



An exoskeleton controlled by an epidural wireless brain–machine interface in a tetraplegic patient: a proof-of-concept demonstration

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Summary

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Background Approximately 20% of traumatic cervical spinal cord injuries result in tetraplegia. Neuroprosthetics are being developed to manage this condition and thus improve the lives of patients. We aimed to test the feasibility of a semi-invasive technique that uses brain signals to drive an exoskeleton.

Methods We recruited two participants at Clinatex research centre, associated with Grenoble University Hospital, Grenoble, France, into our ongoing clinical trial. Inclusion criteria were age 18–45 years, stability of neurological deficits, a need for additional mobility expressed by the patient, ambulatory or hospitalised monitoring, registration in the French social security system, and signed informed consent. The exclusion criteria were previous brain surgery, anticoagulant treatments, neuropsychological sequelae, depression, substance dependence or misuse, and contraindications to magnetoencephalography (MEG), EEG, or MRI. One participant was excluded because of a technical problem with the implants. The remaining participant was a 28-year-old man, who had tetraplegia following a C4–C5 spinal cord injury. Two bilateral wireless epidural recorders, each with 64 electrodes, were implanted over the upper limb sensorimotor areas of the brain. Epidural electrocorticographic (ECoG) signals were processed online by an adaptive decoding algorithm to send commands to effectors (virtual avatar or exoskeleton). Throughout the 24 months of the study, the patient did various mental tasks to progressively increase the number of degrees of freedom.

Findings Between June 12, 2017, and July 21, 2019, the patient cortically controlled a programme that simulated walking and made bimanual, multi-joint, upper-limb movements with eight degrees of freedom during various reach-and-touch tasks and wrist rotations, using a virtual avatar at home (64·0% [SD 5·1] success) or an exoskeleton in the laboratory (70·9% [11·6] success). Compared with microelectrodes, epidural ECoG is semi-invasive and has similar efficiency. The decoding models were reusable for up to approximately 7 weeks without recalibration.

Interpretation These results showed long-term (24-month) activation of a four-limb neuroprosthetic exoskeleton by a complete brain–machine interface system using continuous, online epidural ECoG to decode brain activity in a tetraplegic patient. Up to eight degrees of freedom could be simultaneously controlled using a unique model, which was reusable without recalibration for up to about 7 weeks.

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Introduction

Following cervical spinal cord injury, approximately 20% of individuals have tetraplegia.¹ The extent of sensorimotor deficit depends on the type of spinal cord lesion. Therapeutic approaches aim to restore mobility and improve quality of life. Studies have successfully used neuroprosthetics and brain–computer interfaces to bypass the spinal lesion, using functional electrical stimulation of the muscles^{2,3} or spinal cord in animals⁴ or humans,⁵ or using motorised neuroprostheses and other effectors in humans.^{6–9} Exoskeletons (hand orthoses,^{10,11} arms,¹² and lower limb exoskeletons)¹³ have been used with EEG-based

brain–computer interfaces for rehabilitation¹¹ or neurological recovery¹³ of patients with severe motor impairment caused by stroke¹¹ or spinal cord injury (patients with tetraplegia¹⁰ or paraplegia).¹³ Effectors can be controlled by trigger signals from residual volitional functions or brain electrical activity,^{7,14–17} using penetrating microelectrodes¹⁸ or extracerebral grids.¹⁹

Cortical activity has been used to control effectors since 1998.^{6,11,14} However, despite impressive demonstrations of control of many movements using wire microelectrode recordings,¹⁶ such as short-term, semi-invasive brain–computer interfaces based on wired electrocorticography

Research in context

Evidence before this study

We searched PubMed using the terms (“FES” OR “electrical stimulation”) and (“BMI” OR “BCI” OR “brain-machine-interface” OR “brain-computer-interface”), with no language or date restrictions. We included studies that aimed to improve mobility using wireless, semi-invasive methods, and whole-body neuroprostheses. We found that most studies used invasive intracortical recording methods to control few action effectors or used functional electrical stimulation (surface or transcutaneous) limited to one limb. We found one report on chronic electrocorticographic recording that used a wireless implanted commercial brain-machine interface for written communication. We found no studies that were similar to our study, either in humans or animal models, which used a complete bilateral brain-machine interface from a cortical source with a high density of electrodes to a robotised neuroprosthesis, with a self-paced algorithm and multi-limb activation for long-term follow-up in patients with tetraplegia.

Added value of this study

Our study is the first to describe the control of a four-limb exoskeleton following decoding of epidural electrocorticography (ECoG) data recorded by two fully implanted epidural wireless recorders placed above the functionally located

sensorimotor cortices. The 24-month follow-up shows the feasibility of this technique in a patient with tetraplegia, no surgical and post-surgical complications, the stability of the high-quality recordings, the efficiency of the software to continuously decode many movements, and the compatibility with day-to-day use without requirement for recalibration over a long period (more than 1.5 months). The quality and stability of the signal were similar to those obtained with microarrays, in a relatively less invasive system.

Implications of all the available evidence

Decoding ECoG data could eventually allow patients with tetraplegia to control neuroprostheses that have been designed for different purposes in various environments. When some necessary major improvements (eg, higher resolution electrode grids and data compression) are available, this neuroprosthetic ensemble could reach a satisfactory level of usefulness and have the potential to improve patients' quality of life. Improved spatial resolution at the level of the sensorimotor cortex might allow more precise cortical analysis, leading to better skilled movements of the joints, particularly of the hand, and an increased amount of exported data should allow the software to create additional functions, such as prehension and faster movements of the fingers.

(ECoG) with moderate control dimensionality,¹⁵ a clinically compatible solution to compensate for motor deficits still does not exist.

We designed a programme to provide patients with tetraplegia with an original neuroprosthesis, controlled by the patient's brain, in an unsupervised manner, and fulfilling the requirements of chronically implanted devices (wireless, fully implantable, and biocompatible in the long term). The brain-computer interface system included a fully implantable epidural recorder with 64 electrodes, a motorised exoskeleton with four limbs, embedded decoding algorithms, and software. We present the first clinical application of this system and report initial findings from a clinical trial that aims to assess safety, long-term tolerance, and potential benefits of the designed system for patients with tetraplegia. We report proof-of-concept findings from one of five planned patients. This ongoing trial is registered with ClinicalTrials.gov, NCT02550522 and is ongoing.

