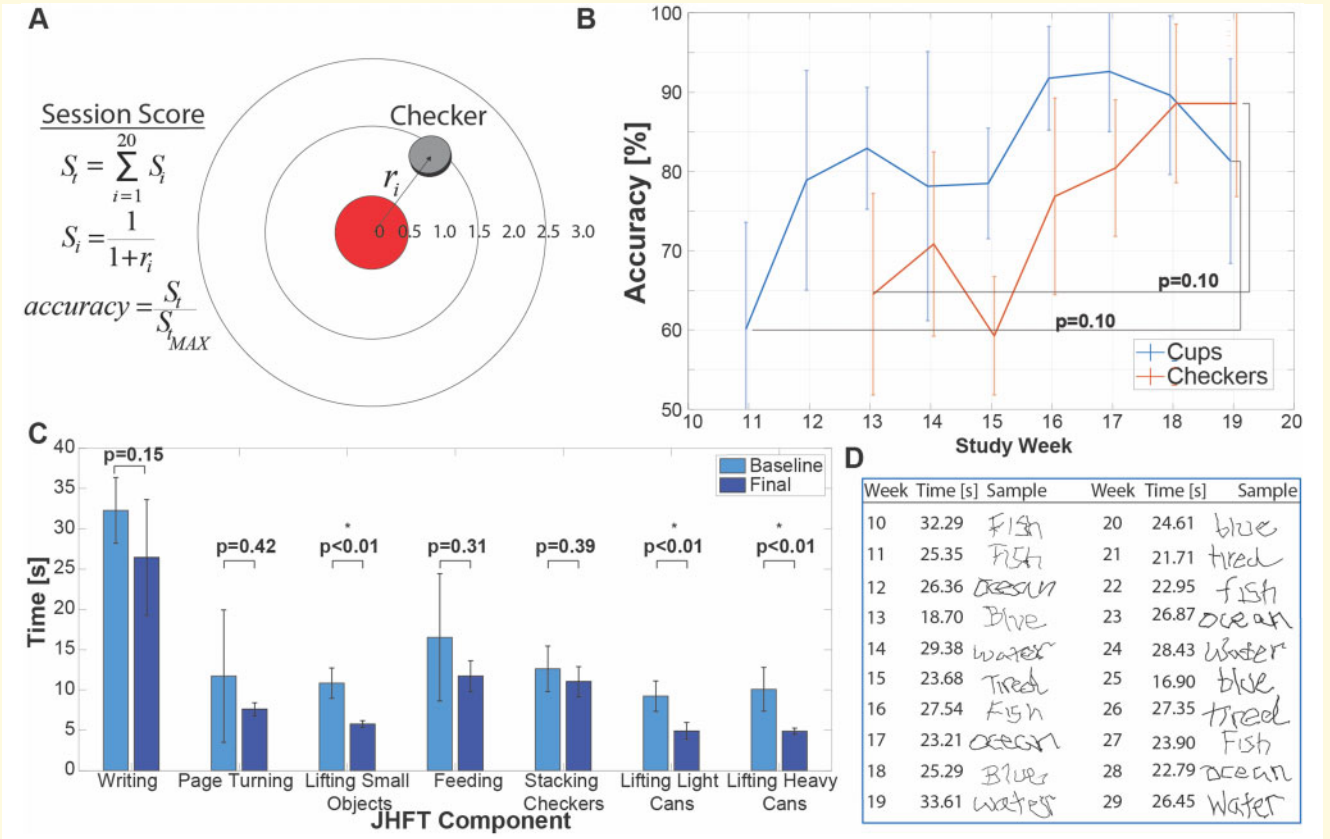
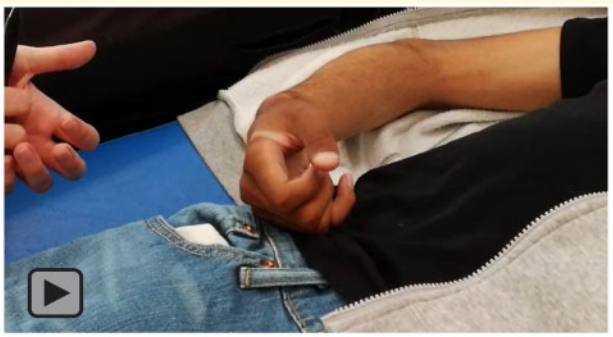


