Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Vansteensel MJ, Pels EGM, Bleichner MG, et al. Fully implanted brain–computer interface in a locked-in patient with ALS. N Engl J Med 2016;375:2060-6. DOI: 10.1056/NEJMoa1608085

SUPPLEMENTARY APPENDIX

Fully Implanted Brain-Computer Interface in a Locked-In Patient with ALS

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CONTENTS

TIMELINE

The study was approved by the Ethical Committee of the UMC Utrecht in November 2013. Recruitment initially focused on rehabilitation and care homes, but was broadened after several months to maximize awareness about our study among potential participants. The present manuscript describes data from the first participant who was included, the informed consent procedure of whom took place in September 2015 after careful initial screening. After informed consent, detailed medical and (neuro-)psychological examination and the fMRI scan were performed before the patient was admitted into the hospital for implantation of the electrodes and device at the end of October, 2016.

INFORMED CONSENT PROCEDURE AND PRESURGICAL ASSESSMENT

INFORMED CONSENT

Since the participant had a severe difficulty to communicate and was not able to sign an informed consent form, a tailored procedure was applied,[S1] and recorded with a video camera. In addition to the participant, one close relative of the participant, a member of the research team and an independent observer (experienced in working with LIS patients) were present. Explanation of the study and implications of participation were explained verbally and a copy of the information letter was left with the participant several weeks before the informed consent procedure. The consent procedure included the following steps to determine the reliability of eye movement communication and full understanding of the burden, risks and potential benefits of participation: 1) The best possible communication channel for the participant was determined by which the participant was able to give clear responses. In this case it was eye blinks. 2) To verify reliability of the communication channel, 20 true/false statements with obvious answers known to all people present were read to the participant (e.g. 'I am a woman'). She needed to answer 19 of these correctly before continuing the procedure (she had 100% correct). 3) The complete project was once more explained verbally to the participant and her relative. 4) To verify that the participant had a full understanding of the procedure, a list of 10 true/false statements about the study was read to the participant (e.g. 'I can terminate participation at any time'). The procedure was continued only after all statements were answered correctly (she answered all correct the first time). 5) The consent form was read to the participant and the question about the willingness to participate in the project was asked three times. Discrepancy between the three given answers would terminate the procedure. The participant gave affirmative statement three consecutive times. 6) All parties present signed the consent form, thereby confirming that each firmly believed that the participant had understood the information about the study, and had given voluntary consent to participate. Signing by the close relative also constituted his approval to support and facilitate the participation of the participant in the study.

MEDICAL AND NEUROPSYCHOLOGICAL ASSESSMENT

Medical examination by a neurosurgeon, anesthesiologist and neurologist revealed that there were no mental or physical issues that would negate participation in the study. The participant was evaluated by a qualified neuropsychologist with experience in evaluating neurological patients. The standard protocol was customized to accommodate the poor communication capabilities of the candidate. Where possible, the candidate filled out questionnaires online. The remaining tests were conducted in person at the home of the candidate mostly with eye blinks for yes/no answers, and writing by eye-tracker. The tests used and adopted for the evaluation included the Raven's Progressive Matrices test, Peabody Picture Vocabulary test, a mental calculation test, the Visual Association Test (VAT), the ALS Depression Inventory (ADI12), the Anamnestic Comparative Self-Assessment test (ACSA), and a mood and motivation VAS test. Test scores were as follows: Raven's

10 correct out of 12, mental calculation 14 correct out of 14, Visual Association Test 100%. Peabody test was considered good and on academic level (not completely administered due to some incompatibility with the communication deficit). Together with the fact that the ADI12, ACSA and mood and motivation VAS results did not indicate any signs of mood problems, these tests gave a clear indication of intact mental capacities, psychological wellbeing and motivation of the candidate.

IDENTIFICATION OF BRAIN REGIONS FOR ELECTRODE PLACEMENT

Functional MRI images were acquired several weeks before electrode implantation using a Philips Achieva 3T MRI scanner. For maximal localization accuracy, we used PRESTO, a technique that minimizes the confounding effects of large blood vessels.[S2–4] An anatomical T1-weighted scan was acquired for presurgical planning purposes. Neuronavigation MRI (with fiducials) was obtained on the day before electrode implantation on a 1.5 Tesla MRI machine (Philips Achieva).

During scanning, invasive mechanical ventilation was provided using an MRI compatible respirator (GE Aestiva), and vital functions of the participant were monitored continuously by an anesthesiology team. Communication with the participant was accomplished via the available MRI intercom system, and an eye-tracker camera (LiveTrack, Cambridge Research Systems) that was directed at one of the eyes of the participant for the only means of communication, and that was monitored continuously by the study team. Localizer tasks (see below) were visually presented using Presentation software (Neurobehavioral systems) on a computer screen that was visible for the participant by a mirror on the head coil (BOLDscreen, Cambridge Research Systems).

ATTEMPT-REST TASK

The Attempt-Rest localizer task consisted of trials of ~15s with a fixation cross in the center of the screen, each preceded by an instruction ('attempt', 'rest'). The participant was instructed to attempt hand movement (sequential tapping of fingers against the thumb) during the presentation of the fixation cross, or to relax, depending on the trial instruction. The task was performed for both the left and right hand separately, and lasted 8.8 minutes in total.

The participant practiced this task, as well as the other localizer tasks, at home before the fMRI session. For this, she was given access to a website with the task as was presented during the fMRI scan. The goal of this was to ensure that she knew exactly what to do in the MRI scanner thus avoiding any delays. After verbal explanation of the task, the participant practiced the task for 3 hours daily during 7 days at her own initiative. We believe less training would suffice based on another, unrelated, fMRI study with amputees attempting more complex hand movements with the amputated arm, where 1.5 hours of similar training resulted in excellent brain activation (unpublished data). Training was not monitored or recorded.

COUNT TASK

The Count localizer task consisted of trials of ~15s, with a number presented in the center of the screen. Every trial was preceded by an instruction (count back, count forward, rest). For count back trials, the participant was instructed to mentally count backwards in steps of 7 from the number (between 80 and 115) presented. During count forward trials, she counted forward in steps of 1, starting from the given number (between 1 and 10), and for rest trials, she relaxed (0 presented on the screen). The task had a duration of 8.5 minutes. The choice of counting in steps of 7 was based on training before scanning, and aimed at reaching sufficient mental engagement. This number can be lower for other participants, depending on calculation proficiency. The count-forward trials served as a possible alternative control condition for subsequent data analysis.

