High-performance neuroprosthetic control by an individual with tetraplegia

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Summary

Background **Paralysis or amputation of an arm results in the loss of the ability to orient the hand and grasp, manipulate, and carry objects, functions that are essential for activities of daily living. Brain–machine interfaces could provide a solution to restoring many of these lost functions. We therefore tested whether an individual with tetraplegia could rapidly achieve neurological control of a high-performance prosthetic limb using this type of an interface.**

Methods **We implanted two 96-channel intracortical microelectrodes in the motor cortex of a 52-year-old individual with tetraplegia. Brain–machine-interface training was done for 13 weeks with the goal of controlling an anthropomorphic prosthetic limb with seven degrees of freedom (three-dimensional translation, three-dimensional orientation, one-dimensional grasping). The participant's ability to control the prosthetic limb was assessed with clinical measures of upper limb function. This study is registered with ClinicalTrials.gov, NCT01364480.**

Findings **The participant was able to move the prosthetic limb freely in the three-dimensional workspace on the second day of training. After 13 weeks, robust seven-dimensional movements were performed routinely. Mean success rate on target-based reaching tasks was 91·6% (SD 4·4) versus median chance level 6·2% (95% CI 2·0–15·3). Improvements were seen in completion time (decreased from a mean of 148 s [SD 60] to 112 s [6]) and path efficiency (increased from 0·30 [0·04] to 0·38 [0·02]). The participant was also able to use the prosthetic limb to do skilful and coordinated reach and grasp movements that resulted in clinically significant gains in tests of upper limb function. No adverse events were reported.**

Interpretation **With continued development of neuroprosthetic limbs, individuals with long-term paralysis could recover the natural and intuitive command signals for hand placement, orientation, and reaching, allowing them to perform activities of daily living.**

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Introduction

Brain–machine interfaces transform neural activity into control signals for an external device. Functional electrical stimulators, exoskeletons, and sophisticated prosthetic limbs are being developed with the goal of restoring natural function. For many activities of daily living, an individual needs to be able to position the hand in space, orient the palm, and grasp an object. These hand movements are normally smoothly coordinated and follow the general principles of natural movement.[1–3] Ideally a brain–machine interface will translate neural activity into control of an external device with the capability of producing natural movements in accordance with the general principles.

The natural features of movement have been captured in recordings of motor cortical neural activity using intracortical microelectrodes in a study in non-human primates.[4] In other animal studies, a robot arm was controlled in four dimensions for self-feeding tasks[5] and in seven dimensions for orientation and grasping.[6] Motor cortical activity has also been used to electrically activate paralysed muscles of the upper limb.[7,8] Results of studies in people have shown three-dimensional translational control,[9–11] and control over a single grasping dimension.[12] We therefore tested whether an individual with tetraplegia could rapidly achieve control of a state-of-the-art anthropomorphic prosthetic limb (modular prosthetic limb [MPL], Johns Hopkins University, Applied Physics Laboratory, Baltimore, MD, USA).

Methods

Participant

The participant was a 52-year-old woman who was diagnosed with spinocerebellar degeneration 13 years before she took part in this study. Thorough chart review and discussions with her neurologist showed no indication of cerebellar involvement. The participant's injury was motor complete with manual muscle test scores 0 of 5 for the upper limb.[13] Physical examination showed that she had generally intact sensation with some hypersensitivity.

This study was approved by the institutional review boards at the University of Pittsburgh (Pittsburgh, PA, USA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA, USA). We obtained verbal informed consent from the woman before her participation in the study; consent was signed by her legal representative.

Array implantation

We implanted two intracortical microelectrode arrays (4 mm × 4 mm, Blackrock Microsystems, Salt Lake City, UT, USA), about 14 mm apart, each with 96-electrode shanks (length 1·5 mm) in the participant's left motor cortex on Feb 10, 2012, using stereotactic image guidance (Brainlab, Westchester, IL, USA) with structural (MRI) and functional imaging (fMRI) to guide placement (figure 1A). The prosthetic arm was mounted on a stand next to the participant. Two cables ran from connectors on the participant's head to the recording apparatus and another cable ran from the computer to the prosthetic arm.

Neural recording

See Online for appendix

Generally, we recorded neural signals three times per week for 13 weeks; each session was about 4 h. The signals were recorded with the NeuroPort data acquisition system (Blackrock Microsystems). Single-unit and multi-unit events were classified with manually set thresholds and time-amplitude windows. Daily setup time, including unit sorting, took about 30 min. The neural activity was converted to a firing rate in 30 ms bins and low pass-filtered using an exponential smoothing function with a 450 ms window.