Methods

Participants

The inclusion criteria were age 18–45 years, with stability of neurological deficits, a need for additional mobility expressed by the patient, ambulatory or hospitalised monitoring, registration in the French social security system, and signed informed consent. The exclusion criteria were previous brain surgery, anticoagulant treatments, neuropsychological sequelae, depression, substance dependence or misuse, and contraindications to MEG, EEG, or MRI.

We included and operated on two patients. In the first patient, at skin closure, the implants were probed, shortly activated, and stopped communicating (appendix p 1). The recorders were explanted and the patient was excluded from the study. The technical problem was identified and corrected before the second patient's implantation. The second patient was a 28-year-old man, who had tetraplegia following a C4–C5 spinal cord injury (figure 1A). The patient applied to take part in our trial online. He was included in the protocol after meeting the criteria and providing written informed consent (by proxy). The patient had little motor control of the upper limbs. Movements were possible only by contraction of biceps (American Spinal Injury Association Impairment [ASIA] scores: 4 right, 5 left) at the elbow, and of extensors of the wrist (0 right, 3 left). All other muscles below were scored 0 on the ASIA scale, not allowing execution of any task. Beyond these muscles, the sensory-motor deficit was complete. He used a wheelchair controlled by a left-arm support-joystick and had no other assistive technologies. Three other patients are being recruited on the same protocol.

Materials

An implantable recording system, WIMAGINE,¹⁹ was designed by our team for permanent bilateral epidural implantation over the sensorimotor cortex. Electronic components were placed in a titanium case (50 mm diameter, 7–12 mm thick, and a convex external face). An array of 64 platinum-iridium (90:10) recording electrodes for epidural ECoG (2 mm in diameter, 4–5 mm pitch,

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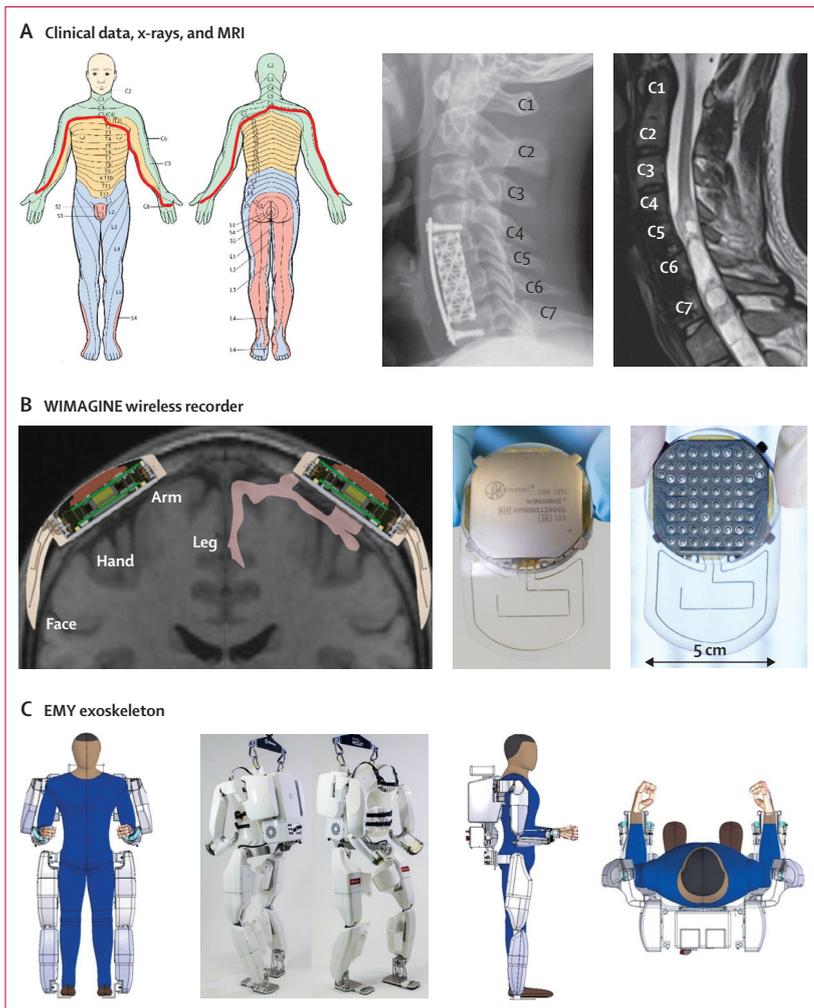


Figure 1: Clinical data, recorder, and exoskeleton

(A) The patient had no motor control or sensitivity below the red metameric level. The spinal cord lesion was slightly asymmetrical, with more severe deficits on the right side (C4: only the biceps and muscles above C5 were under voluntary control) than on the left side (C5: the patient could contract his biceps and wrist flexors). The sensory map is similar on both sides (C4). MRI showed extensive severe spinal cord lesion (total atrophy with syringomyelia). The cervical spine had been stabilised with a cage. (B) The biocompatible wireless WIMAGINE recorder was designed for chronic implantation. (C) The exoskeleton was designed as a wearable humanoid universal neuroprosthesis mimicking the human body shape and its mobility. The exoskeleton is self-supporting, wireless, and autonomous for 2·5 h. Equilibrated walking is not available nor achievable, but can be achieved with software that produces a humanoid walk and a ceiling suspension system (Vector Elite model [Bioness, Valencia, CA, USA]). EMY=Enhancing Mobility.

and five reference electrodes) was placed on the flat inner face of the device (figure 1B). A study on sheep²⁰ showed that epidural ECoG recordings were stable for more than 8 months. Data were radio-emitted through an ultra-high frequency antenna (402–405 MHz). Power was supplied remotely through a 13·56 MHz inductive high-frequency antenna. Both antennas were embedded in a silicone flap under the temporal muscle. Because of limited data rates, caused by restricted radio link (≤ 250 kb/s), only 32 contacts per implant sampled at 586 Hz were used. The wireless connection used two external antennas held in front of the recorders by a custom-designed helmet.