Figure 4 Functional task structure and performance. (**A**) Shows the setup for the checker and cup task. The subject was instructed to try to place the corresponding object at the centre of the target ($n = 20$) and this task was repeated three times during a study week visit. (**B**) Shows significant improvement in accuracy from Week 11 to study Week 19. (**C**) Shows comparison of times between study Weeks 9 and 19 for different components of the JHFT. Each JHFT task was repeated a total of five times per session. Bar height corresponds to mean times ±SD; *P*-values computed with two-tailed *t*-test. (**D**) Shows the best handwriting sample from each week from Weeks 10–29 along with average time to write each of the words. Each word was written a total of five times per week.



Video 4 Volitional abduction of the first digit. During the study, the patient noticed that they were able to slightly abduct the first digit on their dominant right hand without the use of the BCI system or an assistive device.

period and, interestingly, there was a slight increase in the SCIM during home use within the area of self-care as well as changes in pain perception with the laboratory and home setting. The clinical significance and stability of these perceived changes remains unclear at this time but will ultimately be crucial to understand in order to maximize the utility of BCIs to patients with SCI.

Though we only demonstrate this work in one subject, previous studies have successfully used ERD to provide a valuable control signal for motor imagery.[13,14,59,67–72] Though the magnitude of ERD may change after SCI,[69] it has continued to be used successfully to detect motor imagery in both healthy subjects[13,14,67,70–73] and subjects with SCI,[59,68] as well as other neurological conditions.[74] Additionally, the Activa PC+S has been used to detect ERD in other patient populations,[46,75] further supporting the possibility that fully implanted systems can reliably detect ERD for use in the home.

The subject demonstrated an increase in volitional control of their right thumb towards the end of the laboratory phase of the study. While previous work using FES in patients with stroke has shown improvement in volitional control,[30,76,77] without further evaluation of EMG, whether the improvement can be attributed to the use of the BCI or another mechanism is unknown.

Our results show that a BCI that allows control of one degree of freedom (namely hand grasp) may be a helpful tool for patients with paralysis to gain functional independence by allowing them to exert volitional control of external devices. Although this study did not use functional independence measures aside from that captured in the SCIM, we envision that as these technologies transition out of the laboratory setting, the potential improvements in ability to perform activities of daily living will drive functional independence. Additionally, the system can be easily adapted to allow volitional control of a wide range of external devices (e.g. as a trigger for robotic assisted stepping within an exoskeleton as shown in the Supplementary methods), which may open the door for future development of assistive devices within a home environment that can be controlled with the implanted BCI.

For our BCI system at home, the use of implanted ECoG electrodes, asynchronous signal decoding, wireless communication and a simplified user-centred interface helped reduce caretaker setup times to a few minutes, requiring no technical training other than simply positioning the telemeter and turning the components on. While restoring hand grasp might be accomplished using other non-invasive methodologies, including mechanical devices,[78] orthoses[79] or electrically-powered devices driven by functioning movements or EMG,[80] the implant allowed for an unobtrusive design, minimizing both the visible external components that collect the neural data as well as minimizing system maintenance. Additionally, coupling motor imagery from neural signals with an asynchronous decoder eliminated that need for a synchronizing stimulus and enabled the subject to engage the device in a more natural way. These aspects highlight how some of the barriers[36–39] that hold back BCIs from further transitioning into the clinic and community can be overcome. Still, invasive procedures for BCI may be concerning,[36] however, some surveys suggest that this does not affect interest of some potential beneficiaries.[81] As pointed out by Waldert,[82] other neural implant procedures, such as DBS, rarely result in complications, suggesting that procedures for BCIs will have similar outcomes and success, where the benefits of invasive BCIs out-weigh the surgical risks.

The main limitation of this work, the ability to decode only one degree of freedom, is driven by currently available technology. As newer devices with increased recording capabilities (increased number of channels and spatial density, and higher sampling frequency), such as the one recently developed by Benabid et al.[44] become available within the US market, we anticipate that the techniques presented here-in will be generalizable to the restoration of a larger number of degrees of freedom in patients with SCI. Particularly, the development of these new devices in parallel with advanced mobile robotic exoskeleton technology may in the near future allow for the restoration of both upper and lower extremity function for patients with SCI.

Supplementary material

Supplementary material is available at *Brain Communications* online.