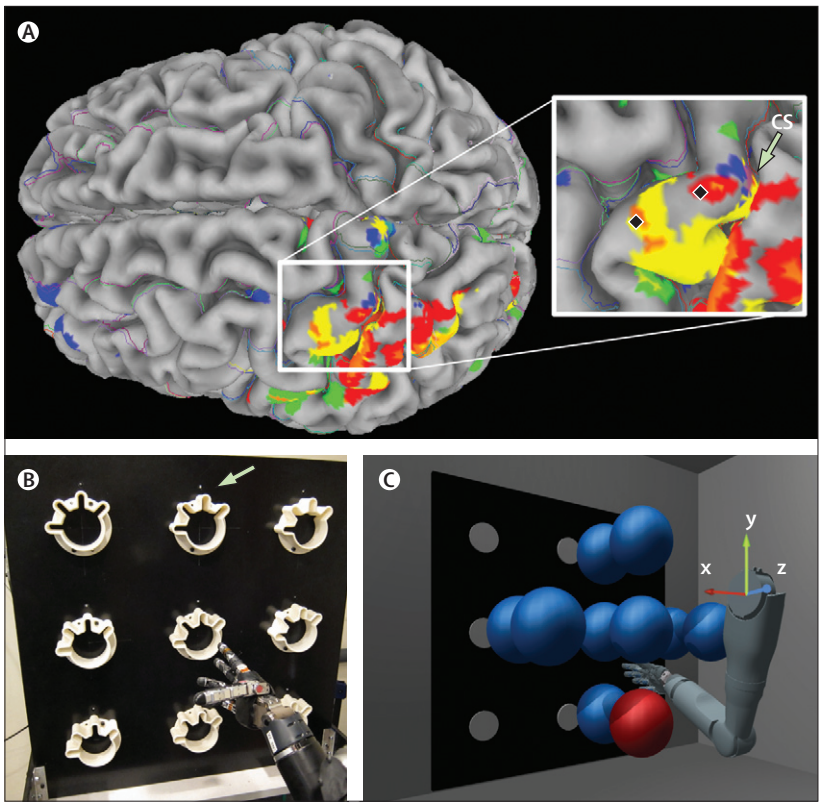

Figure 1: **Array location and setup of experiment**
(A) Preoperative functional MRI activation maps of a participant-specific brain model during video-guided attempted movement. The colours in the activation maps represent blood-oxygenation-dependent activities during video-guided attempted movements—yellow is sequential finger flexion, red hand grasping, blue shoulder shrug, and green lip pursing. Approximate array locations are shown as black squares on the inset figure. (B) MPL and seven-dimensional sequence task setup. The participant was not presented with physical targets, instead light-emitting diodes (indicated by the arrow) were used to instruct the participant to hit the near (0·35 m from the shoulder) or far (0·52 m from the shoulder) translation target corresponding to one of the white circles on the board in front of the MPL. Orientation and grasp targets were presented by a computer-generated verbal command. (C) Diagram of the MPL and translation targets (red and blue spheres) for the seven-dimensional sequence task. The red sphere illustrates the single target of an example trial. The MPL coordinate system (red, green, and blue arrows labelled x, y, and z, respectively) is shown centred at the shoulder. Translation targets had an 8 cm radius and the MPL endpoint (centre of the palm) had to be within this region for a successful trial. The MPL endpoint also had to be within the translation target success region to successfully achieve the orientation (±15°) and grasp the targets that were given as audio cues. The timeout was set to 10 s. CS=central sulcus. MPL=modular prosthetic limb.

Observation-based calibration and neural decoding

Brain–machine-interface training progressed from three-dimensional endpoint translation control (weeks 2 and 3 after implantation), to four-dimensional control of translation and grasp (week 4), to seven-dimensional control of translation, orientation, and grasp (weeks 5–14). Joint angles of the fingers and thumb of the MPL were combined into a single dimension. The neural decoder, based on a model that linearly related neural firing rate to movement velocity (equation 1),[6,14] was calibrated daily with a two-phase calibration similar to the methods used in studies of non-human primates.[5,6]

During the observation phase, the MPL moved automatically, driven by a proportional controller, to targets that spanned the reachable workspace of the arm as part of a seven-dimensional sequence task. In this task, a target was indicated by a light-emitting diode on a board in the frontal plane (80 cm × 80 cm), 70 cm in front of the MPL shoulder (figure 1B). Once the MPL was moved to the correct three-dimensional position, computer-generated verbal prompts described an orientation to be performed by rotating the palm in one of six directions or a grasp target (open or closed hand). Possible orientations included pronation–supination (±45°), ulnar–radial deviation (±20°), and flexion–extension (±45°) of the wrist. The participant was instructed to carefully watch the limb as it moved automatically to the targets. Neural data and information about the MPL state—endpoint position, joint angles, and joint torque—were recorded at a rate of 33 Hz. We gathered data from 80 trials (6 min) of the seven-dimensional sequence task to train the initial observation-based seven-dimensional neural decoder. Equation 1 was used to relate the activity of each unit to MPL movement velocity,[6,14]

$$f = b_0 + b_x v_x + b_y v_y + b_z v_z + b_{\theta x} v_{\theta x} + b_{\theta y} v_{\theta y} + b_{\theta z} v_{\theta z} + b_g v_g$$

where f is the firing rate of a unit during movement described by the seven-dimensional velocity vector V (v_x, v_y, v_z, $v_{\theta x}$, $v_{\theta y}$, $v_{\theta z}$, and v_g), and the coefficients for each unit are b_0, b_x, b_y, b_z, $b_{\theta x}$, $b_{\theta y}$, $b_{\theta z}$, and b_g. V consists of the coordinates for the three-dimensional endpoint translation (x, y, and z), three-dimensional orientation (θx, θy, and θz), and one-dimensional grasp (g) velocities. Units that did not fit the model ($R^2 \leq 0 \cdot 1$) were excluded. Indirect optimal linear estimation[15] with ridge regression[16] was used for the coefficient matrix B (appendix).

During a second phase of calibration, the participant controlled the MPL using the observation-based neural decoder while orthoimpedance was applied to the command signal.[5] In this phase, orthoimpedance attenuated the brain-command component perpendicular to the ideal seven-dimensional trajectory by 100%, restricting movements to directions directly toward or away from the target. Data from 80 trials of the seven-dimensional sequence task gathered during the second phase of calibration were used to build the final decoder with optimal linear estimation as described above. This second round of calibration allowed the participant to actively engage in the task, while minimising errors and corrective movements. Calibration was done daily and took about 15 min. Early in the experiment (weeks 2–4), similar calibration procedures were used to generate lower-dimensional neural decoders. Although this report is a communication of the seven-degrees-of-freedom study, it should be noted that the participant was able to move the MPL in the three-translational dimensions of the workspace, without computer assistance, on the second day of the recording experiments (week 2 after the implant).

