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INVITED ARTICLE

Monkeys playing video games lead to a paralysed man walking

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Abstract

Spinal cord injury (SCI) frequently results in complete, permanent paralysis. Although it is possible to reverse the effects of incomplete paralysis, complete paralysis effects are permanent. At present, there is no cure for SCI, but engineers can bypass the spinal cord and restore the connection from the brain to the muscles through brain-machine or brain-computer interfaces (BMIs or BCIs). These experiments initially began with rodents and non-human primates (NHPs), which were trained to move cursors, joysticks or robots with their minds beginning in the 20th century. Research progressed to human clinical trials in the late 20th century. In this paper, I present the work done to train a new NHP model for behavioural experiments, how these NHPs were trained, and the neurophysiology involved in training BMI algorithms. With this knowledge, we then moved to non-invasive human clinical trials, in which eight SCI and six control subjects were able to control the opening and closing of their hands with a BCI system using electroencephalographic (EEG) signals from the motor cortex. Finally, we used these algorithms on a SCI subject in an invasive human clinical trial. The subject successfully completed activities of daily living (ADLs) and was able to control an ambulatory device that enabled him to walk upright. The overall accuracy for the BMI was approximately 90% for the upper extremity task and 85% for the lower extremity task. In addition, the subject improved in performance and speed on the Jebsen Hand Function Test (JHFT) during the 20 weeks of the study. Our subject was then sent home with a mechanical glove to continue performing upper-extremity ADLs in the home environment.

KEYWORDS
Brain Computer Interfaces (BCI), Neuroprosthetics, Functional Electrical Stimulation (FES), Reinforcement Learning, Marmoset behavioural neuroscience

INTRODUCTION

Paralysis results from damage in the connection between the brain and the muscles. The causes can include stroke, motor neurone diseases (MNDs), spinal cord injury (SCI), or other conditions. The neural pathways of persons suffering from paralysis are disconnected; their neurons and initially the muscles are intact, although over time the muscles become atrophied. Paralysis can be either complete or incomplete. Complete paralysis is usually irreversible. Currently, there is no cure for paralysis. Engineers deploy a new approach that bypasses the spinal cord and connects the nervous system with the muscles through a computer. This research falls within the broad category of brain-machine or brain-computer interfaces (BMIs or BCIs), also referred to as "thought-controlled robots''. In this paper, I discuss the progress of the research I have carried out from animal studies through algorithm development, non-invasive human trials, and finally an invasive human clinical trial that has-amazingly-enabled a paralysed man to walk.

BACKGROUND

A novel animal model for behavioural neuroscience: The first proof-of-concept animal research in this area began in the previous century.[1] It started with rodents and quickly progressed to non-human primates (NHPs).[2] Different experimental paradigms were designed to test BMIs on animals. Animal behavioural training relies on repetitive movements, encouraged by rewards (usually food pellets or juice rewards). These are often designed as video games, either on screens or with joysticks. In our first paper, we discussed a novel animal model for behavioural training.[3] This research focused on the common marmoset *(Callithrix jacchus)* as an NHP model instead of larger primates due to several key advantages. These include the lower risk of zoonotic diseases, the smaller size and the greater development of their visual and auditory cortex. The marmoset's smaller size offers the ability to reach deeper brain structures more easily than with larger primates, thus leading to significant interest in this animal model within the neuroscientific community.[3] Although our research has covered animal training for a variety of behavioural studies, our main focus has been BMI applications.

Brain-machine interfaces: BMIs have several components, as shown in Figure 1: data acquisition, signal processing, external device/actuator and feedback. The data acquisition block collects the neural data from the subject and pre-amplifies it before sending it to the signal processing block. The signal processing block is the hub of the BMI. It does all the filtering and feature extraction needed so that the algorithm can classify the signals or interpret the subject's intention. Next is the external device or the actuator. This can be a robotic arm, a joystick, a computer cursor or the subject's own arm, whatever the subject needs to control in order to carry out the task. The final component is the feedback provided; this can be audio-visual in nature or can be fed directly to the brain or to the algorithm itself. One challenge in BMIs is to give the feedback to the classification algorithm. In able-bodied persons, this signal is taken from the limbs and given as feedback. However, a paralysed person cannot move his or her limbs, leading to the need for a BMI system.