MENTAL CALCULATION TASK

This localizer task consisted of 45 equations combined with a solution (which was correct or incorrect), with three levels of difficulty and containing only additions and subtractions.[S5] The participant was instructed to compute the equation and blink twice when she made a decision about whether the given answer was correct or incorrect. The participant was not required to indicate correct or incorrect, in order to avoid additional complexity and confusion during the task. The experimenter watching the eye-tracker screen then pressed a button to mark the end of the trial. Maximum trial duration was 10s. Intertrial interval was 10s plus the remaining time of the previous trial after the button was pressed. For subsequent data analysis, time between equation presentation until button press was annotated as active, the rest of the time as rest.

FMRI ANALYSIS

Functional scans were realigned and coregistered to the anatomical scan using a PRESTO reference scan. Statistical analysis was performed in subject/native space and involved fitting a General Linear Model (GLM) to the data and the generation of t-maps contrasting the active periods of the tasks against rest. The fMRI analysis was conducted independently by two members of the research team and the results were evaluated for correspondence. Accuracy of locating target regions with PRESTO fMRI scans has been validated against electrical stimulation, electrocorticography and surgical resection in previous studies.[S3,S6,S7]

PLANNING OF ELECTRODE PLACEMENT

Surgical placement coordinates were transferred from a 3D surface rendering of the fMRI data to the navigation MRI scan. Key to the placement was the hypothesis that a bipolar signal from two fMRI-active foci would yield the best brain-computer interface performance. Since fMRI correlates highly with high frequency band (HFB) and low frequency band (LFB) power, we postulated that neural activation under two electrodes (subtracted from each other) would yield a larger difference between rest and active power than one of the electrodes versus a non-active focus. The exact cortical position of the electrode strips was determined such that at least two electrodes per strip were on fMRI-active foci.

An expert (NFR) evaluated the fMRI scans. Foci in predetermined areas (hand knob of primary motor area M1, anterior aspect of dorsolateral prefrontal cortex DLPFC, left hemisphere) with high t-values were selected as targets for electrodes. These regions were based on identification of focal activity in previous electrocorticography studies with epilepsy patients,[S7–8] and application to brain-computer interfacing.[S6] Using custom software, strips were placed virtually on a 3D rendering of the anatomical scan (with fMRI targets overlaid), and points on the cortex were defined for the tip and the tail end of the electrode strips. These points were used to guide the drilling of burr holes, where the tail was to be connected to the skull using a small metal screw-plate, and the tip was to be fixated using a ligature to the skull, thereby allowing exact placement and complete immobilization of electrodes on the target foci. Four strips were planned, of which two on M1/S1 and two on DLPFC. For each region, coordinates were determined for one strip in the optimal position (at least two of the four electrodes on fMRI hotspots), and for a second strip in a second-best position as a backup in case for some reason signal quality was insufficient.

ADVERSE EVENTS

No complications occurred, except for a short period of postsurgical fever on Day-5 (Day-0 being the day of the first surgery). The patient was readmitted into the hospital (after original discharge on the same day), which was reported as a serious adverse event. Fever dropped quickly without treatment and the patient was discharged from the hospital on Day-6. Two adverse events were

reported, which both resolved without treatment within three months: postsurgical feeling of numbness in the skin around the left ear, and increased tiredness.

Of note, infection risk of the surgery is obtained from literature on Deep-Brain Stimulation studies, which use essentially the same materials and surgical procedure. Based on 14 publications and 3 internal documents from Medtronic, the infection risk was found to amount to 4% (274 out of 6689 patients), with individual studies reporting a range of 1.2-14.4% (e.g. Bhatia et al).[S9]

ELECTRODE SELECTION

SELECTION OF ELECTRODE STRIPS

Correct electrode placement was verified after surgery using a CT scan made on the day after electrode implantation, which was coregistered to the neuronavigation scan with the fMRI overlaid, using the NeuralAct toolbox.[S10] To select the two electrode strips to be connected to the device during the second surgery, the participant performed the localizer tasks on Day-1 and Day-2, while the signal from all 16 electrodes was recorded simultaneously using an external, clinical amplifier for electrocorticographic signals (Micromed, Treviso, Italy, sampling frequency 512 Hz, band pass 0.15-134.4 Hz). Signals were analyzed offline. Data were re-referenced to the common average of all 16 electrodes and spectral power was computed using an AR filter (Burg's maximum entropy method, 1Hz bins).[S11] Power was averaged over 65-95Hz. The correlation of the average HFB power with the localizer task (R^2) was computed for all electrodes to find electrodes showing a significant difference between attempted movement, counting backwards or mental calculation, and rest. The sensorimotor data are presented in Figure S3.

SELECTION OF ELECTRODE PAIR

Since the device operates with a bipolar montage, an optimal electrode pair needed to be identified within the sensorimotor strip. The electrode pair to use for the brain-computer interface training was selected by computing the HFB power (65-95Hz)[S12] for all possible bipolar combinations of electrode pairs (Figure S3B). The pair showing the highest R^2 of HFB power with the localizer task (attempted movement vs rest) was e2-e3 (Figures 1A, S1 and S3), which was chosen for further use.

IMPLANT COMPONENTS

All implanted components had medical CE certification, although mostly for other intended use. All components are designated for investigational use in the current study. The ethical committee approved implantation of these materials for use in our study after an extensive verification of essential requirements, including extra biocompatibility testing for cortical use of the Resume II leads. The Activa PC+S device[S13] leverages a general purpose bi-directional brain-computer interface. More information and a schematic of the device and the complete system are given in Figure 1 and S2. The device contains four independent amplifiers connected to two electrode strips. Each amplifier processes signals from a bipolar electrode pair on a single strip. Amplified signals can be passed through an analogue bandpass filter on the device. Once the filtered data is extracted on the device, it is communicated at a rate of 5Hz through a secure wireless telemetry link using an established ISM band. The data are passed, through a telemetry receiver modified specifically to accommodate the brain-computer interface needs for the present study, to the signal decoding computer (laptop or tablet). Specifically, for the purpose of the present study (and future users) all our research was focused on making the system effective, reliable, user-friendly and safe in a home-use environment when operated by a non-expert caregiver. Two of the amplifiers (one per strip) can also be switched to real-time throughput of raw, time-domain signal (200Hz) for research purposes, allowing for offline testing of different digital filters. This setting is substantially more energy consuming than the 5Hz power-mode, and can therefore not be used for long-term home-use, since the device battery would drain too quickly (requiring surgery to replace the device).