Target-based brain-control task

After completing the calibration, we used the seven-dimensional sequence task for brain–machine-interface testing. The computer randomly selected targets from a possible combination of ten translation, seven orientation, and two grasp targets. Endpoint velocities derived from the recorded neural firing rates were sent from the computer to the MPL controller, which converted them to joint motor commands every 20 ms. As with calibration, a translation target was specified by a light-emitting diode and then an orientation or grasp target was announced by a computer-generated voice. The participant had control of all seven dimensions (translation, orientation, and grasp) throughout the task.

Orthoimpedance was adjusted throughout the initial learning phase of the task (up to day 66). In this phase, computer-assisted stabilisation was also used.[5,6] Stabilising control blended an ideal endpoint velocity control signal determined by the proportional MPL controller with the control signal derived from the participant's brain activity. The contributions of each signal were specified by the experimenter. Stabilising control was only applied to domains that were not being actively controlled—ie, the position was stabilised at a specified percentage (10–100%) during the orientation phase or orientation and grasp posture were stabilised during translation. Similarly, the experimenter could also specify the percentage of orthoimpedance. The experimenter adjusted both forms of computer assistance subjectively to keep the participant engaged and motivated with the aim of maintaining a 60–80% success rate. Importantly, after week 10 (day 66), the participant did all tasks without computer assistance. A maximum movement time of 10 s was enforced for each trial phase (translation, orientation, or grasp).

Performance metrics (success rate, completion time, and path efficiency) were calculated during the test sessions. Success was determined by MPL kinematics recorded in real time. All seven dimensions were controlled continually and had to be correct during all three phases of movement for a trial to be judged a success. The experimenter could also manually mark a trial as being successful (or unsuccessful) if the participant rotated too far in the specified direction or if mechanical limitations of the MPL prevented movement along one dimension. The probability of completing the task by chance was ascertained with random-walk signals as input to the assist parameters (if any) and target sizes used

	Day 80	Day 81	Day 84	Day 87	Day 88	Day 95	Day 98
Item							
Block, 10·0 cm × 10·0 cm × 10·0 cm	17·9	..	18·4	12·1	10·9	15·6	7·3
Block, 2·5 cm × 2·5 cm × 2·5 cm	15·0	16·1	12·7	10·2	67·0	8·1	..
Block, 5·0 cm × 5·0 cm × 5·0 cm	18·3	17·8	10·4	7·7	10·5	8·5	14·0
Block, 7·5 cm × 7·5 cm × 7·5 cm	15·6	19·8	12·8	11·2	8·0	16·1	9·0
Ball, diameter 7·5 cm	..	18·3	9·4	8·4	19·7	26·8	9·9
Stone, 10·0 cm × 2·5 cm × 1·0 cm	21·4	12·7	50·9	10·2	28·0	56·2	..
Pour water from one glass to another*	..	..	..	..	..	..	..
Tube, 2·5 cm × 16·0 cm	29·4	..	50·1	8·2	17·1	10·4	26·2
Tube, 1·0 cm × 16·0 cm	..	16·3	..	7·8	9·5	9·0	9·3
Mean time per item (SD)	19·6 (5·3)	16·8 (2·4)	23·5 (18·6)	9·5 (1·7)	21·3 (19·6)	18·8 (16·3)	12·6 (7·0)
Total score (of a possible 27)	15	15	16	17	17	17	15

*During the scoring sessions, the participant was not able to fully complete the task that required pouring water from one glass to another and setting the glass back down on the table; typically the water (simulated as a paper ball) would miss the cup, or the cup would tip over when it was set back down; the participant was able to complete the task twice in practice trials.

Table 1: **Completion times (s) and total scores in the action research arm test**

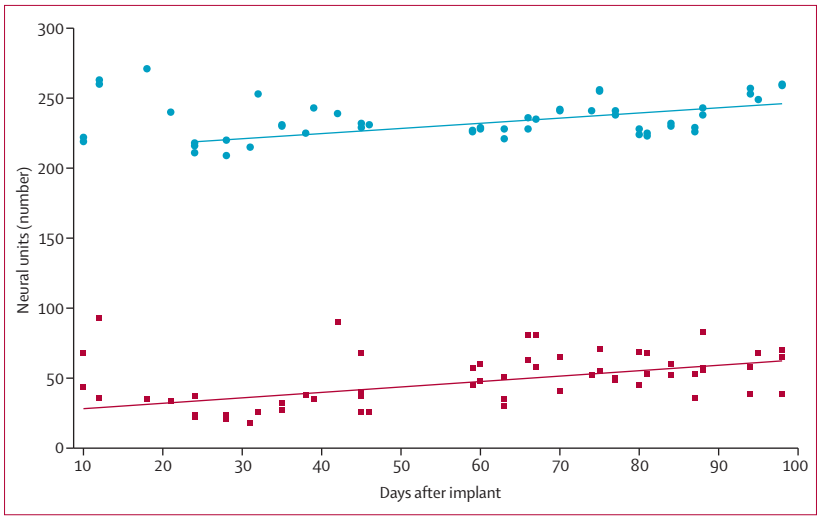

Figure 2: **Neural units during the days after the implant**
The blue dots represent the number of neural units recorded during brain–machine-interface sessions done 10–98 days after the implant. The red squares represent the neural units tuned to movement velocity with R^2>0·1 (equation 1). For reference, four-dimensional training began on day 24 and seven-dimensional training on day 32.

during the experiment. 200 simulations were run per trial and the median daily chance levels from these simulations are reported. For each trial, path efficiency was computed for each control domain with equation 2,

$$\frac{L_{OT}}{L_{BCT}}$$

where L_{OT} is the length of the optimal trajectory from the starting position to the end target location and L_{BCT} is the length of the brain-controlled trajectory for a particular trial; each was calculated in three domains—translation (m), orientation (rad), and grasping (arbitrary units). L_{BCT} was calculated by numerical integration of the magnitude of the velocity vector V for the duration of one trial.

