Using fMRI to localize target regions for implanted brain-computer interfaces in locked-in syndrome

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Abstract
Objective: Electroencephalography (ECoG)-based brain-computer interface (BCI) systems have the potential to improve quality of life of people with locked-in syndrome (LIS) by restoring their ability to communicate independently. Before implantation of such a system, it is important to localize ECoG electrode target regions. Here, we assessed the predictive value of functional magnetic resonance imaging (fMRI) for the localization of suitable target regions on the sensorimotor cortex for ECoG-based BCI in people with locked-in syndrome.

Methods: Three people with locked-in syndrome were implanted with a chronic, fully implantable ECoG-BCI system. We compared pre-surgical fMRI activity with post-implantation ECoG activity from areas known to be active and inactive during attempted hand movement (sensorimotor hand region and dorsolateral prefrontal cortex, respectively).

Results: Results showed a spatial match between fMRI activity and changes in ECoG low and high frequency band power (10 – 30 and 65 – 95 Hz, respectively) during attempted movement. Also, we found that fMRI can be used to select a sub-set of electrodes that show strong task-related signal changes that are therefore likely to generate adequate BCI control.

Conclusions: Our findings indicate that fMRI is a useful non-invasive tool for the pre-surgical workup of BCI implant candidates.

Significance: If these results are confirmed in more BCI studies, fMRI might be used for more efficient surgical BCI procedures with focused cortical coverage and lower participant burden.

1. Introduction

A brain-computer interface (BCI) uses brain activity for computer control (Donchin et al., 2000; Van Gerven et al., 2009; Wolpaw et al., 2002) and as such, has the potential of restoring willful communication in people with locked-in syndrome (LIS). LIS is characterized by (almost) complete paralysis, inability to speak and intact cognition (American Congress of Rehabilitation...
One promising BCI type relies on electrocorticography (ECoG) electrodes to record brain activity. ECoG electrodes offer good spatial and temporal resolution and do not penetrate the cortex (Crone et al., 1998a; Miller et al., 2020). ECoG recordings from the sensorimotor cortex have been shown to offer usable BCI control signals for extended periods of time, allowing for reliable home-use with only minimal calibration and setup time (Vansteensel et al., 2016; Pels et al., 2019; Benabid et al., 2019).

Before implanting an ECoG-based BCI system, it is important to localize a suitable target region for electrode placement. Ideally, electrode coverage does not extend beyond regions used for BCI control to minimize surgery-related risks and participant burden. Also, brain activity in the BCI target region should correlate with a task the user can perform voluntarily, and ideally consists of consistent, easily measurable signal changes. Brain anatomy and the precise location of task-related brain activity may differ between individuals, as does the layout of cortical blood vessels that attenuate brain signals (Bleichner et al., 2011; Branco et al., 2018b). A non-invasive method for probing brain function is functional magnetic resonance imaging (fMRI). Previous work has shown a tight spatial match between the blood-oxygenation-level-dependent (BOLD) signal measured with fMRI and ECoG high-frequency band power (Hermes et al., 2012; Piantoni et al., 2021; Siero et al., 2014, 2013; Winawer et al., 2013). fMRI has therefore been suggested as a useful pre-surgical step to identify ECoG target locations for BCI (Hermes et al., 2011; Vansteensel et al., 2010). However, these earlier results were based on data from able-bodied individuals. Research shows that the structure and function of sensorimotor cortex in people with LIS can be affected in complex ways by the underlying etiology, e.g., in amyotrophic lateral sclerosis (Cosottini et al., 2012; Konrad et al., 2002; Shen et al., 2015) or brainstem stroke (Chen et al., 2021, 2019; Freudenburg et al., 2019; Jiang et al., 2017). This might in turn affect mechanisms underlying BOLD and ECoG signals, i.e., the signals relevant for pre-surgical localization of BCI-target regions and eventual ECoG-BCI control. It remains to be determined whether a tight spatial match between BOLD and ECoG activity is also present in people with LIS.