Acknowledgements

We would like to thank our subject for his continued dedication and enthusiasm throughout the duration of this study. We would like to thank Roberto Suazo for his assistance with the design of the figures and editing of videos; the dedicated staff in the operating room and intensive care unit for their post-operative care of the subject. We are thankful to Dr(s) Roberto C. Heros, Barth A. Green, Alexander Koenig and George M. Ibrahim for their comments on initial drafts of the manuscript.

Funding

Supported by a private institutional grant from the Miami Project to Cure Paralysis. Device was donated by Medtronic. Medtronic provided all components of the implant including the external antenna/receiver free of charge to the University of Miami but did not provide funds directly to the institution, the researchers or the patient. Home deployment orthosis was funded by a private donor. I.C. was supported in part by National Institutes of Health/National Institute of Neurological Disorders and Stroke (R25NS108937-02). K.D. was supported in part by National Institutes of Health (T32GM112601). J.H.A. was supported in part by National Institutes of Health/National Institute of Aging (F32 AG064886).

Competing interests

The authors report no competing interests.

References

1. Anderson KD. Consideration of user priorities when developing neural prosthetics. *J Neural Eng*. 2009;6(5):055003.
2. Aravamudhan S, Bellamkonda RV. Toward a convergence of regenerative medicine, rehabilitation, and neuroprosthetics. *J Neurotrauma*. 2011;28(11):2329–2347.
3. Armour BS, Courtney-Long EA, Fox MH, Fredine H, Cahill A. Prevalence and causes of paralysis-United States, 2013. *Am J Public Health*. 2016;106(10):1855–1857.
4. Nicolelis MA. Brain-machine interfaces to restore motor function and probe neural circuits. *Nat Rev Neurosci*. 2003;4(5):417–422.
5. Wolpaw JR, Birbaumer N, Heetderks WJ, et al. Brain-computer interface technology: A review of the first international meeting. *IEEE Trans Rehabil Eng*. 2000;8(2):164–173.
6. Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. *Clin Neurophysiol*. 2002;113(6):767–791.
7. Ajiboye AB, Willett FR, Young DR, et al. Restoration of reaching and grasping movements through brain-controlled muscle