A biologically realistic BMI architecture: Different areas of the brain specializes in different types of learning: the cerebellum for supervised learning, which is guided by the error signal; the basal ganglia for reinforcement learning (RL), guided by the reward signal encoded in the dopaminergic input from the substantia nigra; and the cerebral cortex for unsupervised learning.[4] The Actor-Critic RL architecture was modelled after the perception-action-reward cycle (PARC) in the brain itself.[5,6] By using the motor cortex (MI) for the actor and a reward centre such as the nucleus accumbens (NAcc) for the critic, it can truly be an autonomous agent without the need for extensive training of the algorithm.[7] Several experiments with simulated data and NHP data were conducted to test the architecture. The simulated data from the motor cortex[6] and the NAcc[8] were used to demonstrate the proof of concept and the theoretical foundations. In our next research, we tested the NHP's ability to touch lights based on cues; based on the action, the NHP received a reward or no reward.[5] Extracting features from these neural data is also an important step in the BMI process.[9] In our subsequent paper, we showed how even amidst neural perturbations, this RL model could self-adjust and maintain its performance.[10] In these experiments, the computer cursor or a robot was moved by the NHP's thoughts rather than by the action of the hands. This process was later translated to a paralysed person who could think about completing an action and thereby execute that action without needing to move the limbs under volitional control.

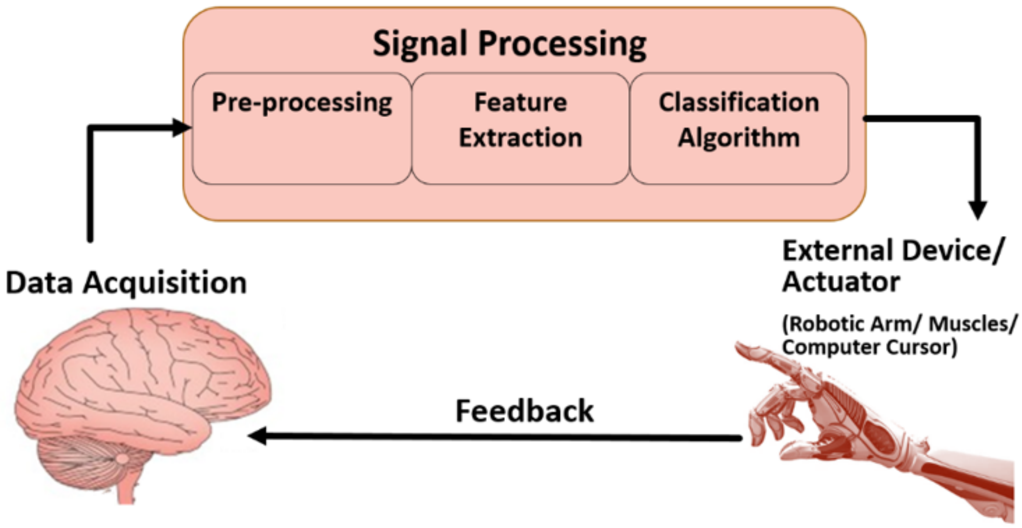

FIGURE 1 Brain-machine interface (BMI) system: data acquisition, signal processing, external device/actuator and feedback.

Application to humans: We next moved on to studying human subjects in a non-invasive manner. In 2018, we showed how we applied BMI with electroencephalographic (EEG) data for eight subjects with SCI and six control subjects.[11] Finally, in our most recent research, we were able to implant an SCI subject with two electrocorticography (ECoG) strips and could send him home to perform activities of daily living (ADLs).[12]

METHODS

Surgical Approach: The surgical approach determined prior to the surgery is shown in Figure 2A. The electrodes used in our research studies were 50µm in diameter and 16 such wires formed an array (Figure 2B). Two such arrays were implanted in the MI and NAcc of the NHP. Each monkey had a 16-channel tungsten, microelectrode array (Tucker Davis Technologies, Alachua, FL) implanted in the motor cortex, targeting the arm and hand areas and a second array in the striatum targeting the NAcc (Figure 2A). A craniotomy was opened over the motor area, and the dura was resected. The MI array placement was completed using stereotaxic coordinates and cortical mapping with a micropositioner (Kopf Instruments, Tujunga, CA). The NAcc array was positioned based on the target location selected prior to surgery (Figure 2A). The implant was secured using anchoring screws, one of which served as reference and ground. The craniotomies were sealed using Genta Cement (EMCMBV, Nijmegen, the Netherlands). Surgical anaesthesia was maintained using either isoflurane or constant rate ketamine infusion, steroids (dexamethasone) were used to minimize brain oedema and swelling, and analgesics (buprenorphine) and antibiotics (cefazolin, cephalexin) were administered postoperatively as prescribed by a veterinary surgeon. Figure 2C shows the NHP's head with the two implants and the surgeon's index and middle fingers (for scale).

Behavioural task for brain-machine interfaces: When we started using this animal model, very little research was available. Hence, our first paper[3] extensively discussed the animal husbandry, training, anaesthesia and the stereotaxic approach, and neurophysiology. The monkey was trained by means of a two-choice decision-making task (with a robot) in which it learned to move a robot arm to one of the two targets to receive a food reward. An audible "go" signal initiated the trials. Those trials in which the monkey either performed the wrong action or was not interacting with the task were removed from the analysis. The length of time to train, the number of trials and the neurophysiology are presented in the results section. During the experiments in which the animal controlled the robot with its thoughts (BMI control), the neural input was changed to test whether the algorithm would be able to maintain its performance. We removed 50% of the neurons in some experiments; in others, we added 50% more neurons. Both of these conditions were realistic, as new neuronal units could be picked up by existing electrodes and units can disappear too. In addition to units disappearing, the breaking of electrodes could also be represented this way (for example, we experienced half of the electrodes breaking, resulting in 50% less neuronal yield).