Here, we investigated the value of fMRI for the pre-surgical localization of ECoG-BCI electrode target areas in the sensorimotor region of people with LIS, by assessing whether BOLD and ECoG activity show a close spatial match (Question 1). To this purpose, we examined data obtained within the ongoing Utrecht NeuroProsthesis (UNP) trial, in which three people with LIS have been implanted with a chronic ECoG-based BCI to test feasibility of BCI-based communication in situations of daily living (Vansteensel et al., 2016; Freudenburg et al., 2019; Pels et al., 2019; Leinders et al., 2020). Pre-surgical fMRI was used to localize regions in the sensorimotor cortex hand area that activated strongly during attempted hand movement, with the rationale that those regions would yield ECoG signals suitable for BCI control. After discharge, data was recorded with the implanted device with the goal of realizing a reliable home-use BCI system. As a secondary research question, we investigated whether BOLD could predict a participant’s overall BCI proficiency (Question 2).

### 2. Materials and methods

#### 2.1. Ethical approval and informed consent

The study (clinicaltrial.gov identifiers: NCT02224469 and NCT04576650) was approved by the Medical Ethics Committee of Utrecht. The study adheres to the principles from the declaration of Helsinki (2013). Participants gave informed consent using a procedure designed for people with severe motor-related communication impairments (see Vansteensel et al., 2016).

#### 2.2. Participants

For the current study, we used data from three individuals with locked-in syndrome who were implanted with a fully implantable ECoG-BCI system (Table 1). None of these participants had residual movement in their hands/fingers and they were all right-handed. Six participants were enrolled in the trial, but only three (UNP1, UNP4, and UNP5) were implanted. Two participants passed away after informed consent and before implantation. Finally, the fMRI results of one participant were inconclusive as no task-related activity was observed. Because a clear task-related fMRI activity pattern was required for electrode implantation and its absence was an exclusion criterion, this individual was excluded from the study.

#### 2.3. Implant & surgeries

For a detailed description of the UNP system, see (Vansteensel et al., 2016). The system was implanted in two surgeries. During the first surgery, ECoG strips (UNP1 and UNP4: Resume-II®, Medtronic, off-label use; UNP5: Subdural Leads, same layout as UNP1 and UNP4, Medtronic, clinical investigational device; layout: 4 platinum electrodes each; exposed electrode diameter 4 mm; center-to-center electrode distance 10 mm) were implanted subdurally through 1 cm burr holes and were placed over cortical target areas in the left sensorimotor cortex and the left dorsolateral prefrontal cortex (DLPFC). Target areas within the regions of interest (sensorimotor cortex and DLPFC) were determined using pre-surgical fMRI. Final placement was based on both functional and anatomical data. Functional data was used to account for interindividual differences and potential reorganization and changes in sensorimotor cortex brain activity in people with amyotrophic lateral sclerosis (Cosottini et al., 2012; Konrad et al., 2002; Shen et al., 2016, 2015) and brainstem stroke (Chen et al., 2021, 2019; Freudenburg et al., 2019; Jiang et al., 2017). Anatomical data was used to prevent placement of individual electrodes on sulci or large

<table>
<thead>
<tr>
<th>Tab 1. Participant information overview.</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Informed Consent</td>
</tr>
<tr>
<td>Age at time of informed consent</td>
</tr>
<tr>
<td>Underlying Cause of LIS</td>
</tr>
<tr>
<td>Communication</td>
</tr>
</tbody>
</table>

LIS = Locked-In Syndrome; UNP = Utrecht NeuroProsthesis.
blood vessels. More electrode strips (three or four) were implanted than could be connected to the implantable amplifier (two). With this approach a somewhat wider area around the fMRI hotspot was covered, which allowed for postsurgical selection of electrode strips, thereby mitigating the potential of electrode placement suboptimal for BCI control. Another consideration in placing extra electrode strips was that we could not be certain that the spatial match observed in able-bodied people would be similarly present in people with LIS.