Functional brain-control tasks

The participant used the MPL under full brain control to do nine tasks (selected from 19 possible tasks, appendix) on the action research arm test (ARAT), which is an

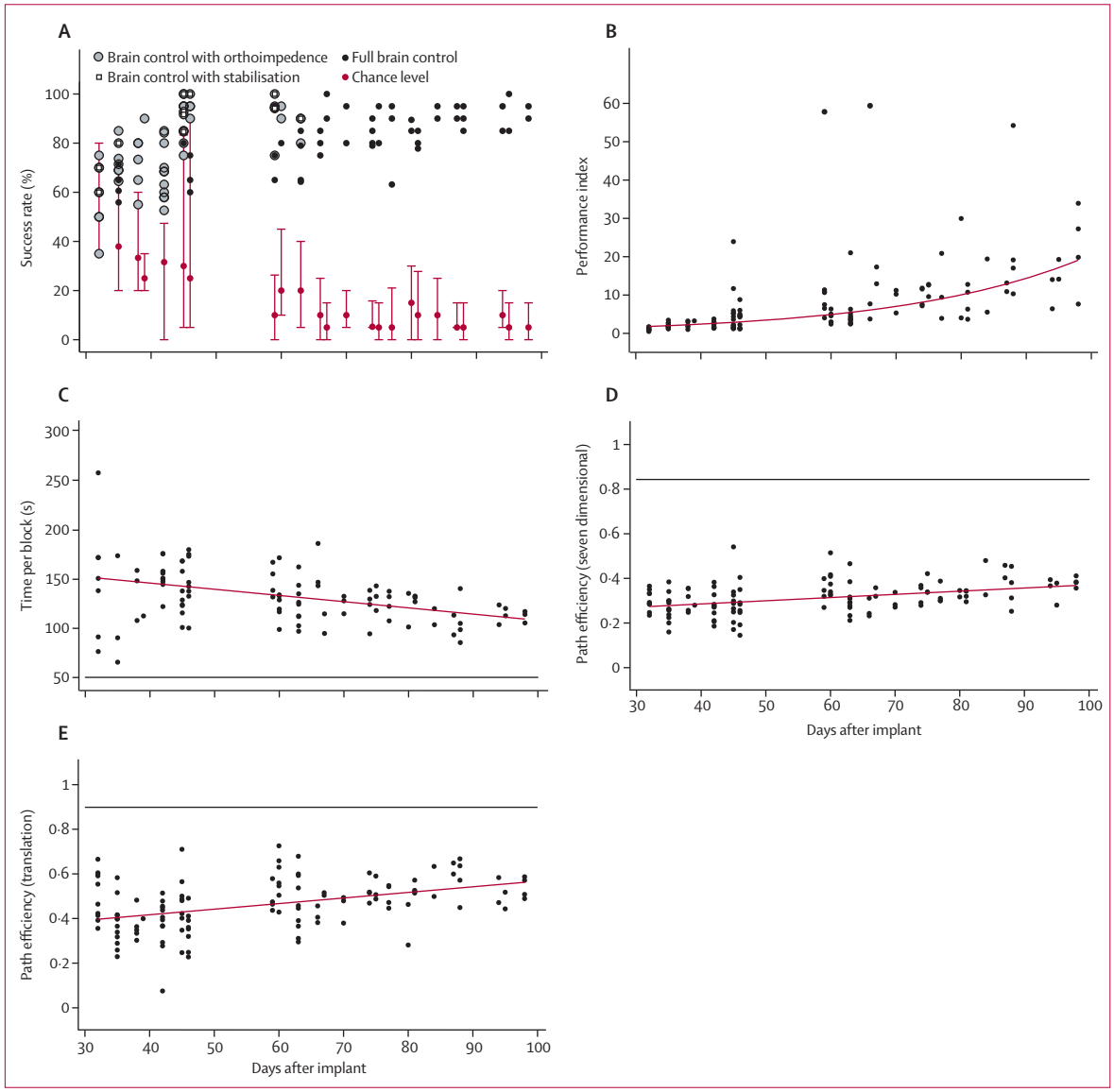

Figure 3: **Summary of seven-dimensional brain-control performance**

(A) Participant's success rate on the seven-dimensional sequence task for each block of 20 trials of brain-control training. The red dots with error bars represent the median chance and 95% CI, respectively, calculated from 200 simulations per trial. (B) Normalised performance index for each day of the seven-dimensional brain control. For each block of 20 trials, the success rate was normalised to the median chance level. (C) Block completion time, excluding the presentation phase time. (D) Mean seven-dimensional path efficiency of the MPL under brain control. (E) Path efficiency for three-dimensional translation during the seven-dimensional sequence task. Only successful trials were included in the calculation of path efficiency. For parts C–E, each dot represents the mean block time or path efficiency for one block of 20 trials of the seven-dimensional sequence task completed by the participant. Linear fits to the participant's data are shown as a red line. The mean block time or path efficiency of the MPL under autocontrol is shown as a solid horizontal black line. MPL=modular prosthetic limb.

assessment of the unilateral upper limb function used commonly in patients who have had a stroke.[17] ARAT is psychometrically sound and tracks the ability of an individual to undertake activities of daily living. The selected tests include all six items from the grasp subscale and three of four items from the grip subscale (table 1). Standard administration procedures[18] were followed with a few modifications. One of the items was a ball, which was positioned inside a loose coil of wire to keep it from rolling off the table, although it was still possible for the participant to bump the ball hard enough to roll outside the wire coil. The MPL hand started about 12 cm from the table surface, with the palm facing towards the left instead of on the table. Each test item was timed and scored as 0 (no movement possible), 1 (task partly done), 2 (task done, but not correctly), or 3 (task done correctly). Movements that required more than 5 s to complete were scored as 2. The participant attempted each assessment three times and was instructed that only the best score counted. This method was designed to keep her motivated and open to trying new strategies.