TRAINING TASKS

TARGET TASK

The Target Task involved controlling the vertical speed of the cursor on the screen (horizontal speed was fixed) in an attempt to hit one of two targets presented on the right side of the screen, using attempted movement to hit the upper target, and rest for the lower target (Video 1, Figure S4A). Performance on this task is expressed as percentage correct hits. For this task, only the HFB power was used since utilization of the LFB power was introduced at a later point in time.

BALL TASK

Direct feedback about the magnitude and timing of the control signal was provided using the Ball Task (Figure S4C). Here, the screen showed blocks of upper and lower targets moving horizontally at a fixed pace from left to right. Also, a cursor (ball) was visible, the horizontal location of which was fixed, but the vertical position of which could be controlled by the participant. The task was to move the ball up and down, thereby keeping it in the targets (i.e. move the cursor down when a lower target passed, and move it up when an upper target passed). The participant was instructed to use attempted hand movement to steer the cursor upwards and to keep it in the upper targets, and to relax to send the cursor down to the lower targets. As such, the task prepared the user to generate timely and short-lasting changes in the control signal (brain-clicks) for spelling.

CLICK TASK

The ability to produce brain-clicks was further investigated using the Click Task (Figure S4E). This task was based on a switch scanning protocol, in which rows of icons (in this case holes, one of which contained a mole, i.e. the target) were highlighted automatically one after the other and could be selected by a brain-click (Video 2). Individual icons of the selected row were subsequently highlighted and could be selected with a second click. This task required the user to generate brain-clicks during designated, short periods (trials), paving the way for spelling. True and false positives and negatives were expressed as a percentage of the total number of trials.

SPELLING AND HOME-USE

Similar to the Click Task, spelling was based on a switch scanning protocol, in which rows of letters were highlighted automatically and sequentially (Figure S4G). A row (containing the desired letter) could be selected with a brain-click at the correct moment, after which individual letters within the selected row would be highlighted sequentially and automatically. With a second brain-click, the desired letter could be selected. To quantify performance, the participant was asked to spell dictated words. True and false positives and negatives were expressed as a percentage of the total number of trials.

The home-use system included a commercial spelling program (Communicator-5, Tobii Dynavox), with the possibility of word-prediction (Video 3).

TRANSLATION OF BRAIN SIGNAL TO CONTROL SIGNAL

The software for acquisition, signal processing and translation of the signal acquired from the receiver was programmed using the BCI2000 platform.[S11] Signals pass through multiple filters developed and tested during the study (Figure S5) and are converted to a single, continuous control signal for the Target and Ball Tasks, and to a binary control signal for the Click Task and ultimately spelling.

CALIBRATION

During all Ball, Click and spelling runs, a 30s pretask recording period was used to obtain data for signal standardization during tasks (calibration by z-transformation), thereby compensating for any signal fluctuation between runs and days. Mean and standard deviation were computed of the data acquired during the 30s calibration period. This mean was subtracted from every sample acquired during subsequent task execution, and the result was divided by the standard deviation, resulting in z-scored data.

FEATURE SELECTION

Data acquired during the Ball Task (time-domain data acquired at 200Hz with the device) was used to determine, offline, the optimal center frequency and bandwidth for control (Figure S6A). The area under the ROC curve was computed over the range of all possible thresholds (see below), and for three different frequency ranges: LFB (10-30Hz), HFB (50-90 Hz) and the combination of the two, in which LFB had a weight of -1 and HFB a weight of 1. Notably, since data was acquired in time-domain on the device, data from many runs could be used to compute performance with LFB, HFB and the combination thereof, irrespective of the frequency band that was used for online feedback during a particular run. The HFB-LFB combination was used for the control signal, allowing us to determine the temporal evolution of power during active (upper) trials of varying duration of the Ball Task. Figure S4D shows the HFB power for 5 increasing durations of upper targets, indicating that the participant was capable of regulating the duration of keeping the control signal high. This encouraged the use of duration for conversion of the control signal to a brain-click. The frequency ranges used in the offline analyses translated to center frequency and bandwidth settings on the device of 20±2.5Hz and 80±2.5Hz, which became the default setting for brain-computer interface control.

SMOOTHING WINDOW AND THRESHOLD

Translation of the continuous control signal into discrete brain-clicks (only for Click Task and spelling) was achieved by thresholding the combined z-scored signal. Data acquired during the Click Task (5Hz power-domain) was used to determine the optimal smoothing and threshold parameters for control. By computationally simulating the software filters, different smoothing (0.2-3s in steps of 0.2s) and threshold (-1 to 2 in steps of 0.01) values were combined and accuracy (TP+TN/number of trials, in percentage, %) was calculated. The offline analysis gave an optimal combination of smoothing and threshold (Figure S6B,C). During spelling and most runs of the Click Task, the value of five subsequent samples (i.e. 1s in total) had to be above the set threshold to be translated into a click. A few runs of the Click Task were set differently: one run with a slightly longer above-threshold period required, and six runs where only 80% of samples had to be over the threshold. Performance was comparable but the participant preferred the final settings.

SIGNAL PROCESSING AND TRANSLATION

The decoding software consists of a series of filters displayed in Figure S5. When replaying time-domain data, an autoregression (AR) filter is used, which computes power for every 40 samples, resulting in power data of LFB and/or HFB, which is transferred to the next filter at 5Hz. All other filters are used during online tasks and spelling as well as during replay. In the Feature Selection filter, power signals are selected for further use. For the Target Task, the resulting signal is normalized to the height of the display and translated into the velocity of y-movement of the cursor. In the Smoothing filter each signal is smoothed with a selected smoothing window. Each smoothed signal is then z-transformed using the mean and standard deviation of the 30s calibration period in the Z-Transform filter. The z-scored signals are combined in one control signal using the Linear Classifier filter, by summing with specific weights (e.g. -1xLFB + 1xHFB). For the Ball Task, the resulting signal is normalized to the height of the display and translated into the y-position of the

cursor. For the Click Task and spelling, the control signal is thresholded using the Threshold Classifier filter and classified into a binary signal were a 1 represents the active state and 0 the rest state. Finally, the binary signal is translated into brain-clicks using the Click Translator, which uses a set minimum duration of continuous active state as criterion for a click. The clicks are then used to select rows and subsequently moles or letters in the respective applications.