Leads of all implanted strips were tunneled subcutaneously behind the left ear towards the chest area and exited the body at the abdomen via percutaneous extension cables between surgeries. Participants stayed at the intensive (UNP1 and UNP5, as they received invasive ventilation through tracheostomy) or medium care (UNP4) unit until the second surgery. Measurements obtained in the days after electrode implantation surgery (henceforth ‘acute measurements’) were used to determine which two strips showed the strongest signal changes during attempted movement tasks. In the second surgery, the extension leads were removed, and the two selected strips were connected to an amplifier/transmitter device (Activa\(^2\) PC + s, Medtronic; off-label use) that was implanted subcutaneously under the left clavicle. UNP1 and UNP4 were originally enrolled in a research protocol in which signals from both sensorimotor and DLPFC regions were tested for BCI use. As planned, we connected one sensorimotor strip and one DLPFC strip to the implanted amplifier for UNP1 and UNP4. UNP5 was enrolled after an amendment of the research protocol, where focus was on signals from sensorimotor cortex for two reasons. First, in UNP1 and UNP4, sensorimotor-based BCI control proved superior to DLPFC (Leinders et al., 2020). Second, we aimed to decode multiple sensorimotor-based BCI control signals from the sensorimotor areas for multidimensional BCI control. The main focus was still on sensorimotor hand cortex. Therefore, two electrode strips were placed on the hand region, one on the face/hand region (placed on face area, with one end of the strip overlapping hand area), and one on the DLPFC region. The DLPFC strip functioned as a backup in case inter-surgical measurements did not provide two sensorimotor electrode strips with good modulation. As planned, for UNP5 two electrode strips (from sensorimotor hand and from face/hand regions) were connected to the amplifier-transmitter device. The remaining strip leads were capped. After 255 weeks (after the new research amendment), the amplifier/transmitter device of UNP1 was replaced by a unit with a full battery to extend home use of the BCI system. During this replacement surgery, in line with the research amendment, the second sensorimotor strip (also placed on hand region) was connected to the newly implanted amplifier and the DLPFC strip was left disconnected. For all participants, training for BCI speller-control and home-use was focused on signals from the hand region on the sensorimotor cortex.

2.4. Data acquisition

A chronological overview of all data acquisition actions relevant to the current study is presented in Fig. 1. The fMRI and ECoG measurements are described in more detail in the remainder of this section. The CT scan is described in the section ‘Calculating Weighted BOLD Activity around Electrode Locations’.

2.5. fMRI tasks

For localization of the cortical sensorimotor hand area, participants performed tasks with attempted movement trials during a presurgical fMRI scan. For UNP5 this was a block-design task with alternating attempt and rest trials (the attempt-rest task; trial duration of 30 seconds; 6 rest trials and 5 attempt trials). For UNP1 and UNP4 the block-design task contained three conditions: attempt, imagine, and rest trials (the attempt-imagine-rest task; trial durations 15 seconds; 10 trials per condition). Imagine trials were not used in the current analyses, because the attempt-rest contrast was larger than the imagine-rest contrast and participants used movement attempt for all BCI measurements. During rest trials, participants were instructed to relax. During attempt trials, partic-
Table 2
An overview of datasets recorded during research visits. Table includes electrocorticography (ECoG) datasets recorded at home with the selected electrode pairs, including which electrode pairs were selected for longitudinal measurements with the attempt-rest task, which pairs were used during brain-computer interface (BCI) control tasks, and the number of recorded datasets for each task. UNP5 performed a large number (237) of short continuous ClickTask runs to practice timing, which explains the large number of datasets relative to his late implantation. Attempt-rest data was recorded over periods of 329, 90, and 90 weeks and BCI control data over periods of 311, 72, and 74 weeks for UNP1, UNP4, and UNP5, respectively.