Non-invasive human experiments: Figure 3 shows the methodology for the EEG experiments. Figure 3A shows the experimental setup with the EEG, algorithm (on laptop) and functional electrical stimulation (FES) to initiate muscle movement. Continuous EEG signals were acquired in real time using a 20-channel wireless EEG system (B-Alert X24, Advanced Brain Monitoring, Carlsbad, CA) at a 256 Hz sampling rate and 16 bits of resolution. Electrodes were arranged on headstrips according to the international 10-20 standards and were referenced to mastoid electrodes.

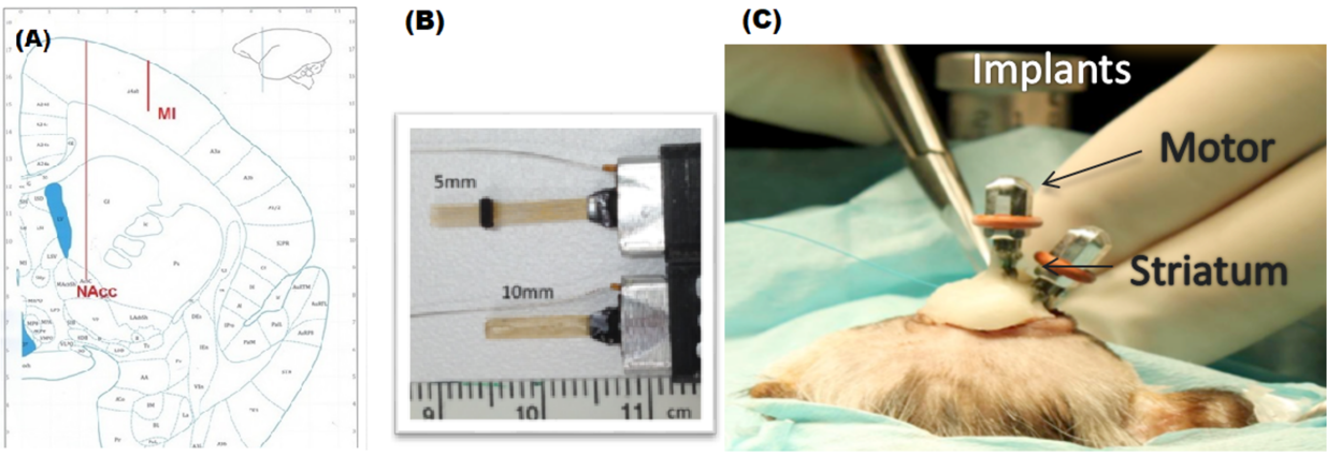

FIGURE 2 **(A) Surgical plan for Motor Cortex (MI) and Nucleus Accumbens (NAcc); (B) the electrodes that were implanted. (C) picture of the implants protruding from the NHP's head, next to surgeon fingers for scale.**

