



Published in final edited form as:

N Engl J Med. 2024 August 15; 391(7): 619–626. doi:10.1056/NEJMoa2314598.

Longevity of a Brain-Computer Interface for Amyotrophic Lateral Sclerosis

Mariska J Vansteensel, Ph.D.^{1,*}, Sacha Leinders, M.Sc.¹, Mariana P Branco, Ph.D.¹, Nathan E. Crone, M.D.², Timothy Denison, Ph.D.³, Zac V Freudenburg, Ph.D.¹, Simon H Geukes, M.Sc.¹, Peter H Gosselaar, M.D.¹, Mathijs Raemaekers, Ph.D.¹, Anouck Schippers, M.Sc.¹, Malinda Verberne, M.Sc.¹, Erik J Aarnoutse, Ph.D.¹, Nick F Ramsey, Ph.D.¹

¹Department of Neurology and Neurosurgery, Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

²Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

³Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Old Road Campus Research Building, Oxford, United Kingdom

Summary

The durability of communication using Brain-Computer Interfaces (BCIs) in people with progressive neurodegenerative disease has not been extensively examined. We report on 7 years of independent at-home use of an implanted communication-BCI by an individual with advanced Amyotrophic Lateral Sclerosis (ALS), the inception of which was reported in 2016. Frequency of at-home use increased over time to substitute for gradual loss of control of an eye gaze tracking device, followed by progressive decrease in use that started 6 years after implantation. At-home use ended when BCI control became unreliable. There were no signs of technical malfunction. Instead, the amplitude of neural signals declined, and Computed Tomography imaging demonstrated progressive atrophy, suggesting that ALS-related neurodegeneration ultimately rendered the BCI ineffective after years of successful use, although there are plausible alternative explanations.

Introduction

People with amyotrophic lateral sclerosis (ALS) develop motor and speech impairments that prohibit communication. Existing augmentative and assistive communication technology relies on residual muscle activity and is ineffective for a substantial portion of people with ALS^{1,2}. Implantable Brain-Computer Interfaces (BCIs) promise to improve the communication impairments of people with ALS by enabling brain-based control over communication technology. We and others have demonstrated the usability of implantable

This Author Accepted Manuscript is licensed for use under the CC-BY-ND license.

*Corresponding author: Dr. Mariska J Vansteensel, UMC Utrecht Brain Center, Department of Neurology & Neurosurgery, University Medical Center Utrecht, P.O. Box 85060, 3508 AB Utrecht, The Netherlands, m.j.vansteensel@umcutrecht.nl.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](https://www.nejm.org).

communication-BCIs for people with ALS to generate click-commands for spelling words and alerting a caregiver in daily-life settings^{3–5}. In addition, several reports have recently shown fast communication rates using implantable BCI technology^{6,7}.

ALS is associated with progressive cerebral atrophy⁸, particularly in the motor cortex, which generates the signals used by the majority of implantable BCIs. Consequently, BCI control signals may be expected to change in the course of the disease. Yet, the question if BCI efficacy can be retained longitudinally to address the unmet communication needs of people with ALS in the face of ALS progression remains unresolved. Here, we report on the frequency and longevity of independent at-home use of an implanted communication-BCI by an individual with late-stage ALS, the original report of which was published in the Journal in 2016³.

Methods

Participant

The participant was a woman diagnosed with ALS in 2008 (age 58 at study inclusion). She was locked-in, received tracheostomy invasive ventilation, and had a score of 2 on the ALS functional rating scale at study inclusion in September 2015³ and a score of 1 in December 2017. No indications of cognitive impairments were observed during formal assessments conducted in October 2015³ and August 2020. In October 2015, a BCI system was implanted as part of her participation in the Utrecht NeuroProsthesis study ([Clinicaltrials.gov: NCT02224469](https://clinicaltrials.gov/ct2/show/study/NCT02224469))³. The BCI system comprised four subdural electrocorticography electrode strips (Resume II, Medtronic, off-label use) and a subcutaneous amplifier/transmitter device placed in the chest area (Activa[®] PC+S, Medtronic, off-label use). Two electrode strips were located over dorsolateral prefrontal cortex and two over sensorimotor cortex. Electrodes were kept in position by connections to the skull³. One strip per area was connected to the amplifier/transmitter device. The amplifier/transmitter device enabled transcutaneous transmission of bipolar referenced data to an antenna attached to the clothing (see Supplementary Material for more details). Because of anticipated unavailability of replacement devices, the amplifier/transmitter device was replaced in September 2020 by a device with a full battery, to enable continuation of BCI use. The new device was connected to both sensorimotor strips. The participant gave informed consent to participate in this research³. The study was approved by the Utrecht Medical Ethics Review Committee and conducted in accordance with the Declaration of Helsinki. Adverse events experienced by the participant are listed in Supplementary Table S1.