<table>
<thead>
<tr>
<th>Electrode Pair(s)</th>
<th>Attempt-Rest Task</th>
<th>BCI Control Tasks</th>
<th>SpellerTask</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNP1 E2-E3</td>
<td>97</td>
<td>113</td>
<td>124</td>
</tr>
<tr>
<td>UNP4 E3-E4</td>
<td>57</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>(and E2-E4 for BCI control tasks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNP5 E2-E4</td>
<td>39</td>
<td>38</td>
<td>70</td>
</tr>
</tbody>
</table>

UNP = Utrecht NeuroProsthesis.

Participants were instructed to attempt fingertapping with their right hand (specifically, attempt to touch the thumb to the four opposing fingers in random order). Conditions were cued visually on a computer screen that was visible to the participants via a mirror. Each participant performed the fMRI task once. During the scanning session, participants used eye blinks to answer yes–no questions in between runs and to signal the need for care or attention at any time.

2.6. fMRI measurements
Pre-surgical fMRI data was acquired on a Philips Achieva 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) and a Sense head coil (Philips). For functional images, a 3D PRESTO pulse sequence was used that minimizes the interference from large blood vessels (Neggers et al., 2008). 40 slices were acquired with a field of view (FOV) of 224 × 256 × 160 mm and with a voxel size of 4 mm isotropic. Volume-to-volume acquisition time was 0.608 s, with a flip angle of 10°, echo time (TE) of 33.2 ms, and repetition time (TR) of 22.5 ms. A single functional volume with increased flip angle (FA; 29°) was acquired to facilitate the registration procedure (see below). In addition, whole-brain T1-weighted 3D TFE structural images were acquired at a resolution of 1 mm isotropic, with FOV: 288 × 288 × 175 mm; flip angle: 8°; TR: 8.4 ms; TE: 3.8 ms.

2.7. ECoG tasks
2.7.1. Attempt-rest task
After electrode implantation, participants performed attempted movement tasks (similar to those performed during the fMRI scan) before the second surgery and on multiple occasions at home (task slightly different; see next paragraph). During these sessions, signals from all electrodes/electrode pairs were recorded. UNP1 performed 3 acute runs (i.e., between the first and second surgery) of the attempt-imagine-rest task (imagine trials not included in analysis), and 13 attempt-rest runs at home over a period of 64 months. UNP4 did 1 acute attempt-rest run and 12 attempt-rest runs at home recorded over 21 months. UNP5 did 2 acute attempt-rest runs and 4 attempt-rest runs at home recorded over 12 months. In addition, based on initial results, one electrode pair was selected for more frequent measurement with the attempt-rest task for longitudinal assessment of signals (more information in section Selection of Electrode Pairs). See Table 2 for an overview of data recorded at home with the selected electrode pairs.

For all participants, the attempt-rest task conducted at home comprised 15-second trials. The number of trials varied between sessions (ranging from 4 to 10; task duration ranged from 2 to 5 minutes). One acute run of UNP5 had a slightly different block design than the regular attempt-rest task. This run contained several additional movement type trials besides the usual right hand fingertapping and rest trials (e.g., attempted foot movement). Results presented here are only based on the attempted right hand fingertapping and rest trials of that run.

2.7.2. BCI control tasks
After initial parameter optimization (for an overview of parameters, see (Vansteensel et al., 2016)), participants performed BCI control tasks. Here, we used the results of these tasks for an assessment of overall BCI performance. All tasks use a scanning-based visual interface and were controlled with brain-clicks, which were based on a combination of LFB and HFB signals. Briefly, z-scored LFB power was subtracted from z-scored HFB power to obtain a single, one-dimensional control signal. This control signal was binarized (0 or 1) based on a threshold. Next, this binary signal was translated into clicks based on click window and click rate settings, which respectively defined the length of the sliding click window and the percentage of samples within that window that should be a 1 (i.e., above threshold) for a click to be made (for more info see (Vansteensel et al., 2016)). Initial click parameter optimization was done for each participant before attempting BCI control tasks, but some parameters were empirically fine-tuned throughout the research period. These small variations in parameters and resulting differences in performance accuracy were compensated for by averaging over large numbers of datasets.