stimulation in a person with tetraplegia: A proof-of-concept demonstration. *Lancet*. 2017;389(10081):1821–1830.
8. Chapin JK, Moxon KA, Markowitz RS, Nicolelis MA. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nat Neurosci*. 1999;2(7):664–670.
9. Collinger JL, Wodlinger B, Downey JE, et al. High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet*. 2013;381(9866):557–564.
10. Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*. 2012;485(7398):372–375.
11. Hochberg LR, Serruya MD, Friehs GM, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*. 2006;442(7099):164–171.
12. Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. *Nature*. 2008; 453(7198):1098–1101.
13. Heasman JM, Scott TRD, Kirkup L, et al. Control of a hand grasp neuroprosthesis using an electroencephalogram-triggered switch: Demonstration of improvements in performance using wavepacket analysis. *Med Biol Eng Comput*. 2002;40(5):588–593.
14. Meng J, Edelman BJ, Olsoe J, et al. A study of the effects of electrode number and decoding algorithm on online EEG-based BCI behavioral performance. *Front Neurosci*. 2018;12:227.
15. Wang W, Collinger JL, Degenhart AD, et al. An electrocorticographic brain interface in an individual with tetraplegia. *PLoS One*. 2013;8(2):e55344.
16. Wolpaw JR, McFarland DJ. Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. *Proc Natl Acad Sci USA*. 2004;101(51):17849–17854.
17. Wang J, Yang C. [Research of controlling of smart home system based on P300 brain-computer interface]. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi*. 2014;31(4):762–766.
18. Aydin EA, Bay ÖF. *In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. 1075–1078.
19. Brennan CP, McCullagh PJ, Galway L, Lightbody G. *In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. 5032–5035.
20. Kosmyna N, Tarpin-Bernard F, Bonnefond N, Rivet B. Feasibility of BCI control in a realistic smart home environment. *Front Hum Neurosci*. 2016;10:416.
21. Gao Q, Zhao X, Yu X, Song Y, Wang Z. Controlling of smart home system based on brain-computer interface. *Technol Health Care*. 2018;26(5):769–783.
22. Sun KT, Hsieh KL, Syu SR. Towards an accessible use of a brain-computer interfaces-based home care system through a smartphone. *Comput Intell Neurosci*. 2020;2020:1843269.
23. Shahriari Y, Vaughan TM, McCane LM, et al. An exploration of BCI performance variations in people with amyotrophic lateral sclerosis using longitudinal EEG data. *J Neural Eng*. 2019;16(5): 056031.
24. Wolpaw JR, Bedlack RS, Reda DJ, et al. Independent home use of a brain-computer interface by people with amyotrophic lateral sclerosis. *Neurology*. 2018;91:e258–e267.
25. Speier W, Chandravadia N, Roberts D, Pendekanti S, Pouratian N. Online BCI typing using language model classifiers by ALS patients in their homes. *Brain Comput Interfaces (Abingdon)*. 2017;4(1-2):114–121.
26. Holz EM, Botrel L, Kaufmann T, Kubler A. Long-term independent brain-computer interface home use improves quality of life of a patient in the locked-in state: A case study. *Arch Phys Med Rehabil*. 2015;96(Suppl 3):S16–S26.
27. Goodrich E, Wahbeh H, Mooney A, Miller M, Oken BS. Teaching mindfulness meditation to adults with severe speech and physical impairments: An exploratory study. *Neuropsychol Rehabil*. 2015; 25(5):708–732.
28. Anderson KD. Targeting recovery: Priorities of the spinal cord-injured population. *J Neurotrauma*. 2004;21(10):1371–1383.