Intracranial data

For BCI control, the participant used short right-hand movement attempts to generate changes in low frequency band (LFB, alpha and beta) and high frequency band (HFB, high gamma) power in the sensorimotor cortex. These features, recorded from a single electrode pair over the sensorimotor cortex, were converted into click-commands for spelling, and into a call caregiver signal^{3,9}. At-home BCI use initially relied on LFB and HFB power of electrode pair E2-E3 over the sensorimotor cortex (see Figure 1 of³). Starting in December

2021, LFB power of E2-E3 was combined with HFB power of electrode pair E10-E12, also located over the sensorimotor cortex, in an attempt to retain reliable BCI control.

At-home BCI use was logged on a tablet computer that ran the BCI decoding pipeline and the communication user interface. To respect the privacy of the participant, upon her request, these logs of at-home use did not contain information about the applications used, the messages conveyed, or the accuracy of at-home BCI use. We report the mean number of hours of at-home use per day for each month after BCI implantation. Periods of at-home use were defined by the system being connected and available to the participant for use. We also report the number of requests for changes to the BCI user interface over time.

During research visits, the participant regularly executed tasks that involved the generation of clickcommands: a Click task in which icons were highlighted sequentially and a target could be selected by a brain-click³, and a Spelling task in which click-commands could be used to select letters and spell words³. Data of these tasks was used to assess the accuracy of click-commands over time (100 times the ratio of the number of correct trials divided by total number of trials).

In addition, the participant regularly executed three tasks that served longitudinal monitoring of neural signal features for BCI control: a Baseline task (duration 2–5min), where she was instructed to relax while fixating on a circle on a computer screen; an Attempt-Rest task (duration 2–5min, trials 15sec), in which she was instructed to attempt right-hand finger tapping during active trials, and to relax during rest trials; and a somatosensory Brush-Rest task (duration 2–5min, trials 15sec), in which the participant's right hand was stroked with a brush during active trials, and no brush strokes were applied during rest trials. Data acquired during these tasks was used to investigate the longitudinal development of 1) baseline LFB and HFB power, 2) the amplitude of changes in LFB and HFB power that were generated by hand movement attempts in the Attempt-Rest task and by somatosensory stimulation of the hand in the Brush-Rest task, and 3) the strength of the relationship (r^2 value) between LFB/HFB power and the Attempt-Rest and Brush-Rest tasks (see Supplementary Material for more details).

Impedance

During every research visit, electrode impedance was measured by applying a brief pulse to each bipolar electrode pair of the implanted strips (pulse width 80 μ s; frequency 100Hz; potential 0.25V or 0.70V).

Imaging

The day after electrode implantation in October 2015, a head computed tomography (CT) scan was made to determine the location of the implanted electrodes. A second CT scan was made in September 2023 to investigate the cause of changes in neural signal features.

The two CT scans were compared to assess any progressive brain tissue loss. The first and second CT scans were aligned using a mutual information criterion to allow for direct topographic comparison. Then, for each voxel in the two CT scans, an estimation was made regarding the probability of it being part of either grey matter, white matter

or corticospinal fluid (CSF) using unified segmentation, while simultaneously establishing warping parameters to transform images from Montreal Neurosciences Institute space (used in image sciences as a common average reference image) to native space¹⁰. The resulting probability maps were used to produce two unique volumes per CT scan: one comprising voxels with a high probability of being brain tissue (grey or white matter), and one comprising voxels with a high probability of being CSF.