Here, we used data from the following three BCI-control tasks: the ClickTask, the SpellerTask (both described in (Vansteensel et al., 2016)), and the continuous ClickTask (van der Vijgh et al., 2019). An overview of the number of datasets for each task per participant is presented in Table 2. The number of datasets recorded with each participant was not only dependent on the duration of study participation, but also on the amount of testing that the individual circumstances allowed.

The ClickTask is based on the ‘Whac-a-mole’ arcade game. A matrix of holes (number of rows and columns can be adjusted) is presented, one of which contains a mole (the target). The software first scans sequentially through rows and after a row is selected using a brain-click, through the individual cells in the selected row. A second brain-click will then select the highlighted cell. Scanning is done at a fixed pace. Participants are instructed to click on targets only. When a target is hit, a new target appears in a random hole until the pre-defined number of targets is hit.

The continuous ClickTask is similar to the ClickTask except that it only has one row with 8 cells. Again, a single target appears at any one time and participants are instructed to only hit the target. A new target appears after a hit or miss. After the pre-defined number of targets is hit or missed, the task ends.

The SpellerTask is functionally similar to the ClickTask, but it contains characters (alphabetical and punctuation). Participants
are instructed to copy a word or short sentence given by the researcher.

An overview of BCI control tasks recorded can be found in Table 2. For every click-based task, there are two trial types, namely targets and non-targets. For each trial type, it is possible to click (positive) or to not click (negative), leading to the four trial outcomes used to quantify performance: true positives (click on target), true negatives (no click on non-target), false positives (click on non-target), and false negatives (no click on target). Performance on BCI control tasks was calculated by the accuracy formula below.

\[
\text{TruePositives} + \text{TrueNegatives} \over \text{TruePositives} + \text{TrueNegatives} + \text{FalsePositives} + \text{FalseNegatives} \times 100
\]

2.8. ECoG measurements

For acute measurements, the percutaneous extension leads were connected to a clinical electrophysiology amplifier (Micromed; sampling rate 512 Hz; high-pass filter 0.15 Hz, low-pass filter at 134.4 Hz). Reference and ground electrodes were placed on the mastoid, forehead, or cheek bone, based on ease of access and signal quality, as assessed by a clinical neurophysiologist. Signals from all implanted sensorimotor electrodes (both sensorimotor hand strips, 8 electrodes per participant) were recorded simultaneously in a unipolar fashion.

After discharge, brain signals were recorded at the participants’ homes with the implanted amplifier, henceforth ‘chronic data’. Chronic data was wirelessly streamed from the implanted amplifier-transmitter to an external clinical investigational transmitter (Nexus-1, investigational device, Medtronic) connected to the research laptop. The Activa^® PC + S amplifier records data using a bipolar referencing method, so all chronic data was bipolar (see Fig. 1 for an overview of all acquired data). Attempt-rest task data was recorded at a 200 Hz sampling rate with a high-pass filter of 0.5 Hz. At 200 Hz, the device can simultaneously record from one bipolar electrode pair of each electrode strip (no bipolar recording across strips is possible). To record data from all six pairs of each strip, the attempt-rest task was performed six times in one session (or sometimes spread over two sessions). For UNP4 and UNP5, home measurements were always done with a single sensorimotor hand strip. For UNP1, three measurements done after the replacement surgery (during which both sensorimotor hand strips were defined as hotspots suitable for electrode placement). Here, we also used the t-maps for detailed comparison with ECoG activity (see below).