The Enhancing MobilityY exoskeleton (figure 1C) is a robotic neuroprosthesis with four limbs that is wearable and fully motorised (14 joints and 14 actuated degrees of freedom). The device is 65 kg and designed to be controlled by decoded epidural ECoG brain signals from the patient. The patient was strapped into the exoskeleton, while a backpack computer station received epidural ECoG signals. These signals were decoded in real time and translated into monodimensional (1D) for a linear translation or a rotation around an axis, bidimensional (2D) for movements in a plane, and three-dimensional (3D) for movements in a volume. These increments were then sent every 100 ms to the exoskeleton controller, to be translated into motor commands producing anthropomorphic movements of the upper limbs. The activation of the lower limbs was achieved by a switch that controlled a programme that simulated walking,^{21,22} without equilibrium, requiring ceiling-mounted support.

The experimental protocol, software, and decoding algorithms were developed and integrated into the Adaptive Brain Signal Decoder framework software²³ to provide adaptive high-resolution decoding of epidural ECoG activity within 350 ms, similar to reaction times measured in healthy participants.²⁴ Initially, a recursive, exponentially weighted, n-way, partial least squares²³ regression algorithm was the decoder. A Markov switching linear model²⁵ was later added to improve the decoding stability and resting state support.

The patient had permanent access to all degrees of freedom of the model and could control any degrees of freedom at any moment. However, when the decoder estimated the probability of a patient's intent to use some degrees of freedom as low, these degrees of freedom were then deactivated.

The adaptive decoding algorithms and software (figures 2, 3) were developed during a previous preclinical study and tested during a pre-operative clinical study using MEG (NCT02790411 and NCT02790424). The adaptive decoder allows rapid calibration and high-speed online decoding of information (decoder update rate 0·1–0·06 Hz; control rate 10 Hz).

Procedures

Under MEG and fMRI, the patient made real or virtual movements with his upper and lower limbs. Each movement was repeated 100 times (random 4–6 s intervals) for MEG and 80 times (random 10–20 s duration) for fMRI.

The activities of the neurons in the sensor-motor cortex during the tasks were detected using a 1·5 T Espree MRI (Global Siemens Healthcare Headquarters, Erlangen, Germany; T1 and T1-Gadolinium-enhanced sequences for anatomy, and Blood Oxygen Level Dependent (BOLD) signals for oxygen-dependent changes; figure 4A, appendix p 2), which generated fMRI images (3D graphs using SPM) to determine the spatial coordinates of the targets. MEG images were obtained similarly (figure 4B, appendix p 2) using the 306-channel Elekta Neuromag

MEG (Elekta Oy, Helsinki, Finland). Superimposition of the fMRI and MEG images outlined the sensorimotor cortex. Additionally, because MEG signals are non-invasive correlates of ECoG, the signals can be used to check the functionality of the sensorimotor cortex, using the decoders used in the pre-operative procedures.

Using fused fMRI-MEG images, we used an image-guided Surgiscope (ISIS SAS, St Martin d'Herès, France; figure 4) to locate the putative centre of the sensorimotor cortex as the target centre of craniotomies.

The electrode grids and the skull were visualised post-operatively using CT (Symbia [Siemens Medical Systems, Erlangen, Germany]), providing anatomical and functional correspondence (MRI-CT) coregistration (figure 4C, 4D, appendix p 2). WIMAGINE recorders are not MEG or MRI compatible, but CT scans (with or without iodine contrast) can be used whenever needed.

Operative and postoperative methods

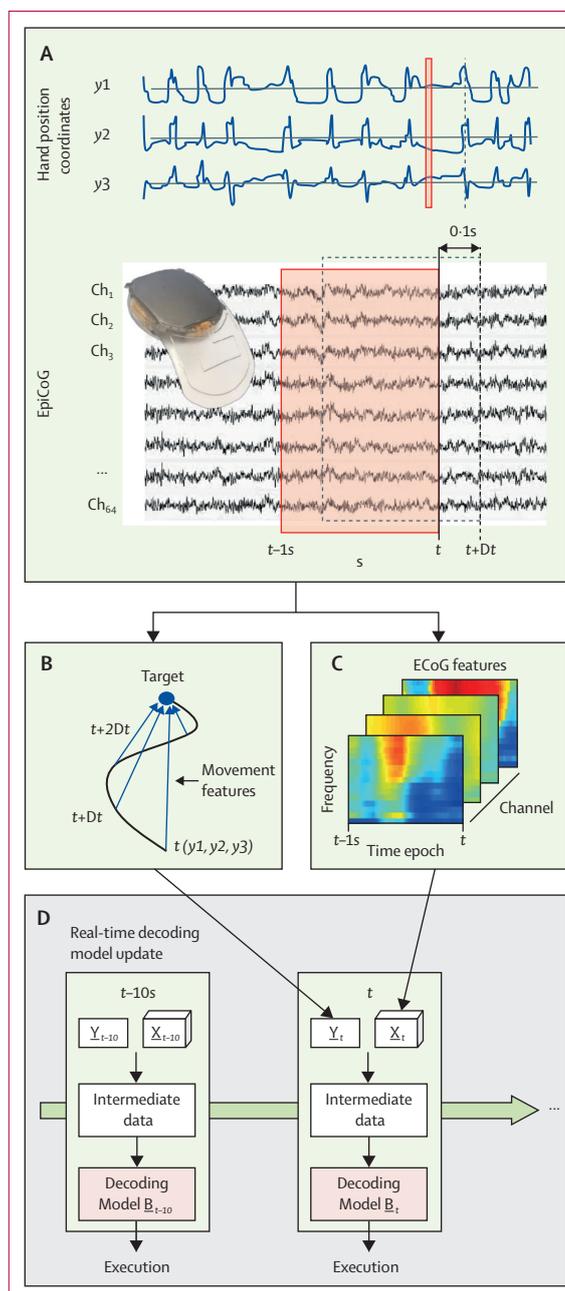
Surgery was done under general anaesthesia. We used the image-guided Surgiscope software for neuronavigation (figure 4D) to bilaterally implant the recorders (figure 4C, D) above the sensorimotor cortex. A semi-invasive (as compared with penetrating recording methods) procedure was used (5 cm diameter craniotomy, with epidural placement preventing intracranial infections, no electrode penetration of the brain, a fully embedded device, and wireless connections, including during tasks). The epidural ECoG signal was intraoperatively recorded before and after the final skin suture, using an antenna in a sterile bag, to assess the extent of surgical damage from the implant. The recorders are not meant to be explanted, except if necessary.

Outcomes

Epidural ECoG recordings were made for 2 min at the beginning of each session to monitor the ECoG signal quality (amplitude, signal-to-noise ratio, presence of artifacts).