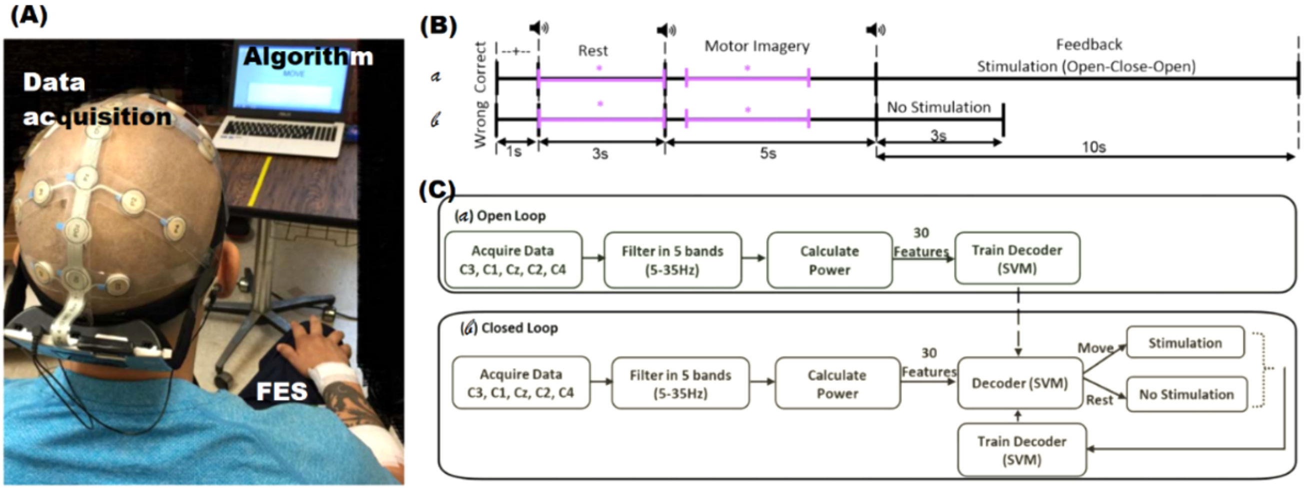

FIGURE 3 **(A) EEG experimental setup showing data acquisition, algorithm (on laptop) and the actuator (person's arm with FES electrodes);[11] (B) experimental timeline for correctly and wrongly interpreted trials;[11] (C) open-loop training and closed-loop prediction block diagram.[11]**

Corresponding sites on the head were abraded and cleaned with alcohol, and foam sensors were attached to the sensor sites using conductive electrode paste (Kustomer Kinetics, Arcadia, CA). Electrode impedances were verified to be less than 40 kΩ at the beginning and end of each session using the manufacturer-provided software. Signals were transmitted wirelessly from the headset to the computer via Bluetooth, and Matlab (MathWorks, Natick, MA) was used for processing and decoding. EEG signals were filtered using a fourth-order bandpass filter between 6 and 35 Hz before analysis.[11]

Figure 3B shows the timeline of the trials and Figure 3C shows the block diagram of the training and testing of the algorithm. A customized stimulation control paradigm that delivered stimulation to the muscles to enable the hand opening and closing necessary to complete a grasp-and-release task was developed. Surface electrodes were placed on the muscles to produce extension and flexion of the fingers. For extension, the active electrode was placed across the extensor, stimulating the extensor muscles for hand opening for 2 s, then stimulating the flexor muscles for hand closing for 3 s, and finally stimulating the extensor muscles again for hand opening for 2 s. Such a stimulation pattern can be used in a grasp-and-release task where stimulating the extensor muscles would enable the subject to position the hand around an object, stimulating the flexor muscles next would cause the hand to grasp the object, and stimulating the extensors again would cause the hand to open and release the object. Prior to running the BCI-FES experiments, muscle stimulation parameters were tested for each subject to produce maximum contraction of the target muscles without excessively fatiguing them. For this, we set the pulse duration at 200 µs and varied the current amplitude to obtain the desired muscle contraction. We used maximum current values of 15-35 mA for SCI subjects and 10-20 mA for control subjects.[11] During a period of 2 to 7 weeks, each subject participated in 6 experimental sessions lasting 2 to 3 hours each, with several breaks in between based on the subject's self-reported degree of fatigue. Here, subjects performed BCI-controlled FES of the dominant hand.

Invasive clinical trials: After sufficient screening of candidates from the EEG clinical trial, we moved on to invasive Electrocorticography (ECoG) implantation.[12] Our subject was a highly motivated 21-year-old male with a C5-C6 level motor complete SCI. He responded well to the EEG and FES treatment, so we moved to the next step of implanting two ECoG electrode strips above the hand and arm knob in the motor cortex as determined by functional magnetic resonance imaging (fMRI) (Figure 4A and 4B). The signals were transmitted wirelessly from the generator implanted under the clavicle. Thus, the system was completely internalized. The signals were decoded by the algorithm and fed back to the subject's paralysed hand by an FES orthosis. Figure 4C shows the experimental setup, which was similar to the EEG experimental setup in Figure 3A.

In addition to the experiments presented here, we wanted to test two additional questions: (i) whether the person would be able to use this setup for walking (Figure 4D) and if so, what changes would be required, and (ii) whether the person could use this system at home (Figure 4E). To use this system in the home environment, we changed the upper limb orthosis to a mechanical glove, thereby avoiding noise contamination in the ECoG due to FES stimulation. To test the person's ability to trigger walking with this system, extensive training on a tilt table was necessary, as he had not stood upright in years. In addition, since we implanted the electrodes in the hand and arm region, we asked the person to imagine moving his hand even when he wanted to walk.