29. Snoek GJ, IJzerman MJ, Hermens HJ, Maxwell D, Biering-Sorensen F. Survey of the needs of patients with spinal cord injury: Impact and priority for improvement in hand function in tetraplegics. *Spinal Cord*. 2004;42(9):526–532.
30. Zulauf-Czaja A, Al-Taleb MKH, Purcell M, Petric-Gray N, Cloughley J, Vuckovic A. On the way home: A BCI-FES hand therapy self-managed by sub-acute SCI participants and their caregivers: A usability study. *J Neuroeng Rehabil*. 2021;18(1):44.
31. Müller-Putz GR. *In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. 5949–5955.
32. Bundy DT, Souders L, Baranyai K, et al. Contralesional brain-computer interface control of a powered exoskeleton for motor recovery in chronic stroke survivors. *Stroke*. 2017;48(7):1908–1915.
33. Kim J, Lee J, Han C, Park K. An instant donning multi-channel EEG headset (with comb-shaped dry electrodes) and BCI applications. *Sensors (Basel)*. 2019;19(7):1537.
34. Lotte F, Bougrain L, Cichocki A, et al. A review of classification algorithms for EEG-based brain-computer interfaces: A 10 year update. *J Neural Eng*. 2018;15(3):031005.
35. Abiri R, Borhani S, Sellers EW, Jiang Y, Zhao X. A comprehensive review of EEG-based brain-computer interface paradigms. *J Neural Eng*. 2019;16(1):011001.
36. Huggins JE, Moinuddin AA, Chiodo AE, Wren PA. What would brain-computer interface users want: Opinions and priorities of potential users with spinal cord injury. *Arch Phys Med Rehabil*. 2015;96(3):S38–S45.e31-e35.
37. McFarland DJ, Vaughan TM. Chapter 13 - BCI in practice. In: D Coyle, ed. *Brain-Computer Interfaces: Lab Experiments to Real-World Applications.Vol 228. Brain-Computer Interfaces: Lab Experiments to Real-World Applications*. Vol. 228. Elsevier; 2016: 389–404. Available at: http://www.sciencedirect.com/science/article/pii/S0079612316300917.
38. Jochumsen M, Knoche H, Kidmose P, Kjaer TW, Dinesen BI. Evaluation of EEG headset mounting for brain-computer interface-based stroke rehabilitation by patients, therapists, and relatives. *Front Hum Neurosci*. 2020;14:13.
39. Kilgore KL, Anderson KD, Peckham PH. Neuroprosthesis for individuals with spinal cord injury. *Neurol Res*. 2020;1–13.
40. Bouton CE, Shaikhouni A, Annetta NV, et al. Restoring cortical control of functional movement in a human with quadriplegia. *Nature*. 2016;533(7602):247–250.
41. Nurmikko A. Challenges for large-scale cortical interfaces. *Neuron*. 2020;108(2):259–269.
42. Simeral JD, Hosman T, Saab J, et al. Home Use of a Percutaneous Wireless Intracortical Brain-Computer Interface by Individuals With Tetraplegia. *Ieee T Bio-med Eng*. 2020;68(7):2313–2325. doi:10.1109/tbme.2021.3069119
43. Gunasekera B, Saxena T, Bellamkonda R, Karumbaiah L. Intracortical recording interfaces: Current challenges to chronic recording function. *ACS Chem Neurosci*. 2015;6(1):68–83.
44. Benabid AL, Costecalde T, Eliseyev A, et al. An exoskeleton controlled by an epidural wireless brain-machine interface in a tetraplegic patient: A proof-of-concept demonstration. *Lancet Neurol*. 2019;18(12):1112–1122.
45. Oxley TJ, Yoo PE, Rind GS, et al. Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: First in-human experience. *J Neurointerv Surg*. 2021;13(2):102–108.
46. Vansteensel MJ, Pels EGM, Bleichner MG, et al. Fully implanted brain-computer interface in a locked-in patient with ALS. *N Engl J Med*. 2016;375(21):2060–2066.
47. Al-Taleb MKH, Purcell M, Fraser M, Petric-Gray N, Vuckovic A. Home used, patient self-managed, brain-computer interface for the management of central neuropathic pain post spinal cord injury: Usability study. *J Neuroeng Rehabil*. 2019;16(1):128.