Brain-computer interface tasks were used for calibration, training, and assessments of performance and progress. The patient was asked to either mentally trigger an on-off switch or do a continuous task.

Generally, experiments included two phases: the first being calibration to create or update a decoder and the second being the use of the decoder to estimate its performance. When the performance of a model was declared as satisfactory, the model could be reused without update for a new session. We assessed the performance of three different types of tasks; one for 4 weeks and two for 7 weeks. (figure 5).



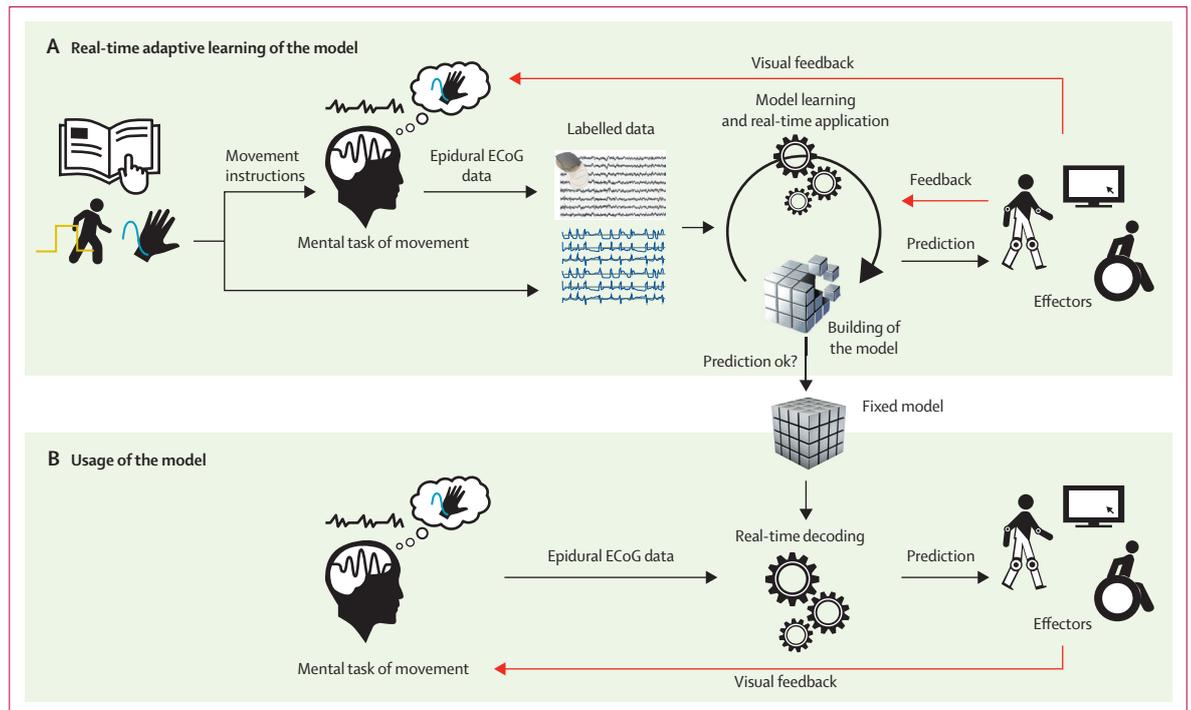


Figure 3: Strategy of real-time adaptive learning

(A) Instructions were communicated to the patient, who created a mental task of the movement, generating neural activity in his sensorimotor cortices. This activity was recorded by WIMAGINE as epidural ECoG data which were sent to the decoder. The ABSD software analysed these data and generated commands to drive the motors and move the patient's or avatar's limbs. Adaptive model learning and real-time application were used throughout. This process provided the patient with visual feedback (red arrow) and, during the calibration phase only, provided kinematic feedback to the decoder (red arrow). Analysis of the initial recording period produced the first decoding model. This model was iteratively updated (every 10–15 s) as the patient completed training tasks. The final model predicted task-specific features online and in real-time (within 350 ms). When the prediction was considered adequate, the experimenter terminated building of the model and it was considered ready for use. (B) When the patient created a new mental task to induce movement, the epidural ECoG data generated by his sensorimotor cortices and recorded by WIMAGINE were decoded online in real-time by the final model. Desired movements were interpreted and commands were generated and communicated to the effectors (eg, motors of the exoskeleton), which could therefore start moving the limbs accordingly. The resulting action provided visual feedback to the patient allowing him to adjust his mental task when executing the next movement. ABSD=Adaptive Brain Signal Decoder. ECoG=electrocorticography.

The patient mentally triggered on-off events on various effectors, such as a video game to initiate a manikin walking, an avatar (representing the exoskeleton), or when wearing the suspended exoskeleton (walking behaviour actuated by an automated 3.5 s walking cycle).

The patient made a continuous spatial movement of his upper limb segments, combining 3D translations and arm rotations, including 1D unidirectional movement (video game involving mental controlling of a paddle to intercept a falling ball, similar to *Pong*), 2D movements (video game involving reaching and touching a target on a virtual black panel), or wearing the exoskeleton and using fingertips to interact with a panel of eight light-emitting diodes (LEDs) on both sides for both arms, 3D and multi-limb movements (using an avatar or exoskeleton, to interact with a panel of 16 LEDs on both sides for both arms), and 4D and multi-limb movements (3D displacements plus rotation of the wrist [60° rotation around arm axis in either direction]).

After completing the set of tasks, the patient was asked to increase the degrees of freedom for mobilisation of the two upper limbs (four degrees of freedom each) and lower

limbs (switch). This control allowed the participant to move each arm freely.

For the mental on-off switch tasks, the patient's success rates were expressed as a true positive rate (ie, the percentage of correct actions out of the number of attempts), false positives per min (ie, the number of unwanted actions per min), or a false positive rate (percentage of unwanted actions or those during rest).²⁶ We also calculated receiver operating characteristic (ROC) curves and areas under curve (AUC; appendix p 5). For all reach-and-touch sessions, we calculated the success rate of reach (percentage of targets hit [SD]),⁷ and the R ratio (ie, the normalised path length of reach, calculated as the distance travelled from the origin to the target by the fingertip *vs* the actual distance), and their change over time (figure 5). For each task, the difficulty was kept unchanged throughout the study. Simple statistical analyses (mean [SD]), were done when appropriate. The progress of the patient was investigated in terms of number of degrees of freedom reached over time (figure 5). Training at home with a researcher (TC; 95 days) reinforced the tasks and skills acquired when using the exoskeleton at the laboratory (45 days).