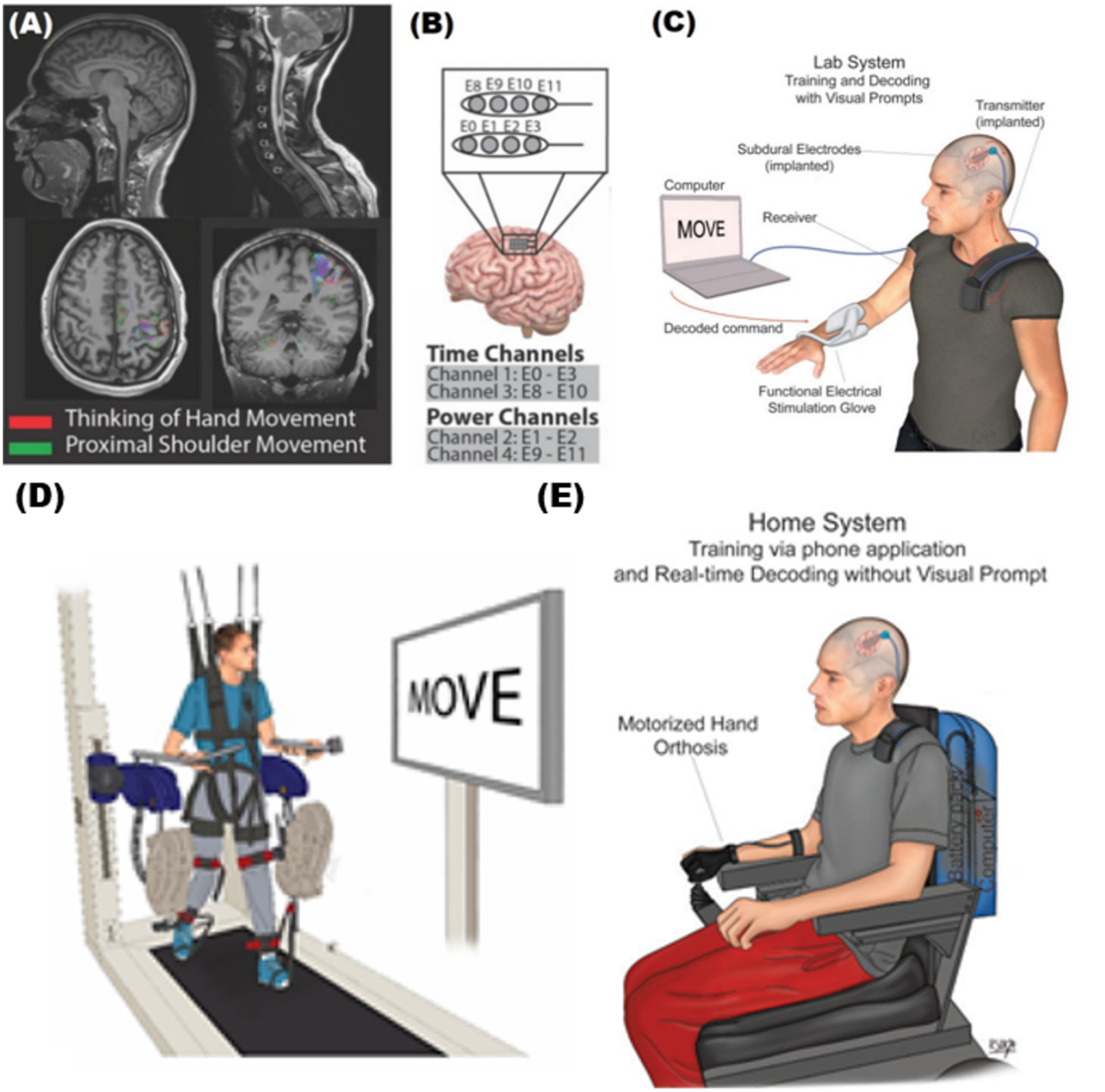

FIGURE 4 **(A) fMRI image showing the active areas during shoulder movement and thinking of hand movement;[12] (B) placement of ECoG channels and its configuration;[12] (C) laboratory setup;[12] (D) lower extremity experiment layout;[12] (E) home system.[12]**

RESULTS

Foundational work on BMI in NHPs: Animals were trained in pairs and electrode implantation neurosurgery was performed when the animals were fully trained. Neurophysiological recordings were pre-processed and used as input to the BMI algorithms. Much of the main research carried out in terms of algorithms was in the area of RL. RL-based BMI systems can maintain their output without intervention by an external agent, thus making them truly autonomous. Figure 5A shows the spike raster plot showing the 50% loss and gain of neurons. Figure 5B shows the offline performance of the system. Even though there were perturbations and a drop in performance, the system was able to correct itself and bring the performance up to acceptable levels. The insets in Figure 5B show the comparison of RL with other approaches (in this case, static decoders). The dashed lines show that the static decoders were not able to increase the performance after perturbations. DU and PR represent data from two animals.