Regions of interest were created in Montreal Neurological Institute space, including the left and right frontal, occipital, temporal and parietal lobes, and the entire right (non-implanted) hemisphere, by combining areas from the automatic anatomical labeling atlas¹¹. The regions were inverse normalized to native space using the warping parameters established for the first CT scan. For each region and CT, we calculated the ratio between brain tissue volume (grey + white matter) and combined brain tissue and CSF volume. Note that the left frontal and parietal cortices in both CTs contained artefacts related to the implanted electrodes, which reduced the quality of the respective measurements.

NFR, MJV and EJA designed the study; SL, SHG, AS, and MV gathered the data; SL, MPB, ZVF, SHG, MR, AS, MV analyzed the data; all authors contributed to the interpretation of the data and vouch for the data and the analysis; MJV wrote the first draft of the manuscript and all authors reviewed the paper and approved of the version to be published.

Other than standard funding agreements with the public funding agencies mentioned in the funding section, no agreements were in place regarding the confidentiality of the data between the sponsor and the authors or institutes mentioned in the acknowledgements.

Results

At-home use of the BCI

The participant started using the BCI independently at home to communicate with her family and caregivers seven months after implantation. Regular requests for adaptations to the user interface (e.g., adding specific buttons, changing sound levels) underline the active use and perceived usability of the system (Supplementary Figure S1). Initial use was limited to outdoor settings, where functioning of the eye gaze device was insufficient⁴. Approximately 2.5 years after BCI implantation, the participant's control of the eye gaze device had deteriorated due to progressive oculomotor impairment (Figure 1A), and she increasingly used the BCI indoors to call for attention and to communicate with family and caregivers (Figure 1B)¹². As of the fall of 2019, she no longer used the eye gaze device (Figure 1A). In September 2020, a 'night-mode' was implemented, which enabled the participant to reliably use the BCI also at night to call a caregiver, for example to request medication or airway suctioning. In the subsequent 11 months, the participant used the BCI system 20–24 hours per day, mainly to call the caregiver. Subsequent interactions regarding the nature of the request were typically accomplished using closed questions answered by residual movements of the corner of the mouth (Figure 1A), the only movement she could still voluntarily generate at this stage. This way of conveying wishes and needs was preferred by the participant, possibly because her vision was regularly impaired due to drying cornea and difficulties keeping the eyes open, which made it difficult to see

the BCI speller interface, or because it was faster than sequentially selecting letters using the BCI. Note that the BCI system allowed her to self-initiate interaction, which was otherwise not possible. Close to 6 years after implantation, at-home BCI use started to decline. This decline coincided with a decline in click-command accuracy, as assessed during research visits (Figure 1C). In addition, the participant's family and caregivers experienced increasing difficulty to assess the reason for a BCI-based caregiver call, because the residual movements of the corner of the mouth were increasingly inconsistent and difficult to interpret (Figure 1A). Consequently, caregivers grew uncertain if caregiver calls were intentional or not, initially at night and later also during the day. In October 2022, nocturnal use of the BCI system was discontinued and as of March 2023, the BCI system was no longer used. In the subsequent months, the participant completely lost the ability to move the corner of the mouth (Figure 1A) and became completely locked-in.

Neural signals

LFB and HFB power of electrode pair E2-E3 during baseline measurements showed a steep decline in the first 12 months after implantation, followed by a slower, apparently linear decline in subsequent years (Supplementary Figure S2A; Supplementary Table S2). Also, the amplitude of LFB and HFB power changes generated by attempted hand movements declined linearly over time in electrode pair E2-E3, as well as in electrode pair E10-E12 (Supplementary Figure S2B; Supplementary Table S3). Despite the decline in the amplitude of LFB and HFB power changes generated by attempted hand movements, a strong relation (r^2) between the neural signals and the Attempt-Rest task conditions was retained during 5 years after implantation, after which this relationship declined and approached zero by the start of the 8th year after implantation (Supplementary Figure S2C and S2D). The amplitude of the LFB and HFB power changes induced by the Brush-Rest task also declined, but to a lesser degree, and the relation (r^2) between the neural signals and the Brush-Rest task remained strong until the end of at-home BCI use (Supplementary Figure S2E and S2F).