OPTIMAL SETTINGS FOR SPELLING

Development and optimization of parameters for translation of the brain signal to the control signal culminated in optimal settings for using the speller software. The settings were unchanged for the duration of all 44 spelling runs since Day-168 and for home-use starting on Day-197. Settings were: smoothing 6 samples, and weights for HFB and LFB power of 1 and -1 respectively. For a selection to be triggered the control signal needed to be above a threshold of z=0.85, for 5 consecutive samples (1s). Several settings in the spelling software were separately optimized, and the following settings were settled upon: scan time 2.5s and a refractory period of 3.6s (during which the system did not respond to the control signal to avoid an immediate false positive).

STABILITY OF BRAIN SIGNAL AND CONTROL SIGNAL

Long-term use of the brain-computer interface implant requires stability of brain signal and the control signal. To assess stability, the same tasks were performed at regular intervals. Since the HFB power was the most useful feature as predicted in literature, we focused on that, and on the control signal.

Stability of task-related changes in HFB power was investigated by regularly performing recordings during the study, using a shortened version of the localizer task (duration 2.5 min), while time-domain power from an individual electrode pair was recorded (200Hz sampling rate). This procedure was repeated five times for all six bipolar pairs of the motor strip. Offline, correlation (R^2) of HFB power with the task was computed for each pair. Figure S3C shows that not all pairs yielded good and reproducible HFB power. The e2-e3 pair, however, produced strong and stable HFB power changes. For this pair, the shortened localizer was performed at least once a week, results of which are shown in Figure S3E. The HFB activity was high from Day-1 and remained high until the end of the study.

Stability of the control signal was also evaluated with repeated Target Task tests (only HFB power, Figure S4B) and Click Task tests (HFB-LFB power, Figure S4F). Performance on the Target Task and Click Task was high from the first session these tasks were attempted after fixing the respective parameters (Day-15 and Day-157, respectively) until the end of the study.

Finally, the control signal was evaluated during spelling, where both HFB and LFB power were used. Performance was high from the start at Day-168 and remained high (Figure S4H, Video 3). On average, across 44 spelling runs, the participant obtained an information transfer rate of 12.6±3.7 bit/min (mean±standard deviation). [S14] Together these findings indicate that the brain signal was quite stable over time, and that the control signal derived from it was robust.

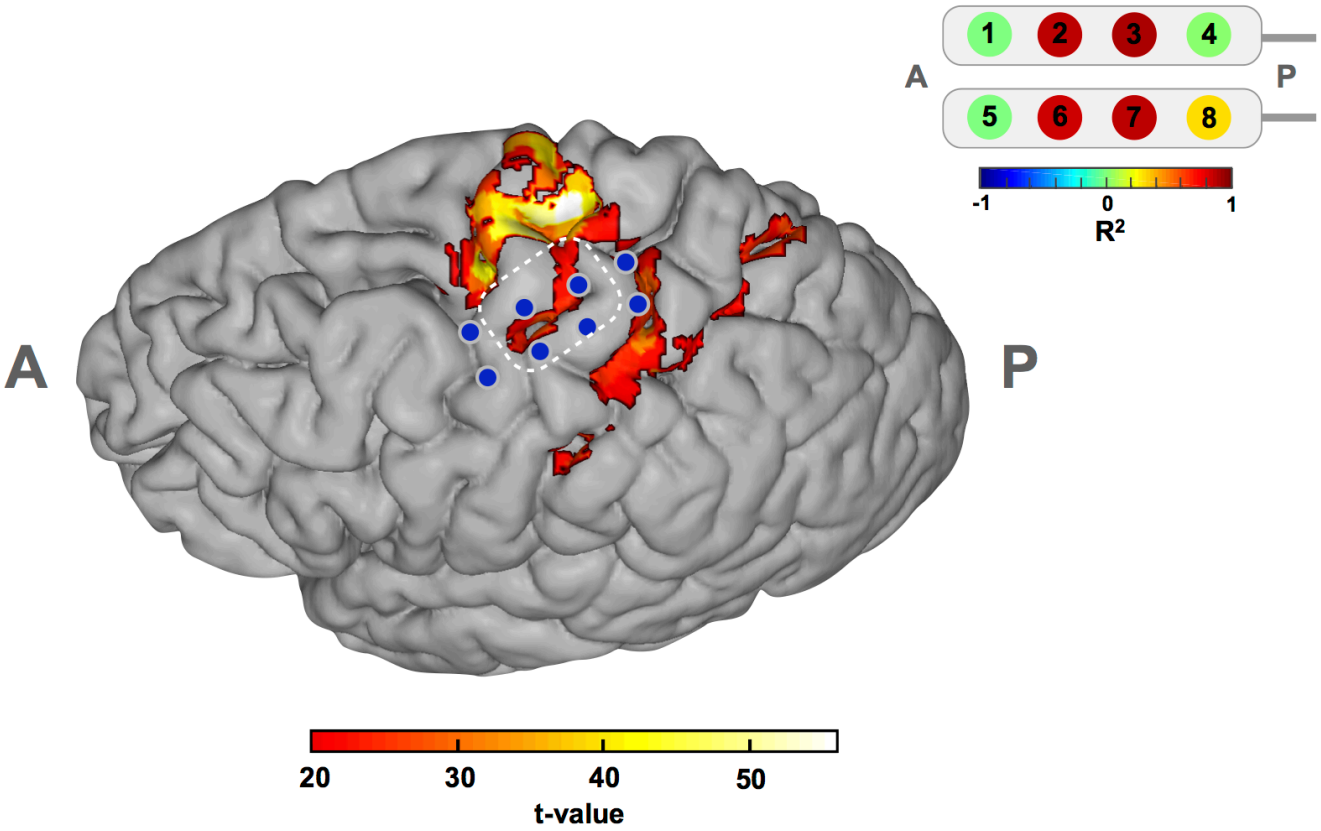


FIGURE S1 – FUNCTIONAL MRI
Rendering of the T1 weighted anatomical MRI scan of the participant, with the fMRI activation pattern of attempted right hand movement (t>20, projection depth 6mm) projected on the surface. The eight contact points of the electrode strips over the sensorimotor cortex are indicated in blue. The hand knob in the motor cortex is indicated with the white dotted line. The insert (top right) shows the R^2 values of the individual electrodes of the motor strips during the attempted movement localizer task (Day-1). Four electrodes (e2, e3, e6, e7) showed a significant HFB response to the task. The superior motor strip was selected for further use based on match with both fMRI and hand knob location, and was connected to the device during the second surgery. Note the large patch of fMRI activity superior to the hand region which anatomically corresponds to lower body movements and which was activated most likely inadvertently in attempting hand movement. This region was not considered for electrode placement since it is not selective for the hand and is thus sensitive to confounding activity (high false positive rate in decoding). A – anterior, P – posterior.