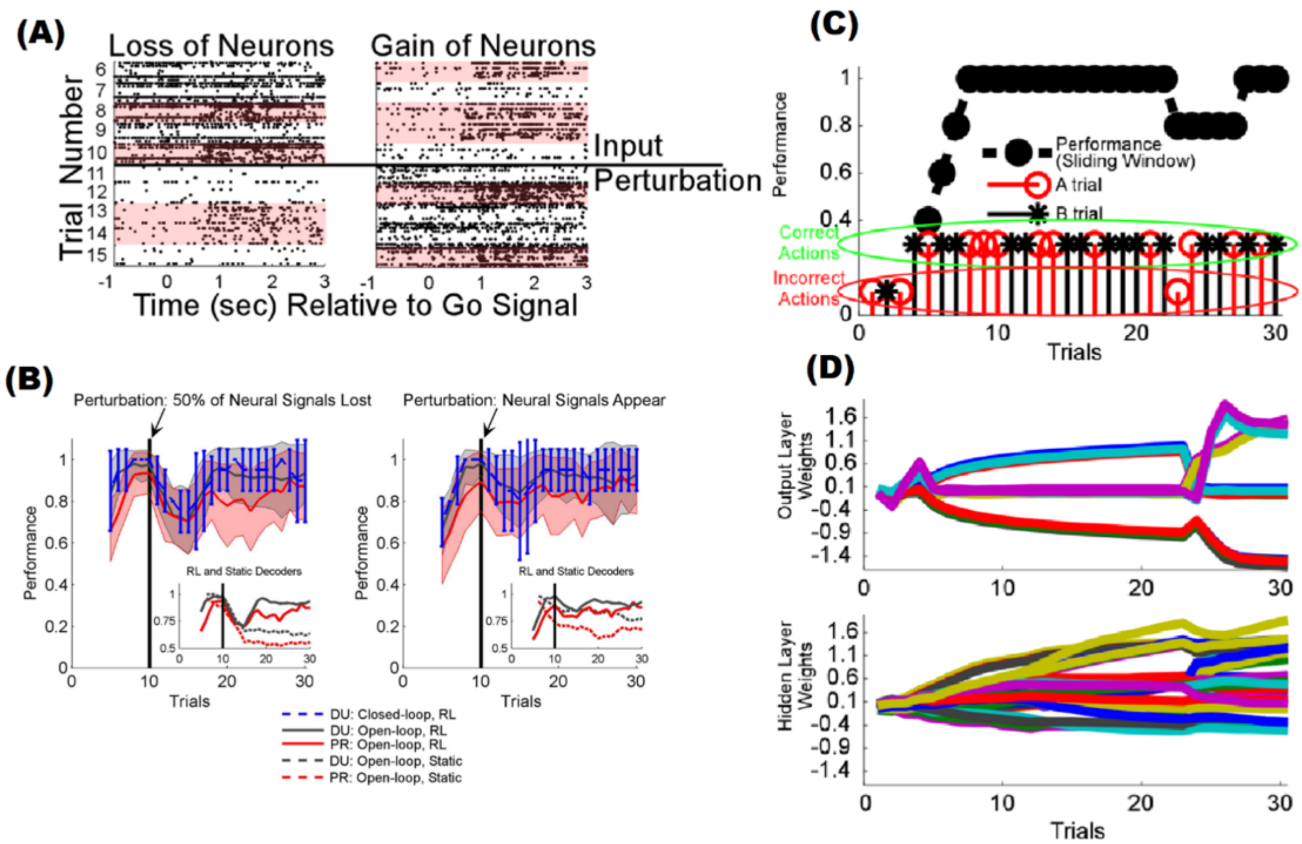

FIGURE 5 **(A) Spike raster plot showing neuron loss and gain halfway through the experiment.[10] (B) The offline performance over time as inputs drop or appear. The inset shows the comparison with static algorithms; DU and PR represent two animals.[10] (C) The online performance when inputs dropped.[10] (D) How the parameters of the algorithm (weights) were adjusted to produce the best outcome.[10]**

Figure 5C shows the trial-by-trial performance during an online experiment in which perturbations were given at trial 20. Similar to the offline experiments, we could notice a drop in performance. However, unlike the static decoders, RL was able to increase its performance within a few trials. Figure 5D shows the parameters (weights) of the RL algorithm. The fluctuations soon after trial 20 indicate the algorithm correcting itself (its weights) in order to maintain its performance. Algorithm was able to maintain its performance, without external intervention.

Human experiments (non-invasive): With the non-invasive EEG experiments using eight SCI and six control subjects over the entire duration of training, the overall accuracy ranged from 70%-100%. No statistical difference was found between SCI and control groups (alpha = 0.05). These results were verified offline as well.

Human experiments (invasive): Figure 6 shows the results from the invasive clinical trials. Figure 6A-C shows the performance on the upper extremity task. We started at 55% accuracy on a naive classification algorithm and achieved 90% accuracy on the same day. Over a period of 10 weeks, the BMI maintained 89% accuracy (Figure 6A). The subject was extremely motivated and asked us to make the tasks even more challenging. He increased his performance and speed on the Jebsen Hand Function Test (JHFT) during the 20 weeks of the study (Figure 6B). His handwriting samples, shown in the figure, illustrate how his fluidity improved from week 9 to week 29 (Figure 6C). Figure 6D presents the overall performance on the lower extremity task (i.e., walking). In this case, the variance was higher; however, we observed that the subject was able to use the BMI to trigger gait cycles successfully (sometimes even with 100% accuracy).