Impedance and Imaging

Impedance measurements of E2-E3 showed an initial rise during the first half year, after which impedance declined linearly (Figure 2A; Supplementary Table S4). Impedance of electrode pair E10-E12 (measured after replacement surgery in September 2020) similarly showed a decline.

Visual inspection of the CT scans revealed substantial ventricular enlargement and brain tissue volume reduction in the second CT (2023) compared to the first CT (2015) (Figure 2B/C). The brain tissue/brain tissue+CSF ratio decreased considerably for all but the occipital lobes (Right hemisphere: Occipital 0.90 to 0.88, Parietal 0.82 to 0.69, Frontal 0.82 to 0.58, Temporal 0.91 to 0.83; Left hemisphere: Occipital 0.91 to 0.87, Parietal 0.64 to 0.47, Frontal 0.64 to 0.43 and Temporal 0.89 to 0.76). For the entire right hemisphere, this ratio was reduced by 0.13, from 0.85 to 0.72, substantially exceeding the average reduction of 0.03 associated with healthy aging¹³.

Discussion and Conclusion

We report on the complete lifecycle, lasting almost 7 years, of independent at-home use of an implanted BCI system by an individual with ALS. In this period, frequency of use of the BCI system evolved. Initially, the BCI was used only in situations where conventional augmentative and assistive communication technology (eye tracker device) was inadequate. As the disease progressed and conventional communication technology became less effective, the participant increasingly relied on the BCI to the point where it was the only way she could initiate communication. BCI use decreased when it was perceived to become less reliable, until its discontinuation 7.5 years after implantation. The BCI was the sole communication technology used by the participant, and the only way in which she could attract the attention of the caregiver, for over 3 years.

Several causes should be considered for the decline in BCI performance beyond ~6 years after implantation. First, the high r^2 values (i.e., strong task-related activity, r^2 values close to 1 and -1) generated by the Brush-Rest task until the end of at-home use, when the r^2 values associated with the Attempt-Rest task approached zero in the same electrodes, make hardware issues unlikely. Second, it is worth noting that the slow longitudinal decline in impedance coincided with a gradual decay in baseline amplitude of LFB and HFB power. The decrease in frontal and parietal brain volume observed in the CT scans made 8 years apart suggests that these gradual changes related to the growing distance between the cortical surface and the electrode strips, which were attached to the skull, as a result of progressive brain atrophy caused by ALS. Notably, the initial rise in impedance over the first months after implantation, and the concurrent decline in baseline LFB and HFB power, are most likely related to local tissue reactions and electrode encapsulation^{14,15}, but were not associated with suboptimal BCI performance. Third, the decrease of the amplitude of the neural signal changes generated by the Attempt-Rest task, and eventually of r^2 values of the Attempt-Rest task but not (yet) those of the Brush-Rest task, suggest that ALS progression caused an increasing difficulty for the participant to consistently and reliably produce neural signal changes in the sensorimotor cortex, perhaps due to a waning ability to sustain attention or to cognitive decline, which are known to occur in ALS¹⁶, or due to ALS-related degeneration of the neurons in the sensorimotor cortex.

We report that an implanted communication-BCI that served as an initially ancillary and later sole communication technology in an individual with ALS was functional for over 7 years of use after implantation. We suggest reasons for its eventual failure and our findings pertain to this person and the particular system used.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the participant and her family and caretakers for their time and effort.