The participant also did a cone-stacking task—moving three plastic cones (height 30 cm, diameter 4·1–6·4 cm) from a base and stacking them sequentially on a second base located at a distance of 30 cm. The time to complete the task and the number of drops were recorded for each attempt. This test was a measure of the participant's ability to grasp, transport, and position objects with precision.

This study is registered with ClinicalTrials.gov, NCT01364480.

Role of the funding source

The sponsors of this study had no role in study design, data gathering, analysis, and interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

The arrays were implanted on Feb 10, 2012, and the first day of testing was on Feb 20, 2012. The last day of testing was May 18, 2012. The range of recorded single-unit and multi-unit neural activity was from 209 units per day to 271 units per day (figure 2). There seemed to be an initial settling period during which the number of units started off high until day 21 after the implant and then fell in week 4 (day 24). Starting at day 24, the neural activity began to increase linearly at a rate of 0·368 units per day or 2·58 units per week ($y=0·368x+210·0$, where x is the number of days after implant, $R^2=0·356$, $p<0·0001$; figure 2). The neural activity tuned to movement velocity with an $R^2>0·1$ (equation 1) increased linearly with time for the duration of the recording at a rate of 0·388 units per day or 2·72 units per week ($y=0·388x+24·3$, $R^2=0·155$, $p=0·0097$; figure 2).

Figure 3A shows the participant's success rate in both computer-assisted and full-brain control trials during all 24 sessions of testing of the seven-dimensional sequence task, and the chance level for each day. Orthoimpedance and stabilising computer assistance were only used until week 10 (day 66). After day 66 following the implant, all performance data (seven dimensional) were gathered with full brain control without computer assistance. We did not do any MPL testing on days 52–58. The participant's performance improved during the 34 sessions over 13 weeks of training. During the last 2 weeks of training, without computer assistance, the participant achieved a mean success rate of 91·6% (SD 4·4) and a median chance level of 6·2% (95% CI 2·0–15·3) calculated by use of simulations with random-walk data as an input signal. The mean success rate at the beginning of the trial was 76·0% (SD 14·9) with a median chance level of 36·7% (95% CI 12·9–72·8).

Figure 3B shows the normalised performance index (success rate/chance level) for the duration of training. The participant's performance increased exponentially with time even as the difficulty of the task increased ($y=1·812e^{0·04(x-32)}$, $R^2=0·114$, $p=0·001$).

The participant also showed improved MPL control—reduced block completion time (figure 3C) and increased path efficiency (figure 3D, E). Block completion time decreased linearly from a mean of 148 s (SD 60) to 112 s (6) during the seven-dimensional training and became less

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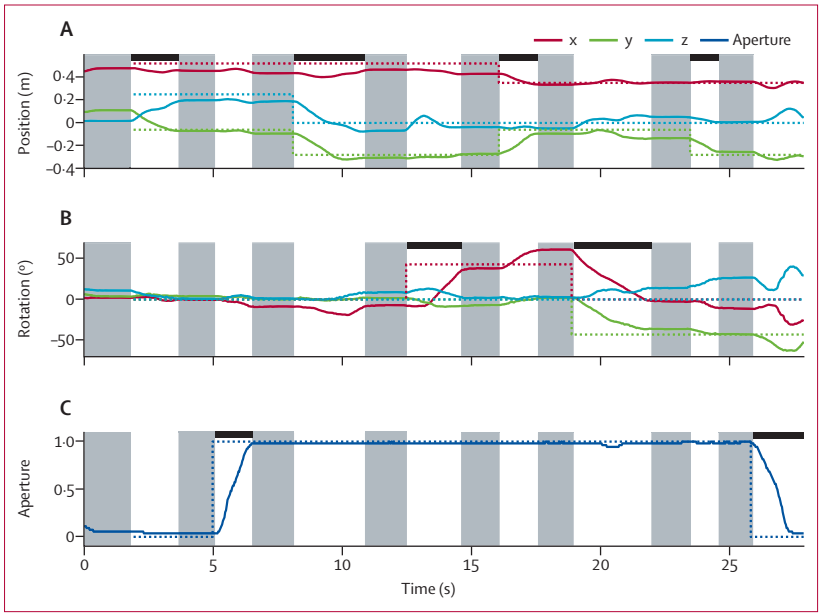

Figure 4: **Translation (A), orientation (B), and grasp aperture (C) of the MPL during four seven-dimensional sequence task trials under full brain control**

The black horizontal bars denote whether a translation, orientation, or grasp target was being attempted in (A), (B), and (C), respectively, although the participant had control of all seven dimensions at all times. The beginning of each new translation target indicates the start of a new trial. MPL kinematics, controlled by the participant, are shown as solid lines (with each colour representing movement in a different direction of the coordinate system). The target for each dimension is shown as a dotted line. Grey regions indicate presentation phases in which the MPL was paused and the participant was listening to a computer-generated verbal command. A grasp aperture of 1 indicates that the hand was fully closed. The participant was successful in maintaining the position of the prosthetic limb in one control domain while changing position in another, as instructed. Video 1 shows the participant's performance of these four trials with the MPL. MPL=modular prosthetic limb.