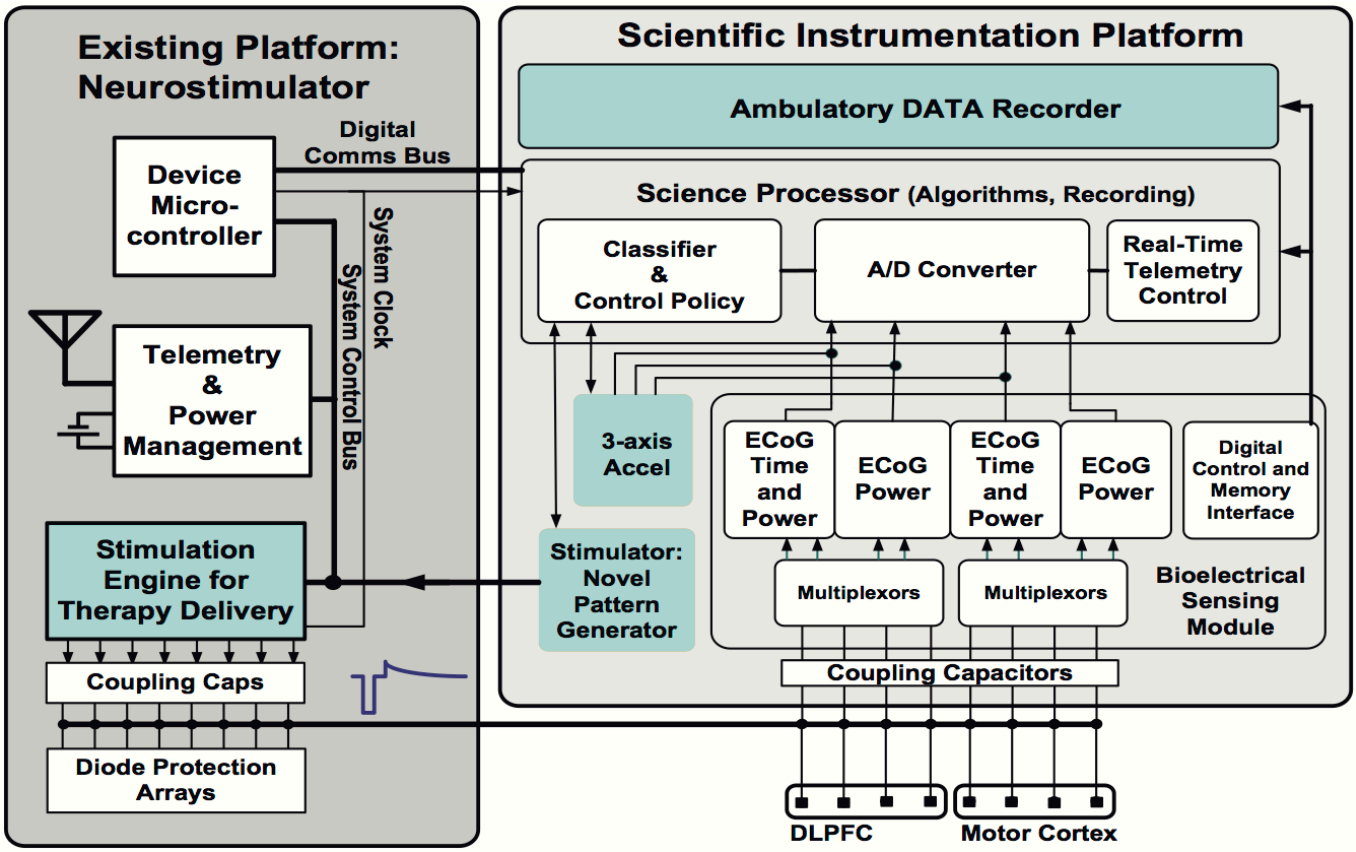
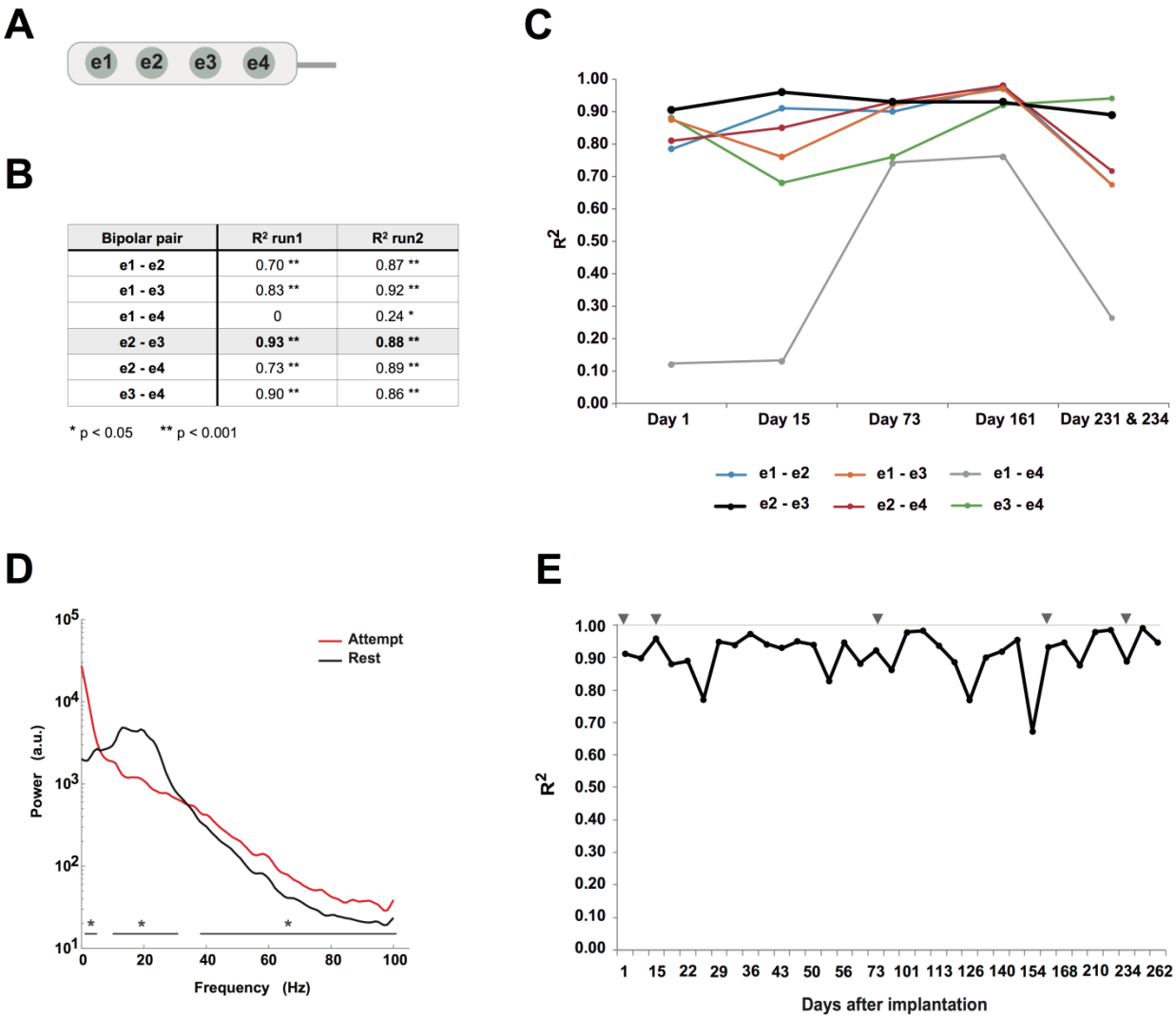