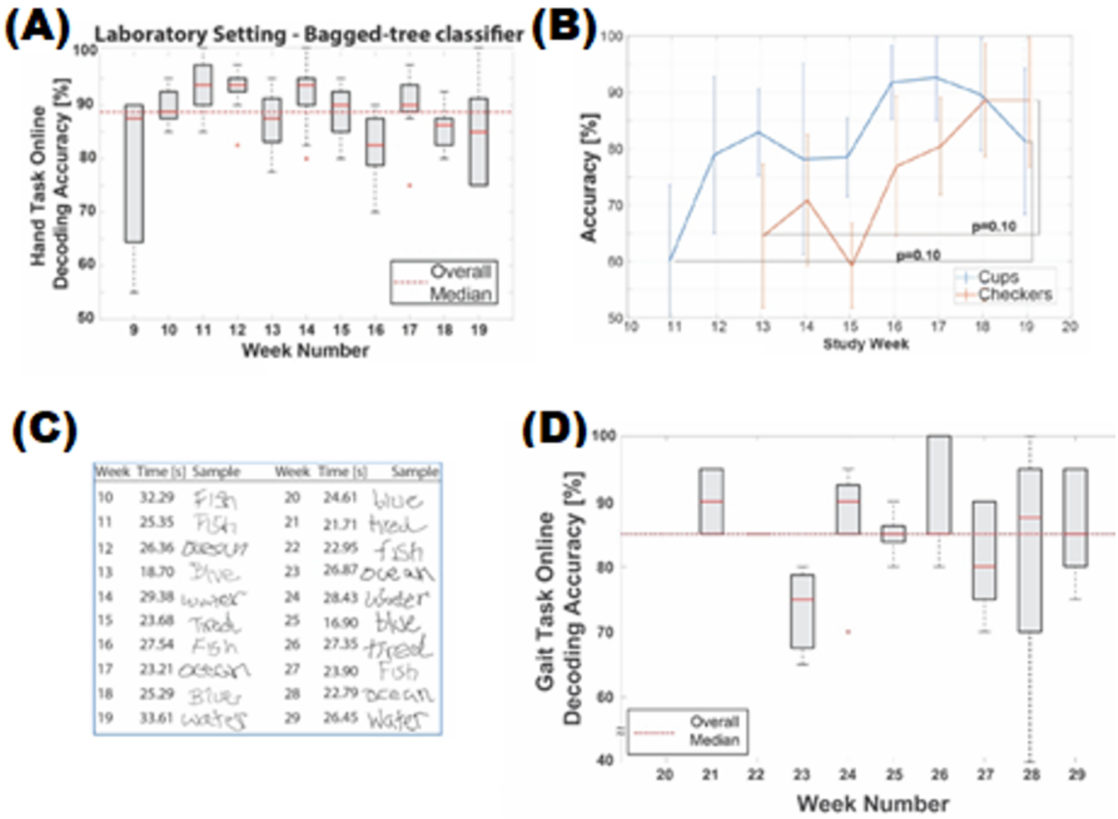

FIGURE 6 **Algorithm accuracy during the real-time experiments;[12] (A) upper extremity task; (B) task accuracy when moving a cup and a piece of checkers;[12] (C) the subject' handwriting;[12] (D) lower extremity task (walking).**

DISCUSSION AND CONCLUSIONS

The first human BMI clinical trials were approved as early as 1998 for a patient with amyotrophic lateral sclerosis (ALS). Using cortical local field potentials (LFPs), researchers demonstrated a proof of concept of the ability to control a cursor in two-dimensional space.[14] Prior to that, NHP neural data were collected while the subjects were playing video games in order to develop algorithms and test other aspects of the BMI, including tissue responses and longevity of the electrodes. In 2018, we applied this work invasively to a C5-C6 SCI subject so that he could control the use of his own upper and lower extremities, and in 2021 he was able to go home with the upper extremity device[12] and complete ADLs independently.

As suggested by the title of this paper, we conducted some gait experiments to help the subject walk again. Initial steps involved training the subject on a tilt table and helping his body become accustomed to the idea of being upright, since he had not walked or stood upright for over 5 years. After 10 weeks of upper extremity experiments, we used the same algorithms to put him on a gait system (Figure 4D) where he could control the BMI by thinking about moving and could maintain his performance. Very few studies have been conducted on brain-controlled walking, as this task entails numerous challenges, including ensuring the subject's safety and decoder challenges due to additional noise in the data.[15] However, at the end of the clinical trial, the subject was more interested in pursuing the upper extremity tasks at home.[16] This was one reason why we did not pursue the lower extremity tasks further.

The algorithms themselves can be further improved to provide more autonomy to the subject. The system with which the subject went home was a self-paced system. This meant that at any time the subject could volitionally open and close his hands, provided that the system was on. However, there is room for further improvement in the speed of control and speed of the algorithm to enable smooth control of the system. At present, the system is turned on manually now done by the subject (supplementary videos[12]). This system can be further improved to be turned on from the subject's thoughts.