Role of the funding source

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

Results

The patient was enrolled on June 12, 2017, received surgery on June 21, 2017, and was followed up on July 21, 2019 (ongoing). Before the start of this study, the participant used a wheelchair and had very little motor control. However, his fMRI and MEG recordings indicated a good capacity to produce cortical signals when imagining himself moving all his limbs. None of our results indicated a clear improvement, with time or repetition, of the intrinsic performance of the patient for each task. Clinical improvement of the patient's deficits was neither observed nor expected from this clinical trial. No adverse effects were reported at follow-up.

No intraoperative nor postoperative complications occurred during the study. Epidural ECoG recordings were done 1 day after operating to test the functionality of the entire system. The high signal amplitude (13.7 μ Vrms [SD 4.47]), which was observed before day 15, increased after resorption of the serohematic epidural collection after operation (18.7 μ Vrms [6.54]) from day 30 to day 379. The signal-to-noise ratio (dB) normalised by the bandwidth (from 34.9 dB for 0:10 Hz to 4.6 dB for 100:200 Hz) before day 15, also increased (from 36.5 dB for 0:10 Hz to 5.0 dB for 100:200 Hz) from day 30 to day 379. The long-term, high quality epidural ECoG recordings of the sensorimotor cortex allowed the patient to progress through the various learning steps.

To achieve high-dimensional control of the exoskeleton, the number of degrees of freedom was increased gradually from a brain switch to eight degrees of freedom. The decoder was calibrated and updated regularly. Three tests to explore the usability of the model without calibration or updates during long periods were done, early in the project for walking using the avatar within 4 weeks, and in more recent tasks eight degrees of freedom within 7 weeks, controlling either the avatar or the exoskeleton. The initial decoder was updated twice at months 10 and 16 after surgery (figure 5).

In the walking tasks, the patient achieved a true positive rate of 82.5% (SD 8.6), false positive rate of 12.5% (5.9), and AUC 0.78 (0.14) in 18 experiments using the walking video game; and a true positive rate of 92.1% (4.3), false positives 4.9 (1.9) per min, and AUC 0.84 (0.05) in 15 tasks with the avatar using the same model without recalibration during 1 month (figures 5, 6A). When wearing the suspended exoskeleton, the true positive rate was 72.6% (15.3%), false positives were 7.1 (5.6) per min, and AUC was 0.84 (0.06) in six experiments done 2 months post-surgery. The total distance covered was 145 m (480 steps in 39 periods of walking [figures 5, 6A; video 4).

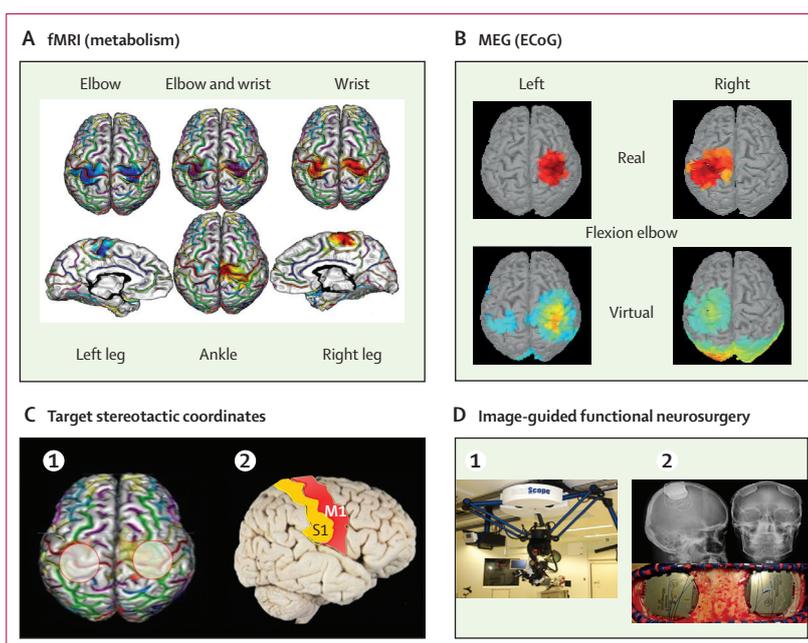


Figure 4: Cortical location of sensorimotor cortex, targeting, and surgery

A pre-operative strategy based on (A) fMRI and (B) MEG was designed to identify the precise surgical target where recorders should be placed to capture the epidural ECoG signatures of the intended movements. When the patient repeated motor tasks (real or virtual), metabolic changes were detectable by fMRI as BOLD signals. These signals were used to produce task-related functional images, visualised using Brainvisa software (3D projections in statistical parametric mode) of the contralateral sensorimotor cortex and ipsilateral cerebellum. Similar MEG images were obtained, using the Brainstorm software, for both real and virtual flexion of the right and left elbows. fMRI and MEG data from all limb segments were combined; the results were projected onto stereotactic atlas maps and a 3D rendering of the patient's brain. (C) fMRI and MEG data were combined to determine the coordinates of the most active sensorimotor cortex target (white circles), centred near the Rolandic sulcus (in red). (D) These coordinates were transferred to the image-guided SurgiScope (ISIS SAS, St Martin d'Hères, France). According to Penfield's homunculus, the 4 × 4 cm ECoG grid covers the cortical primary motor and sensory functional areas controlling the upper limbs, but not the lower limbs (located in the interhemispheric fissure). Photographs taken during the surgical procedure show the placement of implants before closing the scalp; post-operative x-rays show their final positions (far from the superior longitudinal sinus on the midline). ECoG=electrocorticography. M1=primary motor cortex. S1=primary sensory cortex. BOLD=blood oxygen level dependent. MEG=magnetoencephalography.

The switch control of the avatar lower limb was also successfully used to trigger independent movements of each leg as well as alternating bipedal activity. ROC curves are presented in the appendix (p 5).