FIGURE S2 – ACTIVA PC+S DEVICE CONFIGURATION
The Activa PC+S system was configured to allow for chronic measurement of cortical signals through the Resume II electrodes. The signal processing chain passed amplified, processed and digitized signals through the wireless telemetry system of the neuromodulator. The areas highlighted in blue, in particular the stimulation circuits, were disabled to prevent stimulation of the cortex or minimize power consumption. Of note, the Classifier & Control Policy unit was not used in this study.



Bipolar pair	R^2 run1	R^2 run2
e1 - e2	0.70 **	0.87 **
e1 - e3	0.83 **	0.92 **
e1 - e4	0	0.24 *
e2 - e3	**0.93 ** **	**0.88 ** **
e2 - e4	0.73 **	0.89 **
e3 - e4	0.90 **	0.86 **

* $p < 0.05$ ** $p < 0.001$

FIGURE S3 – ELECTRODE PAIR SELECTION

A) Electrode layout of the strip used for brain-computer interface control. B) Bipolar analysis of all combinations of the selected electrode strip over the sensorimotor cortex recorded twice (Run 1 and 2) during days between surgeries (Day-1 and Day-2). Results revealed that pair e2-e3 showed the most consistent and high correlation (R^2) of HFB power with the localizer task (attempted movement versus rest, * $p<0.05$, ** $p<0.001$). C) R^2 values of all bipolar pairs (HFB power) obtained during repetitions of the localizer tasks on five occasions after implantation. Data on Day-15 and beyond were acquired with the implanted device, which was set to transmit time signal at 200Hz for offline frequency analysis (Day-1 is average of data in B). Note that R^2 values of electrode pair e2-e3 used for brain-computer interface control are stable over time. D) Spectral power distribution of attempted movement (red) and rest (black) of the e2-e3 pair during the performance of a localizer task (Day-15). The gray horizontal line at the bottom indicates a significant difference between the two distributions (two-sampled t-test, * $p<0.05$). E) R^2 values of the bipolar pair used for brain-computer interface control (e2-e3, HFB power), measured frequently with the localizer task. The grey pointers indicate data points that are also shown in panel C.