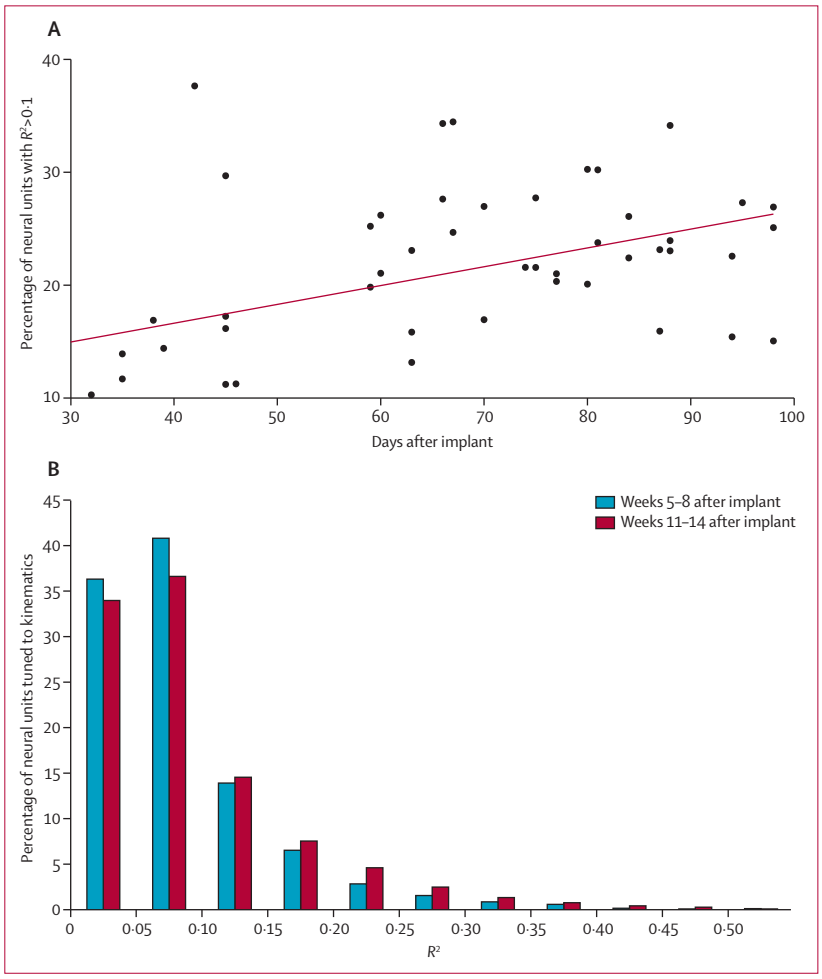

Figure 5: **Changes in neural units tuned to seven-dimensional kinematics with time**
(A) Percentage of neural units for which firing rate predicted seven-dimensional MPL endpoint velocity (equation 1) with an R^2>0·1 on each day of seven-dimensional brain-control training. Each dot represents data from a single decoder. The red line is the regression to the data (y=0·002x+0·100, R^2=0·119, p=0·066). On a single day, decoders were trained with observation data and brain-control data with orthoimpedance. (B) Percentage of units tuned to MPL kinematics with given R^2 values for early training (weeks 5–8) of seven-dimensional brain–machine-interface training compared with late training (weeks 11–14). Each bar is centred between the upper and lower bound of R^2 values for a particular bin. All R^2>0·5 were combined into a single bin. With time, the percentage of units with an R^2<0·1 decreased and the percentage of units tuned to kinematics with 0·1≤R^2≤0·5 increased. MPL=modular prosthetic limb.

	Day 81		Day 87		Day 88		Day 95	
	Time (s)	Drops	Time (s)	Drops	Time (s)	Drops	Time (s)	Drops
Right to left	214	5	140	1	223	11	126	7
Left to right	96	2	123	1	84	1	87	2

Table 2: **Performance in the three-cone-stacking task**

variable (y=–0·632x+171·4, R^2=0·142, p<0·0001). Mean path efficiency increased linearly from 0·30 (0·04) to 0·38 (0·02) as the participant moved along a straighter, more coordinated path (y=0·001x+0·228, R^2=0·160, p<0·0001; figure 3D). Mechanical constraints sometimes forced the MPL to deviate from an ideal linear trajectory, causing the maximum achievable efficiency under autocontrol to be less than 1 (figure 3D). The greatest improvement in control seemed to be in the translation domain, which increased linearly with time (y=0·003x+0·317, R^2=0·165, p<0·0001; figure 3E).

Figure 4 shows an MPL kinematics sample of four consecutive trials. The participant was able to rapidly reach the target position in the specified control domain (translation, orientation, or grasp; figure 4) while maintaining her position in the other two domains (video 1).

Neural changes were also noted during the seven-dimensional brain control testing. The percentage of units tuned to seven-dimensional MPL velocity (equation 1) showed a linear increase (figure 5A). The percentage of units with R^2 greater than 0·1 increased during the late training phase (weeks 11–14) compared with the early phase (weeks 5–8). Early values of R^2 had a median of 0·038 (IQR 0·019–0·077) and the late values had a median of 0·041 (0·019–0·093); the late values were significantly larger (Wilcoxon rank-sum test, p<0·0001). The increase in the number of units with R^2 in the range 0·15–0·30 (figure 5B) suggests that the participant was learning to modulate her brain activity to better fit the neural encoding model to improve performance.[19]

Table 1 shows the completion time and total score, for each test item on the days that ARAT was completed. If no time is listed, the score for that item was 1 because the task was partly completed. For items with completion times listed, the score was 2 because it took longer than 5 s (roughly equivalent to the time taken by an adult without any impairment to complete the task[18]). The participant's performance was consistent as indicated by her total score of 15–17 on the 7 days of testing. She was unable to move her own upper limbs volitionally and therefore scored 0 without the use of the brain–machine interface or other assistive technology. Video 2 shows her ARAT performance on day 87. The movements were generally smooth, direct, and fast. The participant reported that she was thinking about the goal of the action, such as "grab the block," rather than issuing specific kinematic commands to the MPL, suggesting that the control was intuitive.