See Online for videos 1–5

For the *Pong* video game task, involving upper limb control, the patient achieved 54% (SD 12.7) of hits in 19 experiments when using his left hand (figure 6B, video 1). In the target task, the patient did 2D tasks with his left hand (17 experiments, 80% (15.5) success, ratio 2.8 [1.4]) and with his right hand (19 trials, 82.2% [12.0]) success, ratio 3.3 [1.5]; figures 5, 6C; appendix p 4). In the target tasks with the avatar, the patient completed 3D tasks with his left hand (seven experiments, 56.9% [15.3] success, ratio 6.8 [4.1]) and with his right hand (11 experiments, 52.5% [11%] success, ratio 6.6 [3.6]; figures 5, 6D; appendix p 4).

The final part of the avatar training programme was multi-limb activation of the avatar to generate models that simultaneously controlled several degrees of freedom in combined tasks. The patient did 2D, two-handed

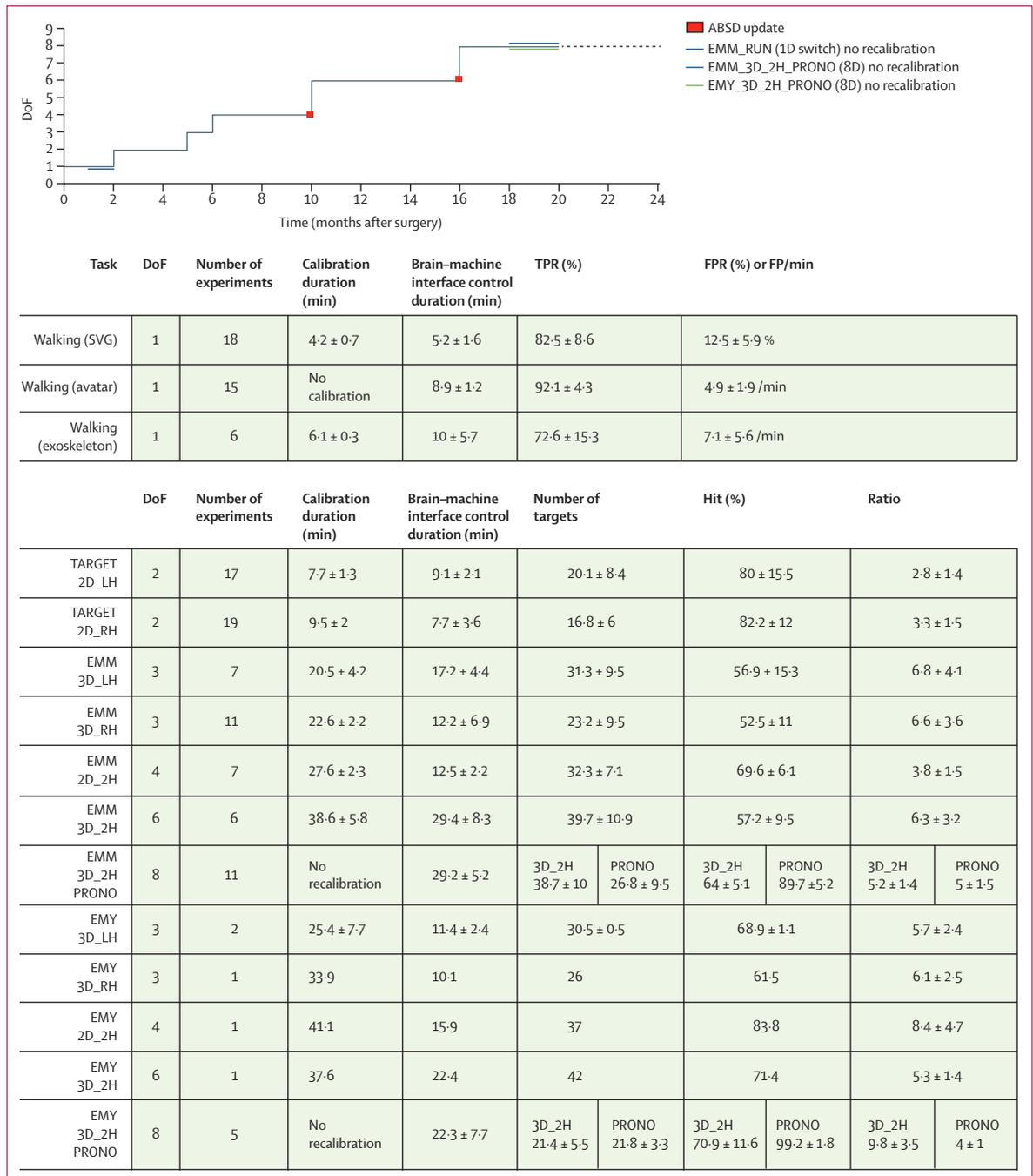


Figure 5: Cumulative performances, with increasing dimensionality

The timeline shows the development of the number of DoF over a period of 20 months (solid black line) and the dotted black line indicates tasks that were not included in this Article (20–24 months). Labels for the ABSD update are shown (red squares). During month 10, the initial algorithm REW-NPLS was combined with MSLM. At month 16, the parameters were modified for high dimensional control. Periods of no recalibration are depicted. The ratio column denotes the ratio of the distance travelled (dT) by the effector from the origin to reach the target over the real origin-to-target distance (d_{0t}). In a perfect case, the ratio would be 1. The cutoff time for ending the attempt was when the ratio was approximately 30. ABSD=adaptive brain signal decoder. DoF=degrees of freedom. FP=false positive. FPR=false positive rate. MSLM=Markov switching linear model. REW-NPLS=recursive, exponentially weighted, n-way, partial least squares. SVG=serious video game. TPR=true positive rate.

(seven trials, 69.6% [SD 6.1] success, ratio 3.8 [1.5]; figures 5, 6E; appendix p 4) and 3D, two-handed tasks (six experiments, 57.2% [9.5] success, ratio 6.3 [3.2];

figures 5, 6F; appendix p 4, video 2). Finally, the patient successfully did 8D tasks (3D, two-handed and using both hands in pronation and supination; figures 5, 6G;