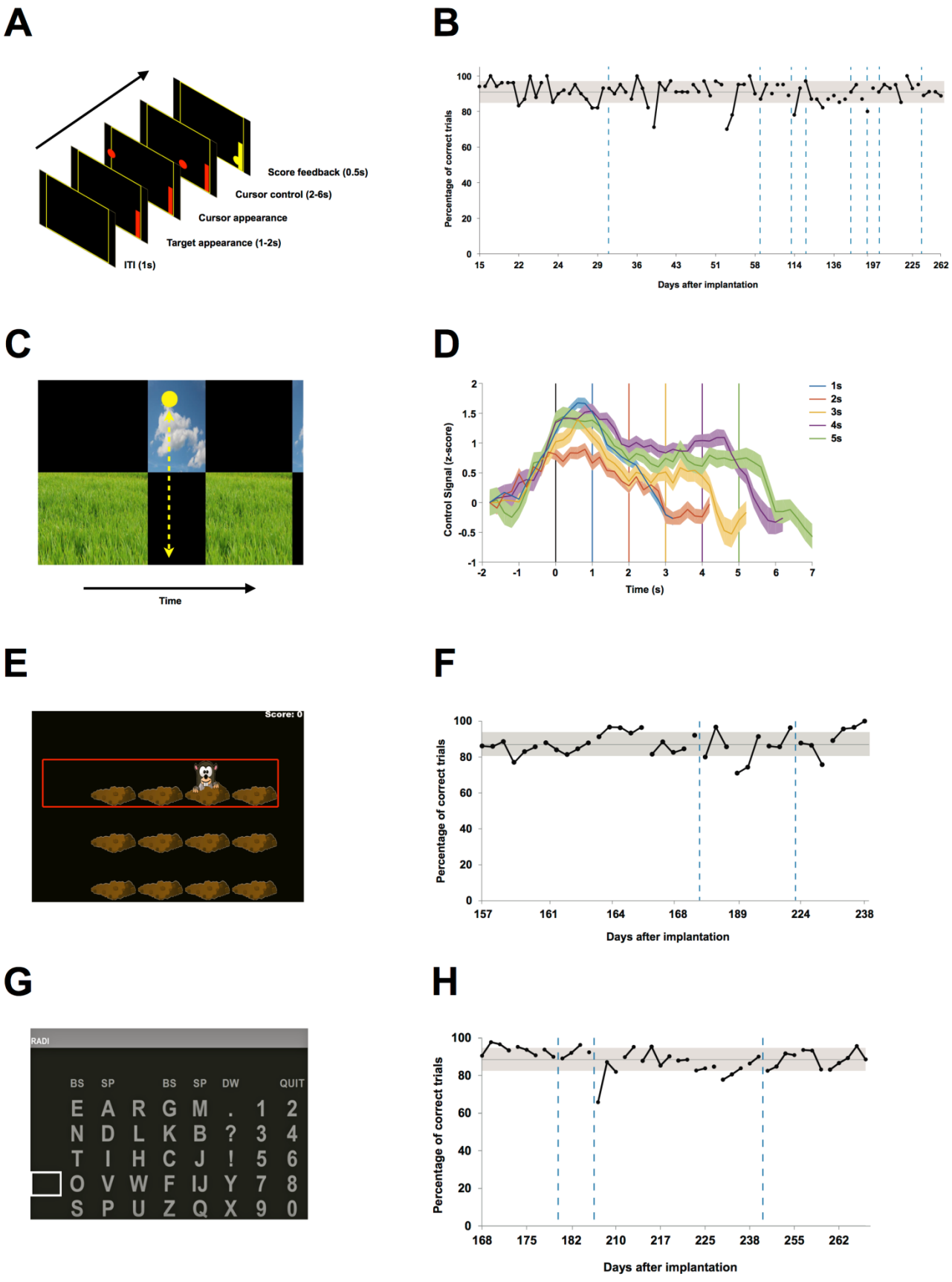


FIGURE S4 – TRAINING TASKS AND PERFORMANCE

A) Target Task design. The control signal controlled the vertical speed of the cursor (red circle) on the screen in an attempt to hit the target (red bar) randomly placed at either the top or the bottom.

With training, continuing high performance allowed the trial durations to be shortened. Since the total duration of each run was maintained at 300s, the number of trials per run increased from 24 to 47. B) Target Task performance development over the 262 days of the study. Each black dot represents a single run. Multiple runs on the same day are indicated by connecting black lines between the dots. The horizontal gray line and shading represent mean and standard deviation computed across all runs. Blue vertical dashed lines at, roughly, 30-day intervals indicate a decline of Target Task frequency as the participant engaged more in the Click Task and spelling (note that the x-axis scale is not linear). HFB power was used as a control signal during this task. Permutation tests on the control signal data revealed that the chance score level in the task was 48.4% with a confidence interval of 1.3%. C) Ball Task design. The control signal controlled the vertical position of a ball while the background moved to the right at a fixed pace. Goal was to keep the ball in the lower targets (grass) or upper targets (sky). The duration of the sky targets varied between 1 and 5 seconds. D) Temporal evolution of the power traces of the HFB-LFB combination during the Ball Task. Data was acquired in time domain, was converted to power and was z-transformed (see section on Translation of brain signal to control signal). Lines represent the control signal for each of 5 sky target durations, averaged over varying numbers of trials (ranging from 58 to 235). Shading represents standard error. The offset of each trace was set at zero for the first sample of each trial. Trials were time-locked relative to the moment the sky target reached the ball (t=0). Colored vertical lines indicate the end of sky trials of different durations. E) Click Task design. Rows of icons were highlighted sequentially at a fixed pace (red box) during which it could be selected by a click. Individual icons of the selected row were subsequently highlighted and could be selected with a second click. Goal was to select only the mole (see Video-2). F) Click Task performance development over time. Each black dot represents a single run. Multiple runs on the same day are indicated by connecting black lines between the dots. The horizontal gray line and shading represent mean and standard deviation computed across all 37 runs with HFB-LFB power for the control signal. Twelve runs were acquired in time-domain, the others in power-domain. Blue vertical lines indicate, roughly, 30-day intervals. Note that the x-axis is not linear. G) The research speller display used for training. In each run a word was given that needed to be spelled (here 'radio'). The white box shifts a row or column at a fixed pace (set between 2s and 3s), and a brain-click results in selection of the boxed item. H) Speller performance over time. Each dot represents a single run (HFB-LFB as a control signal). Multiple runs on the same day are indicated by connecting black lines between the dots. The horizontal gray line and shading represent mean and standard deviation across all runs. Blue vertical lines indicate, roughly, 30 day intervals. Note that the x-axis is not linear.

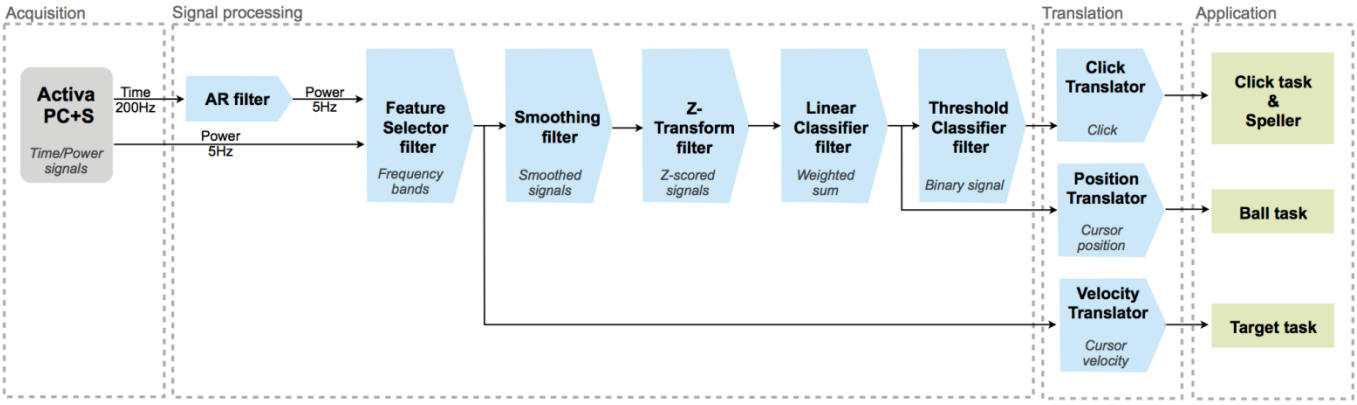


FIGURE S5 – FILTER PIPELINE
Filter pipeline implemented on the BCI2000 platform. After data acquisition, the following signal processing filters can be distinguished: 1) Auto-Regressive (AR) filter; 2) Feature Selector filter; 3) Smoothing filter; 4) Z-Transform filter; 5) Linear Classifier filter; 6) Threshold Classifier filter. Explanations are given in the Section on Translation of brain signal to control signal.