We have shown how EEG experiments can be implemented for SCI subjects. There are many other therapeutic applications in neurology for which these algorithms and similar systems could be utilized. Currently we have an ongoing clinical trial (partially funded by an Association of Sri Lankan Neurologists (ASN) grant) to apply BCI for stroke rehabilitation at Teaching

Hospital, Karapitiya. The therapy for the hand is controlled by the subject's own volition through the BCI rather than by passive movements directed by a therapist.

The results here demonstrated that a fully implanted BCI can be safely and reliably used to decode movement intent from the motor cortex, allowing for volitional control of the hand by a patient with SCI in laboratory and home environments. In closed-loop experiments, movement intent was decoded from real-time ECoG recordings obtained by placing electrodes on the hand/arm motor cortex, and the output from the classification algorithm was used to trigger an external assistive device with a high degree of accuracy. The decoder's performance has remained stable for the 22 months since initial device implantation, with median accuracy around 90%. Unlike many other cases which have a pedestal protruding from the patient's skull, our system was completely internalized.

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REFERENCES

1. Lebedev MA, Nicolelis MA. Brain-machine interfaces: past, present and future. *Trends Neurosci*. 2006; 29(9): 536-46. doi: 10.1016/j.tins.2006.07.004.

2. Carmena JM, Lebedev MA, Crist RE, et al. Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS Biol*. 2003;1(2): e42. doi: 10.1371/journal.pbio.0000042.

3. Prins NW, Pohlmeyer EA, Debnath S, et al. Common marmoset (Callithrix jacchus) as a primate model for behavioral neuroscience studies. *J Neurosci Methods*. 2017;284:35-46. doi: 10.1016/j.jneumeth.2017.04.004.

4. Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. *Curr Opin Neurobiol*. 2000;10(6): 732-9. doi: 10.1016/s0959-4388(00)00153-7.

5. Pohlmeyer EA, Mahmoudi B, Geng S, et al. Brain-machine interface control of a robot arm using actor-critic rainforcement learning. *Annu Int Conf IEEE Eng Med Biol Soc*. 2012;4108-11. doi: 10.1109/EMBC.2012.6346870.

6. Prins NW, Sanchez JC, Prasad A. A confidence metric for using neurobiological feedback in actor-critic reinforcement learning based brain-machine interfaces. *Front Neurosci*.2014;8:111. doi: 10.3389/fnins.2014.00111.

7. Mahmoudi B, Pohlmeyer EA, Prins NW, et al. Towards autonomous neuroprosthetic control using Hebbian reinforcement learning. *J Neural Eng*. 2013;10(6):066005. doi: 10.1088/1741-2560/10/6/066005.

8. Prins NW, Sanchez JC, Prasad A. Feedback for reinforcement learning based brain-machine interfaces using confidence metrics. *J Neural Eng*. 2017;14(3):036016. doi: 10.1088/1741-2552/aa6317.

9. Prins NW, Geng S, Pohlmeyer EA, et al. Feature extraction and unsupervised classification of neural population reward signals for reinforcement based BMI. *Annu Int Conf IEEE Eng Med Biol Soc*. 2013;5250-3. doi: 10.1109/EMBC.2013.6610733.

10. Pohlmeyer E, Mahmoudi B, Geng S, et al. Using Reinforcement Learning to Provide Stable Brain-Machine Interface Control. *PLoS One*. 2014;9(1):e87253. doi: 10.1371/journal. pone. 0087253.

11. 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. doi: 10.1088/2057-1976/aabb13.

12. Cajigas I, Davis KC, Meschede-Krasa, et al. Implantable brain-computer interface for neuroprosthetic-enabled volitional hand grasp restoration in spinal cord injury. *Brain Commun*. 2021; 3(4):fcab248. doi: 10.1093/braincomms/fcab248.

13. Prins NW, Geng S, Pohlmeyer EA, et al. Representation of natural arm and robotic arm movement in the striatum of a marmoset engaged in a two choice task. 2013 6th International IEEE/EMBS Conference on Neural Engineering (NER) 2013; 399-402. doi: 10.1109/NER.2013.6695956.

14. Kennedy PR, Kirby MT, Moore MM, et al. Computer control using human intracortical local field potentials. *IEEE Trans Neural Syst Rehabil Eng*. 2004;12(3):339-44. doi: 10.1109/TNSRE.2004.834629.

15. 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):1112-22. doi: 10.1016/S1474-4422(19)30321-7.

16. Davis KC, Meschede-Krasa B, Cajigas I, et al. Design-development of an at-home modular brain-computer interface (BCI) platform in a case study of cervical spinal cord injury. *J Neuroeng Rehabil*. 2022;19(1):53. doi: 10.1186/s12984-022-01026-2.