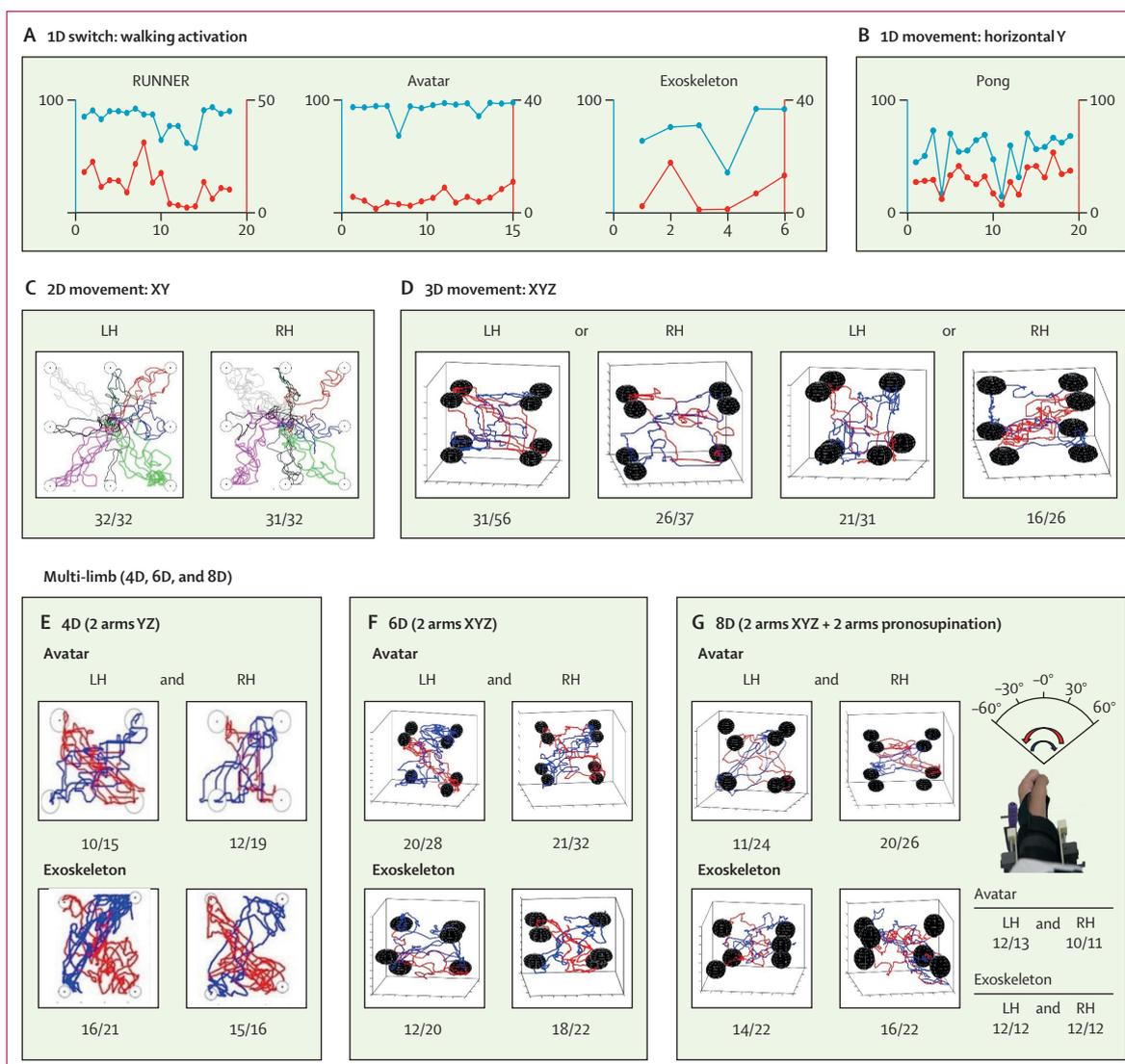


Figure 6: Cumulative results of motor tasks

1D tasks were done by (A) activating a switch (running video game, controlling the avatar, or exoskeleton) or as (B) a 1D displacement (Pong video game horizontal axis). For the switch triggering the initiation of walking, the results can be classified into true positive activation (the true positive rate as a percentage of positive responses vs the number of intended activations [blue line]) and random false positive activation (the false positive rate for the running video game or false positives per min for the avatar and exoskeleton [red curve]). For the Pong video game, the success was estimated on the basis of the percentage of hits when the falling ball was intercepted by the paddle (blue curve, y axis) and the number of the falling balls (red curve, y axis). (C) 2D tasks involved using the hands to reach for eight targets on a square in a virtual representation at home. (D) 3D tasks involved using the hands to reach for 16 targets on a cube. (E) Multi-limb 4D tasks involved using both hands to reach for eight targets on two flat panels. (F) Multi-limb 6D tasks involved using both hands to reach for 16 targets on two cubes. (G) Multi-limb 8D tasks involved using both hands to reach for 16 targets on two cubes. This task was done with the same settings as for 6D tasks with the addition of pronosupination of the wrist (60° in either direction), which add one degree of freedom per hand. The graphs in (C–G) show the actual trajectories cumulated during one task, using the left and right hands, and the number of targets reached over the number presented. All tasks in (D–G) were performed using both the avatar at home and the exoskeleton at the laboratory.

appendix p 4). The same model without recalibration was used for all tasks for 7 weeks (11 experiments; 64·0% [5·1] success and ratio 5·2 [1·4] for 3D, tow-handed tasks; and 89·7% [5·2] success and ratio 5·0 [1·5] for tasks involving pronation and supination of both hands; figures 5, 6G; appendix p 4).

In the reach-and-touch tasks using the exoskeleton, the patient did 3D tasks with his left hand (two experiments, 68·9% [SD 1·1] success, ratio 5·7 [2·4]) or right hand (one

experiment, 61·5% success, ratio 6·1 [2·5]; figures 5, 6D; appendix p 4).

The final part of the exoskeleton training programme was multi-limb activation of the exoskeleton to generate models that simultaneously controlled several degrees of freedom in combined tasks. The patient did a 2D, two-handed task (83·8% success, ratio 8·4 [4·7]; figures 5, 6E; appendix p 4) and a 3D, two-handed task (71·4% success, ratio 5·3 [1·4]; figures 5, 6F; appendix p 4).

Finally, the patient completed five 8D tasks using the same model, without recalibration over 7 weeks (70·9% [11·6] success, ratio 9·8 [3·5] in five 3D, bimanual tasks, and pronation and supination of both hands (99·2% [1·8] success, ratio 4·0 [1·0]; figure 6G, appendix p 4, video 3).