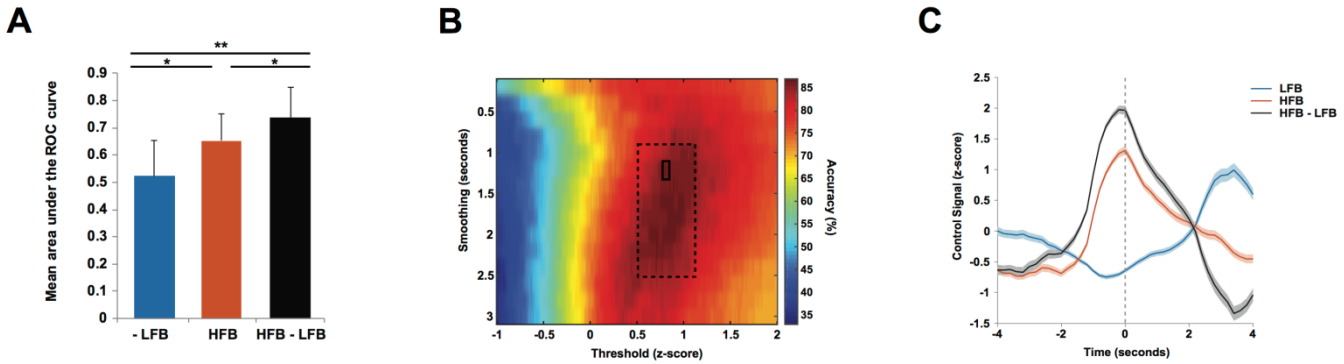


FIGURE S6 – OPTIMIZATION OF FILTER PARAMETERS

Parameters were optimized offline using data from the Click and the Ball Tasks. A) For all 16 runs of the Ball Task acquired from electrodes e2-e3 with HFB-LFB (weights 1 and -1) and upper target trial durations of 2s (acquired at 200Hz), the area under the ROC curve was computed offline over the range of all possible thresholds, and for either LFB power, HFB power or the combination HFB-LFB power. Performance with the latter was significantly higher than with only LFB or HFB power (* $p<0.01$, ** $p<0.0001$, paired t-tests). B) Average heat map (smoothing versus threshold, color bar representing task performance) for Click Task runs with 1/-1 weights for HFB minus LFB power (computed for each of 18 power-domain runs and then averaged). Effects of smoothing and thresholding (see Figure S5) on performance were determined by replaying the data through the Click Task for a range of values (steps of 0.2s for smoothing and steps of 0.01 for thresholding of z-transformed data). Performance was computed as the percent correct trials (no click on non-target trials plus correct clicks on target trials, see Video 2). The black dashed square roughly indicates the region of optimal parameter settings. The black solid square indicates the parameters selected for brain-computer interface control. C) Time-locked control signal in target trials (only correct clicks) during the 18 Click Task runs used in panel B. Data were obtained online with 1/-1 weights for HFB/LFB, a 1.2s smoothing window and a threshold of 0.8 or 0.85. Trials were locked to the actual click moment (dotted vertical line, time-0). Lines represent mean evolution of the control signal based either on LFB power, HFB power or the weighted sum (-1xLFB + 1xHFB). Shading along the lines denotes standard error.

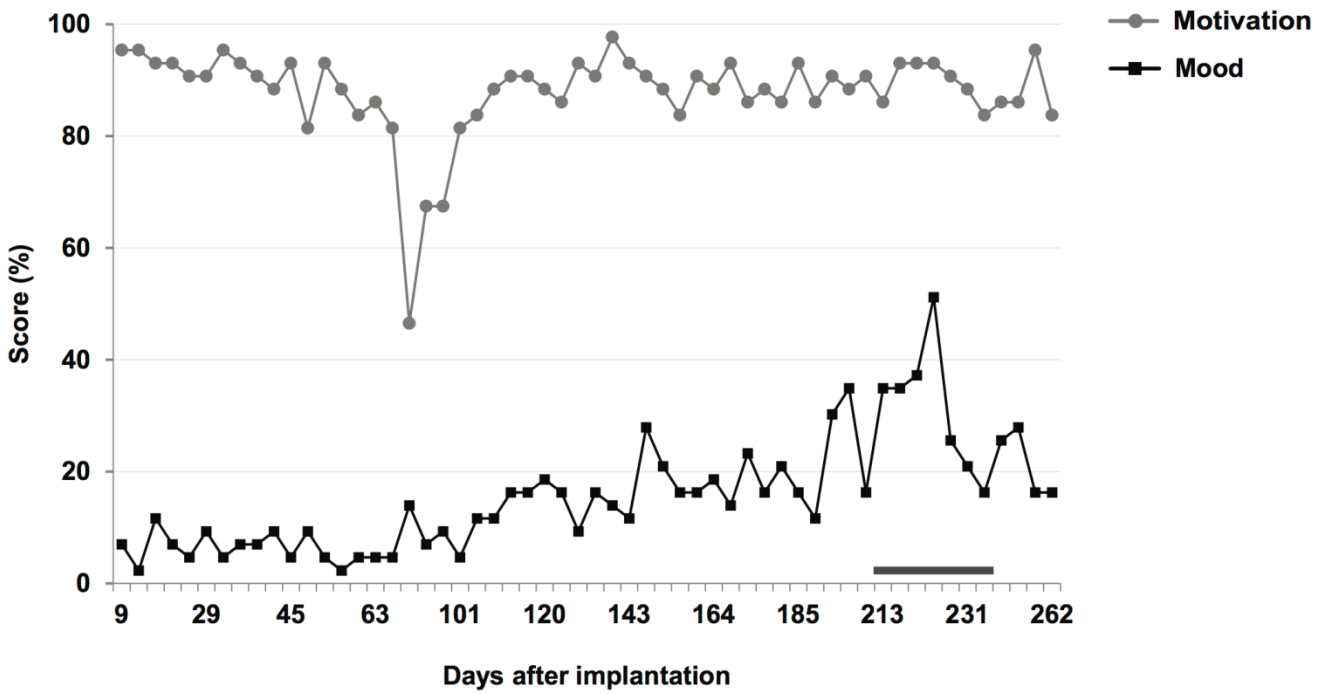


FIGURE S7 – MOOD AND MOTIVATION SCORES
VAS scores given every session by the participant for her mood (low score indicates low depression), and motivation (high score indicates high motivation). A dip in motivation (Day-73 until 79) occurred when parameter testing led to poor decoding. A rise in depression (black bar at Day-213 until 231) occurred due to medical problems unrelated to the study.

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