2.9. Selection of electrode pairs

As part of the UNP project, a BCI control pair was selected for each participant based on a post-implant electrode selection procedure (Vansteensel et al., 2016). Shortly, measurements done between surgeries and after discharge of all available electrode pairs during the attempt-rest task were used to choose the optimal pair, based on the strength and consistency of the task-related signal changes. This approach was based on the assumption that the electrode pairs showing the strongest response to attempted hand movement during the attempt-rest task would also provide the best BCI control, since BCI control was based on brain activity elicited upon attempted hand movement. The selected control pair was used for BCI control and was measured regularly for longitudinal assessment of signals. UNP1 and UNP5 accomplished BCI control based on the signals from a single electrode pair. For UNP4, a primary electrode pair (E3–E4) was selected for longitudinal assessment, but in her BCI control sessions, signals from two electrode pairs were combined. For UNP1, UNP4, and UNP5 respectively, we used the following pairs for regular measurement and BCI control: UNP: E2–E3; UNP4: E3–E4 (combined with E2–E4 for BCI control); UNP5: E2–E4 (Table 2).

2.10. Data analysis

2.10.1. fMRI data analysis

Preprocessing and statistical analysis of the fMRI data was done using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The preprocessing of the fMRI data entailed realignment and co-registration to the structural T1-weighted image, using the image with increased flip-angle as an intermediate reference. A general linear model (GLM) was created using a design matrix with factors representing activity for the attempted movement condition versus rest. Motion parameters from realignment were not added to the GLM since head movements during the scan were minimal or absent, due to the locked-in state of the participants. Subsequently, the structural image was skull-stripped and a cortical rendering was created in MIRcron (Rorden and Brett, 2000), with the t-maps as overlay. The exact thresholding of the overlay was done separately for each participant by an fMRI expert (NFR), The obtained visualizations were inspected and patches with increased activity over cortical sensorimotor hand regions were defined as hotspots suitable for electrode placement. Here, we also used the t-maps for detailed comparison with ECoG activity (see below).

2.10.2. ECoG data analysis

Analysis of ECoG data was done in MATLAB 2021a (The Mathworks, Inc.; Natick, MA; USA). Data recorded acutely was re-referenced in two ways: 1) using common-average re-referencing across the 8 electrodes placed on sensorimotor region (providing information of 4 unipolar electrodes per strip); and 2) using bipolar re-referencing (providing information for 6 bipolar pairs per strip), to simulate the bipolar measurements of the implant. As a result, we obtained three ECoG datasets per participant: 1) Acute unipolar data; 2) Acute bipolar data; 3) Chronic bipolar data.

Power conversion of ECoG data acquired during the attempt-rest tasks (both acutely and with the implanted device) was done using an autoregressive model with the maximum entropy method (Burg’s method; Schalk et al., 2004) model parameters: model order 20; window length 200 ms; bin width 1 Hz, non-overlapping; evaluations per bin 5; frequency range 1–100 Hz. The frequency bands of interest were the low frequency band (LFB: 10—30 Hz), and the high frequency band (HFB: 65—95 Hz; Vansteensel et al., 2016). The power in these frequency bands was computed by taking the average power of all individual 1 Hz bins within each frequency range. Power was averaged across all windows for each active and rest trial and the resulting sequence of power values was correlated (Pearson’s r) with the task conditions (rest and active trials coded as 0 and 1 respectively). This correlation coefficient was then squared while keeping the correlation sign intact to obtain the coefficient of explained variance (r^2; a metric used in other BCI work, e.g.; Leuthardt et al., 2004; Schalk et al., 2008). For readability, these signed r^2 values are henceforth referred to as r^2 values. r^2 values were averaged across all runs within each ECoG dataset, to obtain one mean value for each unipolar electrode or bipolar electrode pair.
2.10.3. Calculating weighted BOLD activity around electrode locations

Electrode locations were determined using a head-CT scan done on the day after the electrode implantation. Using the ALICE pipeline (Branco et al., 2018a; Hermes et al., 2010), electrode locations were extracted from the CT scan and projected onto the surface rendering of each participant’s T1-weighted structural scan. To compute the BOLD activity around the center of each electrode location, we weighted voxels around each electrode center using a 3-D Gaussian kernel with a sigma of 9 mm. This sigma has been shown to generate the best match between BOLD (3 Tesla) and ECoG in able-bodied people (Piantoni et al., 2021). The analysis only included voxels in the gray matter. To obtain the BOLD activity corresponding to a bipolar electrode pair, we computed the average weighted BOLD signal from the two electrode locations comprising the electrode pair.