Funding

National Institute on Deafness and Other Communication Disorders (U01DC016686)

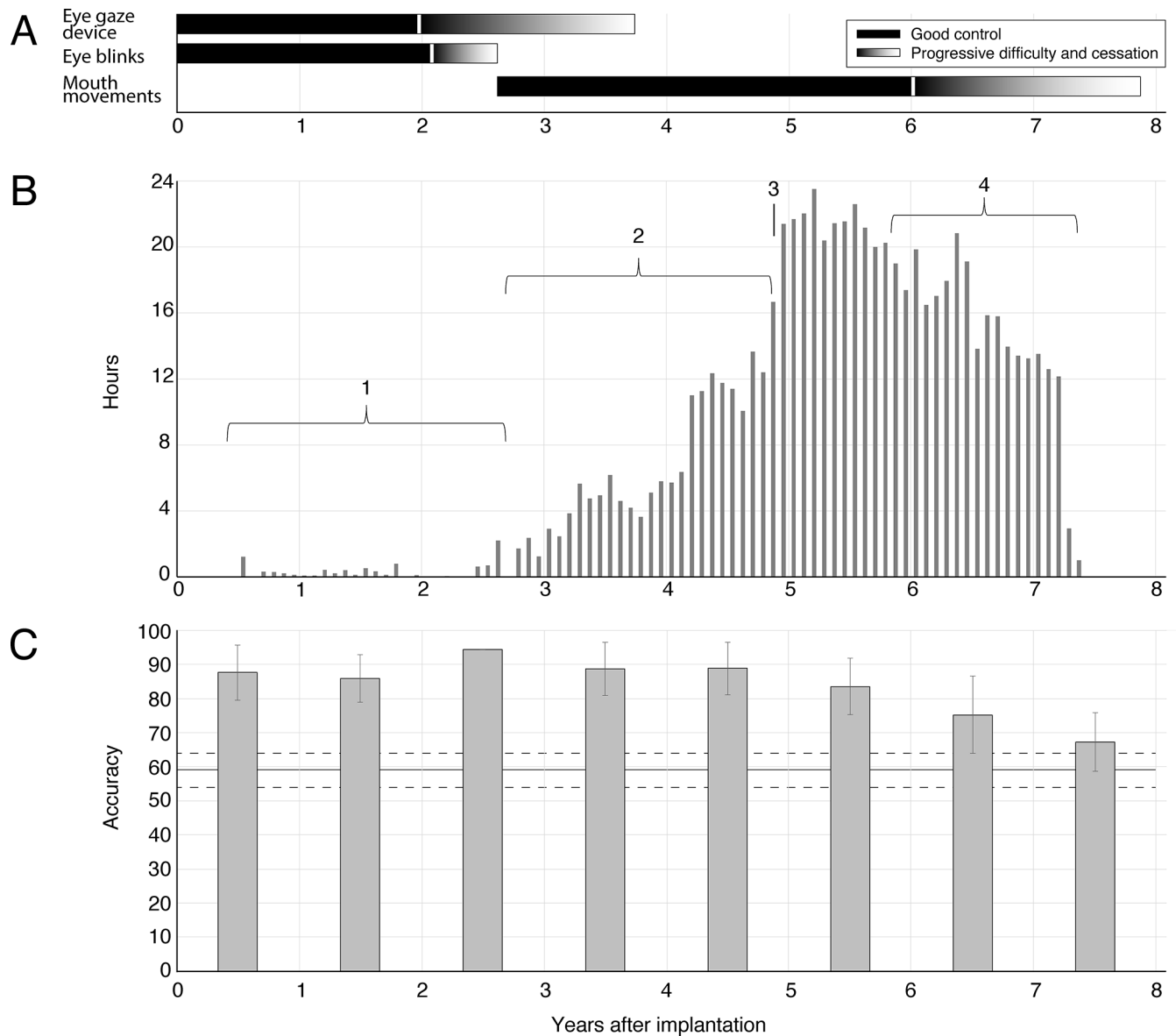
National Institute of Neurological Disorders and Stroke (UH3NS114439)

Dutch Research Council (INTENSE, 17619)

Dutch Government (UGT7685, Economic Affairs SSM06011 and STW 12803, investigator-initiated study where Medtronic provided financial support and technical support, but did not have input on experimental design, data analysis and manuscript preparation)