Table 2 shows the completion time for the cone-stacking task and the number of drops for each day of testing (video 3). Dropped cones were repositioned by the experimenter. The participant achieved her fastest performance on the last day of testing (day 95), although she dropped the cones more often than on day 87. The participant knocked the first cone off the base six times before quickly moving all three cones, with only one additional dropped cone. She completed this task consistently on all 4 days of testing.

No adverse events have been noted so far in the study.

Discussion

In this study, an individual with tetraplegia rapidly learned to routinely reach and grasp using coordinated and robust seven-dimensional control (three-dimensional translation,

three-dimensional orientation, one-dimensional grasping) of a high-performance anthropomorphic prosthetic limb. The participant did the manoeuvres with coordination, skill, and speed almost similar to that of an able-bodied person. Performance on reaching and grasping tasks consistently improved during the 34 training sessions in 13 weeks. The improvement was steady and robust, and the participant was consistently learning. In this context, learning is defined as the modification of the correspondence between neural activity and action. Although the mechanism of this modification is not known, clear and consistent change in neural tuning is a feature of the brain–machine-interface model[19–22] and our results show that the population of neurons became more tuned to MPL movement velocity with time. The use of neural extraction algorithms derived from natural movement with an anthropomorphic effector is likely to have increased the acquisition of the skill necessary to achieve the MPL performance. This type of brain–machine-interface control is model based, by contrast with classifiers that operate on predefined libraries of discrete input–output categories. With our approach, continuous three-dimensional translation of the hand was achieved with a few hours of training, and seven-dimensional control was done routinely in less than 4 months. The movements were smooth, coordinated, and skilful. The participant had the flexibility to explore a range of arm or hand configurations to complete tasks with different strategies (video 4).

The use of observation-based calibration, computer-assist methods, and extraction algorithms used in our study was established in studies of non-human primates.[5,6] The findings of previous human studies have shown that intracortical electrodes could be used to provide rudimentary control of computer cursors[23] and robotic manipulators (panel).[12] Our study builds on this work by adding degrees of freedom that allow for more natural and coordinated movements, a broader workspace, and the ability to interact with various objects in different orientations (video 4). During several days of testing, the participant was able to improve her ARAT score from 0 to 15–17 of 27. This range is much greater than the threshold of 5·7 points for a clinically significant improvement in function,[21] showing that use of a neuroprosthetic device has the potential to provide clinically significant functional benefit. As shown in video 2, movements were smooth and coordinated, with speeds nearly similar to those of able-bodied adults. Because we used a velocity-based decoding model, the MPL speed was controlled directly by the participant. The level of control achieved by the participant allowed for subtle corrective movements and object manipulation (video 3). ARAT testing began once the participant had achieved consistent seven-dimensional control on the target-based task and her performance in terms of clinical measures was consistent during the last 3 weeks of testing.

Panel: Research in context

Systematic review

We did a literature review in PubMed without date or language restriction using the search terms "neuroprosthetics", "brain-machine interface", or "brain-computer interface". Because our goal was to restore upper limb function, we restricted our survey to studies in which robotic technology or functional electrical stimulation was used to achieve the same goal as ours. Additionally, we drew from our own substantive reference libraries. Two published reports of robotic arm[12] and hand[24] control in individuals with motor impairments were identified. The four-dimensional control of a robotic arm in a self-feeding task was investigated in one study of non-human primates,[5] and in studies of functional electrical stimulation of the upper limb.[7,8] For some individuals with amputation or residual muscle activity, other prosthetic control techniques, including non-invasive approaches,[25] targeted reinnervation,[26] or direct peripheral neural control,[27,28] might be appropriate.

Interpretation

The results of previous work[5–10,12] have shown that neural activity can be recorded from the motor cortex and translated to movement of an external device or the individual's own muscles. However, until now, the results of human studies have not shown whether the natural and complex movements can be done consistently for different tasks. Here, we have shown that a person with chronic tetraplegia can do complex and coordinated movements freely in seven-dimensional space consistently over several weeks of testing. This study is different from previous studies in which investigators had little control in translation dimensions, used staged control schemes, or had insufficient workspace to complete very structured tasks. Increasing dimensional control allows our participant to fully explore the workspace by placing the hand in the desired three-dimensional location and orienting the palm in three dimensions. This study is the first time that performance has been quantified with functional clinical assessments. Although in most human studies only a few days of performance data were reported, we have shown that the participant learned to improve her performance consistently over many days using different metrics. By using training methods and algorithms validated in non-human primate work, individuals with long-term paralysis can recover the natural and intuitive command signals for hand placement, orientation, and reaching to move freely in space and interact with the environment.

We expect further developments in brain–machine-interface technology in the near future. A wider range of tasks will become possible by adding hand shape to the repertoire of volitional control. Tactile feedback will be transduced by fingertip sensors and transmitted to the sensory cortex. Telemetry will remove the need for transcutaneous leads and connectors. Paralysed arms will be reanimated by activation of the individual's own muscles, which we know is one of the priorities for people with tetraplegia.[6,7,29] Our results and the very rapid developments in this specialty show the potential to restore much of the function lost in individuals with tetraplegia or upper limb amputation, allowing them to regain natural behaviours to interact with the world around them. With further development of neuroprosthetic technology and use of validated training methods and algorithms, these individuals could more fully recover their innate and intuitive command signals for routine arm and hand manoeuvres.