The tangential CT-scan done immediately after surgery associated the grid contacts with the functional cortices. Using the TapfingerPsychomotorTarget (NCT02790411, NCT02790424) paradigm, the patient exerted movement intentions of single joints to show the correspondence between the hand–wrist–finger representation and virtual movements. Lower limb activity correlated with more medial contacts than those that were related to upper limb activity but was still far from the interhemispheric fissure (figures 1B, 4). Movement intentions were associated with neuronal activity detected by epidural ECoG and oxygen consumption detected by fMRI. The group of contacts, involved with brain–computer interface decoding, colocalised with the epidural ECoG and fMRI signals (appendix p 3).

Discussion

This study describes the first successful long-term use of wireless epidural multi-channel recorders that were bilaterally implanted in a patient with tetraplegia. In this study, all the technical elements that are required for long-term human clinical application (epidural recording, wireless power and emission, online decoding of many ECoG channels, and being totally embedded) have been combined for the first time. This long-term combination of many bilateral electrodes made it possible to explore high-dimensional control in multiple limbs. Our intervention showed no signal degradation, no side effects, and long-lasting tolerance. This study shows the capacity of our system, using data recorded with epidural ECoG, to decode brain activity in a self-paced manner online and in real-time, without recalibration for several weeks, with minimal reductions in performance.

Dimensionality of control increased progressively from walking tasks to 8D bimanual tasks. Results were obtained using subsequent algorithms, starting from an adaptive real-time linear decoder to an adaptive real-time nonlinear dynamic decoder for asynchronous control of multiple limbs. This first clinical proof-of-concept warrants the extension of our system out of the laboratory to a home environment and to other applications.

The successful control of eight degrees of freedom (the patient had permanent access to all dimensions), suspended walking capability during the 24 months after surgical implantation, and continued control after several weeks without recalibration are the highest performances reported so far. None of the brain–computer interface tasks presented here could have been done using exclusively the patient's residual capabilities.

The best high-dimensional control (10D control of a robotic arm) was reported in a patient using invasive

microelectrode wire recordings.¹⁶ However, chronic applications of such systems are limited because of biocompatibility issues and safety problems, and further technological developments are required to make them compatible with long term human use. Additionally, long-term (2–5 months) stable switch decoding from local field potentials recorded with microelectrodes has been reported in patients with tetraplegia.¹⁷ Other decoders are also capable of high dimensional control without re-training for several days, with only 20–50% performance drop.²⁷ Despite good progress, unstable calibration still limits the clinical application of brain–computer interfaces that are based on microelectrode recordings. Epidural ECoG recorders cover a larger cortical surface than do microrecording devices. The invariant spatial positioning of the implant prevents the need for recalibration. The initial goals of our study were met, proving that brain–computer interface technologies can involve a high level of sophistication, such as the control of a whole-body exoskeleton. The exoskeleton is a biomimetic anthropomorphic neuroprosthesis and is possibly the best solution to totally compensate for the impairment in a patient with tetraplegia. The exoskeleton used in this study does not allow autonomous walking with equilibrium. The next goal is to solve the problem of the self-equilibrated walking of the patient. In the meantime, the demonstration that patients with tetraplegia can use their brains to control neuroprosthetic effectors, while simultaneously combining several degrees of freedom, might allow for the extension of this concept to higher-level control. This extension will allow patients to drive their wheelchairs using only brain activity (video 5), eventually leading to progressive integration of patients with tetraplegia in the domestic, urban, and professional environment. Our patient already considers his rapidly increasing prosthetic mobility to be rewarding. However, this progress has not changed his clinical status. The main goal of this report is to show that bilateral, semi-invasive, epidural chronic implants that control an exoskeleton with four limbs move us closer to achieving the expected progress in the field of deficit compensation.

Further studies with these systems will also help us better understand brain function, owing to the analysis of the cortical events triggered during a task. Future studies will provide information on the roles of the sensorimotor cortex's continued capacity to virtually generate the signals that are usually needed to achieve real movements. In several instances, performance was better when using the exoskeleton than with avatars by an average of 10–20%. This finding might be due to differences in feedback and patient perception. In the 2D screen projection with the avatar, the direct (and only) feedback is visual, and therefore requires additional cognitive effort to conceptualise the third dimension. In the real environment of the exoskeleton, the patient was moving in the real world with a richer feedback. Whether the improvement of the patient along the course of his training was due to his

improved control of his neuroprosthesis or due to an improvement of his cerebral or mental capacities is unclear. Despite the tendency toward an increase in task success, as well as a trend for decreasing ratios in the reach-and-touch tasks, we cannot be certain whether neural changes took place because the model was regularly recreated and the algorithm was improved. Because the control of eight degrees was reached, the model was not changed for 7 weeks. The next stage of the trial aims to document learning processes during brain–computer interface training. Our results suggest that this system can accurately harness information from several cortical areas to recreate some degree of assisted mobility in disabled people. The hotspots of epidural ECoG activity related to movement intention corresponded to the usual representation on the sensorimotor cortex, as described by Roux,²⁸ and defined as the hand knob by Yousry and colleagues.²⁹ Interestingly, this study might support the hypothesis of training-induced neuroplasticity to develop new functionalities in deafferented unused cortical areas. Although the lower limb representation is buried in the interhemispheric fissure, the most intense lower limb-related epidural ECoG activity was often recorded on the most medial contacts of the primary sensory cortex. This activity might spread from the primary motor cortex via transversal intracortical fibres, or from long-distance detection of epidural ECoG activity related to lower limb activity. Alternatively, cortical areas might be recruited by the neighbouring motor cortex in response to functional pressure from the prefrontal cortex. This apparent spreading of motor representation over initially sensory cortices might also support evidence that the motor cortex exhibits sensory responses in a variety of modalities, including vision and somatosensation.³⁰ As a result, these studies will provide information on the roles of the sensorimotor cortices from the cortex's continued capacity to generate the signals needed to achieve real or virtual movements.

Contributors

GC, TA, AE, SK, AM, and MCS developed and implemented the algorithm and software. GC, FSS, MF, AL, AV, BM, and NA developed the brain–computer interface system. VA and LL did the functional imaging. TC, GC, SK, and SP did the experiments. ALB, TC, TA, GC, and SK analysed and interpreted the data. SC, ALB, and MO contributed to the surgical design and implantation. SC and SP provided post-surgical care. ALB, TC, and TA wrote the manuscript. GC and FS contributed further to the writing of the manuscript. TC, CMO, NTM, and DR did the preclinical experiments. MP assessed the neuropsychological status of the patient, according to what was required in the clinical protocol.

Declaration of interests

We declare no competing interests.

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