48. Dekleva BM, Weiss JM, Boninger ML, Collinger JL. Generalizable cursor click control using grasp-related neural transients. *Medrxiv*. Published online 2020:2020.09.03.20186973. doi:10.1101/2020.09.03.20186973
49. Kober SE, Pinter D, Enzinger C, et al. Self-regulation of brain activity and its effect on cognitive function in patients with multiple sclerosis - first insights from an interventional study using neurofeedback. *Clin Neurophysiol*. 2019;130(11):2124–2131.
50. Leeb R, Perdikis S, Tonin L, et al. Transferring brain-computer interfaces beyond the laboratory: Successful application control for motor-disabled users. *Artif Intell Med*. 2013;59(2):121–132.
51. Martin S, Iturrate I, Millan JDR, Knight RT, Pasley BN. Decoding inner speech using electrocorticography: Progress and challenges toward a speech prosthesis. *Front Neurosci*. 2018;12:422.
52. Pels EGM, Aarnoutse EJ, Leinders S, et al. Stability of a chronic implanted brain-computer interface in late-stage amyotrophic lateral sclerosis. *Clin Neurophysiol*. 2019;130(10):1798–1803.
53. Sellers EW. Clinical applications of brain-computer interface technology. *Clin EEG Neurosci*. 2011;42(4):IV.
54. Serruya MD, Napoli A, Satterthwaite N, et al. Neuromotor Prosthetic to Treat Stroke-Related Paresis. *Medrxiv*. Published online 2021:2021.02.03.21250720. doi:10.1101/2021.02.03.21250720.
55. Vaughan TM, McFarland DJ, Schalk G, et al. The Wadsworth BCI research and development program: At home with BCI. *IEEE Trans Neural Syst Rehabil Eng*. 2006;14(2):229–233.
56. Vernon S, Joshi SS. Brain-muscle-computer interface: Mobile-phone prototype development and testing. *IEEE Trans Inf Technol Biomed*. 2011;15(4):531–538.
57. Weiss JM, Gaunt RA, Franklin R, Boninger ML, Collinger JL. Demonstration of a portable intracortical brain-computer interface. *Brain Comput Interfaces*. 2019;6(4):106–117.
58. Agha RA, Franchi T, Sohrabi C, et al. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. *Int J Surg*. 2020;84:226-230. doi:10.1016/j.ijsu.2020.10.034 ,
59. Gant K, Guerra S, Zimmerman L, et al. EEG-controlled functional electrical stimulation for hand opening and closing in chronic complete cervical spinal cord injury. *Biomed Phys Eng Express*. 2018;4(6):065005.
60. Kirshblum SC, Burns SP, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med*. 2011;34(6):535–546.
61. Bhatia S, Zhang K, Oh M, Angle C, Whiting D. Infections and hardware salvage after deep brain stimulation surgery: A single-center study and review of the literature. *Stereotact Funct Neurosurg*. 2010;88(3):147–55. doi: 10.1159/000303528. Epub 2010 Apr 1. PMID: 20357522.
62. Fenoy AJ, Simpson RK Jr. Risks of common complications in deep brain stimulation surgery: Management and avoidance. *J Neurosurg*. 2014 Jan;120(1):132-9. doi: 10.3171/2013.10.JNS131225. Epub 2013 Nov 15. PMID: 24236657.
63. Jebsen RH, Taylor N, Trieschmann RB, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch Phys Med Rehabil*. 1969;50(6):311–319.
64. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.
65. Itzkovich M, Gelernter I, Biering-Sorensen F, et al. The spinal cord independence measure (SCIM) version III: Reliability and validity in a multi-center international study. *Disabil Rehabil*. 2007;29(24):1926–1933.
66. Jasper H, Penfield W. Electrocorticograms in man: Effect of voluntary movement upon the electrical activity of the precentral gyrus. *Archiv Für Psychiatrie Und Nervenkrankheiten*. 1949;183(1-2):163–174.
67. Pfurtscheller G, Aranibar A. Evaluation of event-related desynchronization (ERD) preceding and following voluntary self-paced movement. *Electroencephalogr Clin Neurophysiol*. 1979;46(2):138–146.
68. Onose G, Grozea C, Anghelescu A, et al. On the feasibility of using motor imagery EEG-based brain–computer interface in chronic tetraplegics for assistive robotic arm control: A clinical test and long-term post-trial follow-up. *Spinal Cord*. 2012;50(8):599–608.
69. López-Larraz E, Montesano L, Gil-Agudo Á, Minguez J, Oliviero A. Evolution of EEG motor rhythms after spinal cord injury: A longitudinal study. *PLoS One*. 2015;10(7):e0131759.
70. Daly I, Blanchard C, Holmes NP. Cortical excitability correlates with the event-related desynchronization during brain–computer interface control. *J Neural Eng*. 2018;15(2):026022.
71. Guger C, Harkam W, Hertnaes C, Pfurtscheller G. "Prosthetic control by an EEG-based brain-computer interface (BCI)". 1999.
72. Huang D, Qian K, Fei D-Y, et al. Electroencephalography (EEG)-based brain–computer interface (BCI): A 2-D virtual wheelchair control based on event-related desynchronization/synchronization and state control. *IEEE Trans Neural Syst Rehabil Eng*. 2012;20(3):379–388.
73. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin Neurophysiol*. 1999;110(11):1842–1857.
74. Kübler A, Nijboer F, Mellinger J, et al. Patients with ALS can use sensorimotor rhythms to operate a brain-computer interface. *Neurology*. 2005;64(10):1775–1777.
75. Herron JA, Thompson MC, Brown T, et al. Chronic electrocorticography for sensing movement intention and closed-loop deep brain stimulation with wearable sensors in an essential tremor patient. *J Neurosurg*. 2017;127(3):580–587.
76. Kapadia N, Moineau B, Popovic MR. Functional electrical stimulation therapy for retraining reaching and grasping after spinal cord injury and stroke. *Front Neurosci*. 2020;14:718.
77. Popovic MR, Kapadia N, Zivanovic V, et al. Functional electrical stimulation therapy of voluntary grasping versus only conventional rehabilitation for patients with subacute incomplete tetraplegia: A randomized clinical trial. *Neurorehabil Neural Repair*. 2011;25(5):433–442.
78. Rzyman G, Szkopek J, Redlarski G, Palkowski A. Upper limb bionic orthoses: General overview and forecasting changes. *Appl Sci*. 2020;10(15):5323.
79. Sayegh F et al. *In: 2017 2nd International Conference on Bio-engineering for Smart Technologies (BioSMART)*. 1–4.
80. Peckham PH, Keith MW, Kilgore KL, et al.; Implantable Neuroprosthesis Research Group. Efficacy of an implanted neuroprosthesis for restoring hand grasp in tetraplegia: A multicenter study. *Arch Phys Med Rehabil*. 2001;82(10):1380–1388.
81. Collinger JL, Boninger ML, Bruns TM, et al. Functional priorities, assistive technology, and brain-computer interfaces after spinal cord injury. *J Rehabil Res Dev*. 2013;50(2):145–160.
82. Waldert S. Invasive vs. non-invasive neuronal signals for brain-machine interfaces: will one prevail? *Front Neurosci*. 2016;10:295.