References

1. Spataro R, Ciriacocono M, Manno C, La Bella V. The eye-tracking computer device for communication in amyotrophic lateral sclerosis. *Acta Neurol Scand* 2014;130(1):40–5. [PubMed: 24350578]
2. Kageyama Y, He X, Shimokawa T, et al. Nationwide survey of 780 Japanese patients with amyotrophic lateral sclerosis: their status and expectations from brain-machine interfaces. *J Neurol* 2020;267(10):2932–40. [PubMed: 32488296]
3. Vansteensel MJ, Pels EGM, Bleichner MG, et al. Fully Implanted Brain-Computer Interface in a Locked-In Patient with ALS. *N Engl J Med* 2016;375(21):2060–6. [PubMed: 27959736]
4. Pels EGM, Aarnoutse EJ, Leinders S, et al. Stability of a chronic implanted brain-computer interface in late-stage amyotrophic lateral sclerosis. *Clin Neurophysiol* 2019;130(10):1798–803. [PubMed: 31401488]
5. Oxley TJ, Yoo PE, Rind GS, et al. Motor neuroprosthesis implanted with neurointerventional surgery improves capacity for activities of daily living tasks in severe paralysis: first in-human experience. *J Neurointerv Surg* 2021;13(2):102–8. [PubMed: 33115813]
6. Willett FR, Kunz EM, Fan C, et al. A high-performance speech neuroprosthesis. *Nature* 2023;620(7976):1031–6. [PubMed: 37612500]
7. Metzger SL, Littlejohn KT, Silva AB, et al. A high-performance neuroprosthesis for speech decoding and avatar control. *Nature* 2023;620(7976):1037–46. [PubMed: 37612505]
8. Dadar M, Manera AL, Zinman L, et al. Cerebral atrophy in amyotrophic lateral sclerosis parallels the pathological distribution of TDP43. *Brain Commun* 2020;2(2):fcaa061. [PubMed: 33543125]
9. Leinders S, Pels E, Vansteensel M, et al. Using a one-dimensional control signal for two different output commands in an implanted BCI. *Proceedings of the 7th Graz Brain-Computer Interface Conference 2017*;270–3.
10. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* 2005;26(3):839–51. [PubMed: 15955494]
11. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15(1):273–89. [PubMed: 11771995]
12. Aarnoutse E, Leinders S, Freudenburg Z, et al. Long-term home use of a fully implanted BCI for communication: visual and auditory spelling. *Proceedings of the 8th Graz Brain-Computer Interface Conference 2019*;309–11.
13. Vågberg M, Granåsen G, Svenningsson A. Brain Parenchymal Fraction in Healthy Adults-A Systematic Review of the Literature. *PLoS One* 2017;12(1):e0170018. [PubMed: 28095463]
14. Cui Jie, Mivalt Filip, Sladky Vladimir, et al. Acute to long-term characteristics of impedance recordings during neurostimulation in humans. *medRxiv* 2024;2024.01.23.24301672.
15. Sillay KA, Rutecki P, Cicora K, et al. Long-term measurement of impedance in chronically implanted depth and subdural electrodes during responsive neurostimulation in humans. *Brain Stimul* 2013;6(5):718–26. [PubMed: 23538208]
16. Abrahams S Neuropsychological impairment in amyotrophic lateral sclerosis-frontotemporal spectrum disorder. *Nat Rev Neurol* 2023;19(11):655–67. [PubMed: 37828358]

**Figure 1.**

At-home use of the implanted BCI. A) Methods of communication other than the BCI used by the participant in the course of time since implantation in October 2015. B) Frequency of at-home use of the BCI. For every month, the mean number of hours per day of at-home use of the BCI is indicated. Numbers 1–4 refer to noteworthy periods/instances, namely 1) predominantly outdoor use of the BCI system, 2) increasing (indoor) use of the BCI system, related to progressive inability to use the eye gaze device, 3) implementation of the night-mode feature, and 4) gradual decline in BCI use, initially during the night, later also during the day. C) Accuracy (%) of click-commands during research visits (mean $\pm$ standard deviation over all click-command-tasks per year). The horizontal lines denote the mean (solid line) $\pm$ standard deviation (dashed lines) chance level over all click-command-tasks.