Contributors

JLC, WW, ECT-K, DJW, MLB, and ABS designed the study. JLC, BW, and JED completed most of the data gathering and analysis with all authors

contributing to the development of analysis techniques and interpretation of results. ECT-K developed and did the surgical implantation procedures. BW, JED, AJCM, and MV developed the software for the real-time experiments. JLC, MLB, and ABS wrote the report and all authors provided critical review and approval of the report.

Conflicts of interest

MV and ABS have a patent application pending in the USA that covers some of the methods used in this study. The other authors declare that they have no conflicts of interest.

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References

1 Santello M, Flanders M, Soechting JF. Postural hand synergies for tool use. *J Neurosci* 1998; **18:** 10105–15.

2 Soechting JF, Ross B. Psychophysical determination of coordinate representation of human arm orientation. *Neuroscience* 1984; **13:** 595–604.

3 Desmurget M, Prablanc C, Rossetti Y, et al. Postural and synergic control for three-dimensional movements of reaching and grasping. *J Neurophysiol* 1995; **74:** 905–10.

4 Moran DW, Schwartz AB. Motor cortical representation of speed and direction during reaching. *J Neurophysiol* 1999; **82:** 2676–92.

5 Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. *Nature* 2008; **453:** 1098–101.

6 Clanton ST. Brain-computer interface control of an anthropomorphic robotic arm. PhD thesis. Carnegie Mellon University, 2011.

7 Moritz CT, Perlmutter SI, Fetz EE. Direct control of paralysed muscles by cortical neurons. *Nature* 2008; **456:** 639–42.

8 Ethier C, Oby ER, Bauman MJ, Miller LE. Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature* 2012; **485:** 368–71.

9 Degenhart AD, Collinger JL, Tyler-Kabara EC, et al. Three-dimensional control using an electrocorticographic brain-machine interface by an individual with tetraplegia. Neural Interfaces Conference; Salt Lake City, UT, USA; June 18–20, 2012.

10 McFarland DJ, Sarnacki WA, Wolpaw JR. Electroencephalographic (EEG) control of three-dimensional movement. *J Neural Eng* 2010; **7:** 036007.

11 Doud AJ, Lucas JP, Pisansky MT, He B. Continuous three-dimensional control of a virtual helicopter using a motor imagery based brain-computer interface. *PLoS One* 2011; **6:** e26322.

12 Hochberg LR, Bacher D, Jarosiewicz B, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature* 2012; **485:** 372–75.

13 Kendall FP, McCreary EK, Provance PG. Muscles: testing and function. Philadelphia, PA: Lippincott Williams and Wilkins, 1993.

14 Georgopoulos AP, Schwartz AB, Kettner RE. Neuronal population coding of movement direction. *Science* 1986; **233:** 1416–19.

15 Wang W, Chan SS, Heldman DA, Moran DW. Motor cortical representation of position and velocity during reaching. *J Neurophysiol* 2007; **97:** 4258–70.

16 Marquardt DW. Generalized inverses, ridge regression, biased linear estimation, and nonlinear estimation. *Technometrics* 1970; **12:** 591–612.

17 Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res* 1981; **4:** 483–92.

18 Yozbatiran N, Der-Yeghiaian L, Cramer SC. A standardized approach to performing the action research arm test. *Neurorehab Neural Repair* 2008; **22:** 78–90.

19 Taylor DM, Tillery SI, Schwartz AB. Direct cortical control of 3D neuroprosthetic devices. *Science* 2002; **296:** 1829–32.

20 Jarosiewicz B, Chase SM, Fraser GW, Velliste M, Kass RE, Schwartz AB. Functional network reorganization during learning in a brain-computer interface paradigm. *Proc Natl Acad Sci USA* 2008; **105:** 19486–91.

21 Ganguly K, Carmena JM. Neural correlates of skill acquisition with a cortical brain-machine interface. *J Mot Behav* 2010; **42:** 355–60.

22 Ganguly K, Dimitrov DF, Wallis JD, Carmena JM. Reversible large-scale modification of cortical networks during neuroprosthetic control. *Nat Neurosci* 2011; **14:** 662–67.

23 Simeral JD, Kim S-P, Black MJ, Donoghue JP, Hochberg LR. Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *J Neural Eng* 2011; **8:** 025027.

24 Yanagisawa T, Hirata M, Saitoh Y, et al. Real-time control of a prosthetic hand using human electrocorticography signals. *J Neurosurg* 2011; **114:** 1715–22.

25 Losier Y, Englehart K, Hudgins B. Evaluation of shoulder complex motion-based input strategies for endpoint prosthetic-limb control using dual-task paradigm. *J Rehabil Res Dev* 2011; **48:** 669–78.

26 Kuiken TA, Li G, Lock BA, et al. Targeted muscle reinnervation for real-time myoelectric control of multifunction artificial arms. *JAMA* 2009; **301:** 619–28.

27 Benvenuto A, Raspopovic S, Hoffmann KP, et al. Intrafascicular thin-film multichannel electrodes for sensory feedback: Evidences on a human amputee. *Conf Proc IEEE Eng Med Biol Soc* 2010; **2010:** 1800–03.

28 Dhillon GS, Horch KW. Direct neural sensory feedback and control of a prosthetic arm. *IEEE Trans Neural Syst Rehabil Eng* 2005; **13:** 468–72.

29 Collinger JL, Boninger ML, Bruns TM, Curley K, Wang W, Weber DJ. Functional priorities, assistive technology, and brain-computer interfaces after spinal cord injury. *J Rehabil Res Dev* (in press).