2.11. Research questions

2.11.1. Spatial Match between BOLD and ECoG (Question 1)

To assess the spatial match between BOLD and ECoG activity patterns we correlated the r² values of each electrode or electrode pair computed from the ECoG recordings with the weighted average of the BOLD around each electrode or electrode pair (Piantoni et al., 2021) separately for each participant using SPSS (IBM, version 27). Shapiro-Wilk normality tests were performed and a non-parametric correlation coefficient method (Kendall’s Tau-B Test, denoted by τ_b) was applied when data was not normally distributed. In other cases, we used the Pearson’s correlation coefficient (denoted by r). For each correlation analysis, we report the correlation coefficient and significance values. Results were based on 1-tailed significance tests, because we expected positive and negative correlations for high and low frequency band power data, respectively, based on the consistent results from (Hermes et al., 2012; Piantoni et al., 2021; Siero et al., 2014, 2013).

First, we used data from all areas covered by electrodes. For an overview of which strips and how many datapoints were included in each analysis, see Table 3. In this analysis, we included electrodes from DLPFC and sensorimotor face regions, which were not or only weakly activated during attempted hand movement. These were included to maximize the range of potential values in the analyses and to study whether regions with lower fMRI activity would show lower ECoG activity as well.

Because most BCI systems focus on sensorimotor regions, we also investigated the strength of the correlation between BOLD and ECoG data within the sensorimotor cortex only. We focused on the electrode strips placed on the sensorimotor hand region. For the acute data recorded in the days after electrode placement, we looked at two electrode strips for each participant (Table 3). For the chronic data, we included data from the electrode strip initially connected to the amplifier (i.e., for UNP1, we did not include data...
from the second sensorimotor electrode strip, which was connected during the replacement surgery). When limiting the electrodes to those over the sensorimotor regions single-subject analyses were no longer possible, since the number of observations per subject (lowest for the three datasets: 4, 6, and 6) was too low (leading to a power of 0.50 (Algina and Olejnik, 2003)). To perform a statistically sound correlation analysis on the sensorimotor data, we z-scored and then pooled data from the three participants. Z-scoring essentially removes offsets between participants, allowing for pooling of data from different individuals. Even though no statistical tests were done on a single-subject level, single-subject trend-lines were added to scatterplots to indicate the direction and strength of the BOLD-ECoG relation for the three participants.

2.1.12. Prediction of BCI proficiency (Question 2)

To investigate whether BOLD can predict BCI proficiency, we performed three analyses based on three different datasets: 1) attempt-rest data from all electrode pairs on the sensorimotor hand cortex; 2) attempt-rest data from the selected/control electrode pairs; 3) BCI control task data based on the control electrode pairs. These analyses were done after across-subject z-scoring of BOLD values and ECoG values to easily compare between participants, as opposed to the within-subject z-scoring used earlier, which would eliminate any between-subject differences.

First, we assessed whether a participant with higher BOLD also had stronger ECoG LFB and HFB r² values during the attempt-rest task. Considering that the BCI control signal was based on a combination of LFB and HFB signals, we assumed that stronger modulation of BOLD surrounding electrodes comprising electrode pairs (Table 6) and at-home attempt-rest datasets from all available electrodes/electrode pairs from one sensorimotor strip. For each participant and for each dataset type, we inspected boxplots for a potential relation between task-related BOLD and ECoG (LFB and HFB), used ANOVA to detect differences between participants, and used linear regression to obtain a measure of the predictive strength of BOLD for the strength of the LFB and HFB signal modulation.