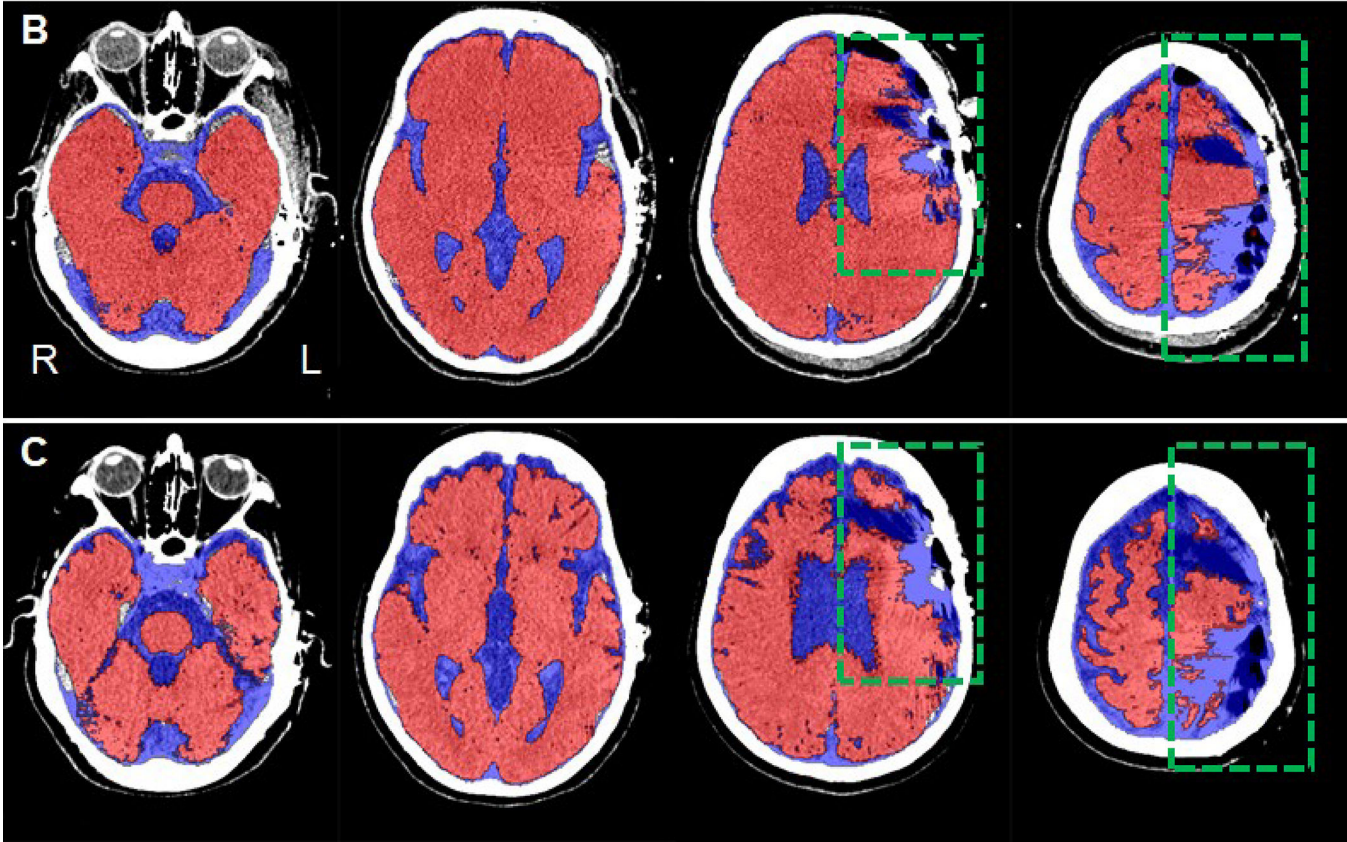
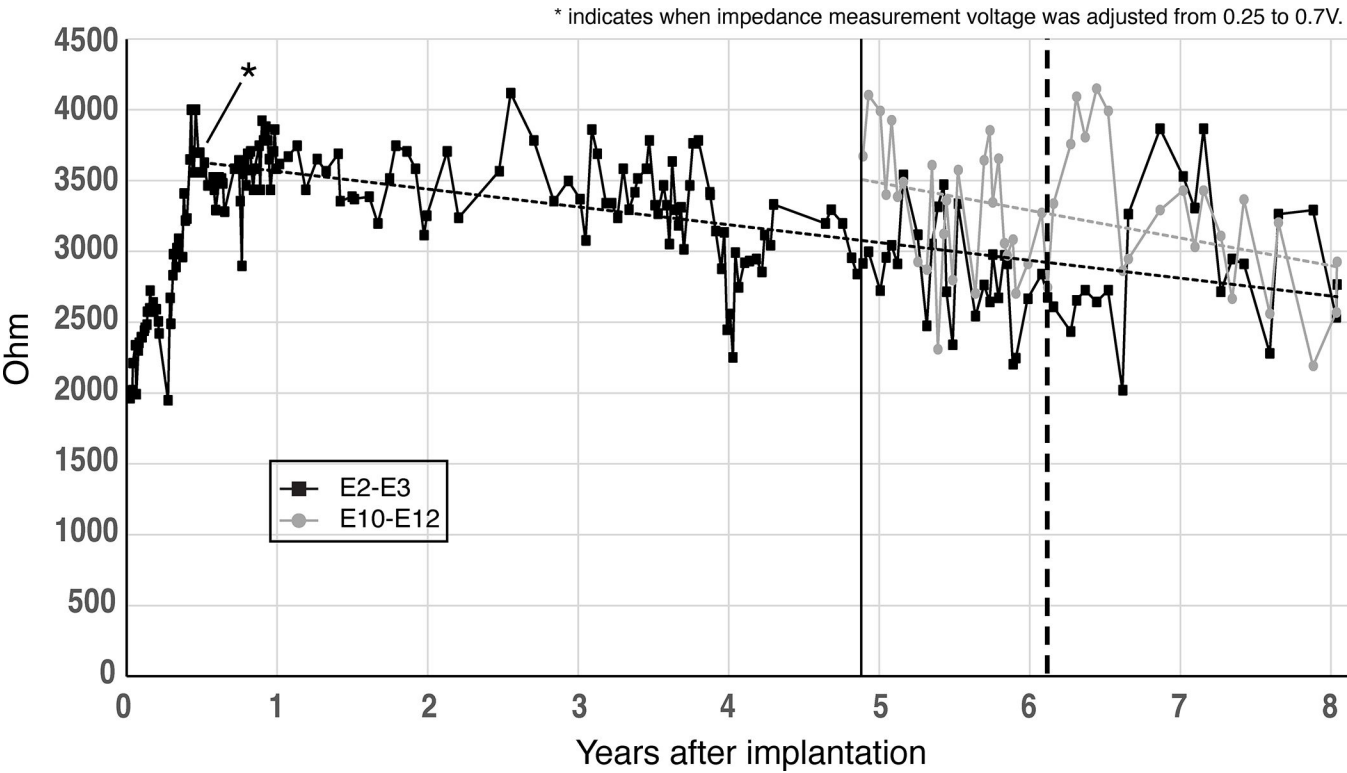


Figure 2.

A) Impedance of electrode pairs E2-E3 (black) and E10–12 (grey), with trend lines for E2-E3 on data after 6 months, and for E10-E12 for data after the replacement surgery, which is indicated by the solid vertical line. The dashed vertical line indicates the change of the at-home use BCI control features from a combination of LFB and HFB power of E2-E3 to a combination of LFB power of E2-E3 and HFB power of E10-E12. B and C) Exemplar slices with the brain tissue (red) and CSF (blue) transparently superimposed on the first (B) and second (C) CT scan. The slices of the two CT scans are exactly matched as a result of the alignment procedure. R and L mark Right and Left hemisphere for all slices. The green box indicates an area that is rich in artefacts due to the implanted electrodes, and a consequently less reliable distinction between brain tissue and CSF.