Second, we looked at the relation between BOLD and ECoG for attempt-rest data from the electrode pair selected for regular measurement and BCI control. Finally, we looked at the relation between BOLD and actual BCI performance based on the BCI control pairs. We compared the BCI performance on these tasks with the BOLD associated with the control pair(s). Because UNP4 used a combination of two electrode pairs for BCI control, we used the average BOLD of those two pairs for this comparison.

Table 3
Correlation analysis data overview. This table indicates which electrode strips were included in each correlation analysis between blood-oxygenation-level-dependent signal and electrocorticography data. Numbers in parentheses indicate the number of datapoints (i.e., electrodes or electrode pairs for bipolar data). The terms ‘hand’ and ‘face’ refer to the sensorimotor cortex hand and face regions, respectively.

<table>
<thead>
<tr>
<th>Electrodes included in analysis</th>
<th>Acute unipolar dataset</th>
<th>Acute bipolar dataset</th>
<th>Chronic bipolar dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNP1 Electrodes from all strips</td>
<td>2 × DLPFC strips, 2 × hand strips (16 electrodes)</td>
<td>2 × DLPFC strips, 2 × hand strips (24 electrode pairs)</td>
<td>1 × DLPFC strips, 2 × hand strips (18 electrode pairs)</td>
</tr>
<tr>
<td>Electrodes from the sensorimotor hand strips</td>
<td>2 × hand strips (8 electrodes)</td>
<td>2 × hand strips (12 electrode pairs)</td>
<td>1 × hand strip (6 electrode pairs)</td>
</tr>
<tr>
<td>UNP4 Electrodes from all strips</td>
<td>1 × DLPFC strip, 2 × hand strips (12 electrodes)</td>
<td>1 × DLPFC strip, 2 × hand strips (18 electrode pairs)</td>
<td>1 × DLPFC strip, 1 × hand strip (12 electrode pairs)</td>
</tr>
<tr>
<td>Electrodes from the sensorimotor hand strips</td>
<td>2 × hand strips (8 electrodes)</td>
<td>2 × hand strips (12 electrode pairs)</td>
<td>1 × hand strip (6 electrode pairs)</td>
</tr>
<tr>
<td>UNP5 Electrodes from all strips</td>
<td>1 × DLPFC strip, 2 × hand strips, 1 × face strip (16 electrodes)</td>
<td>1 × DLPFC strip, 2 × hand strips, 1 × face strip (24 electrode pairs)</td>
<td>1 × hand strip, 1 × face strip (12 electrode pairs)</td>
</tr>
<tr>
<td>Electrodes from the sensorimotor hand strips</td>
<td>2 × hand strips (8 electrodes)</td>
<td>2 × hand strips (12 electrode pairs)</td>
<td>1 × hand strip (6 electrode pairs)</td>
</tr>
</tbody>
</table>

DLPFC = Dorsolateral Prefrontal Cortex; UNP = Utrecht NeuroProsthesis.

3. Results

3.1. fMRI results and electrode locations

For all participants, fMRI results of the attempt-rest task revealed clear fMRI activity in the contralateral (i.e., left hemisphere) hand region (Fig. 2).

3.2. Spatial Match between BOLD and ECoG (Question 1)

3.2.1. Electrodes from all Strips

BOLD correlated positively with ECoG HFB and negatively with ECoG LFB in all participants in all three datasets (Fig. 3). All but two correlations were statistically significant (Table 4). Averaged across datasets and participants, HFB and LFB ECoG correlations with BOLD were 0.492 and −0.655, respectively.

3.2.2. Electrodes from the sensorimotor hand strips

Z-scored HFB ECoG and BOLD data from all participants combined correlated positively in all three datasets (Fig. 4) when limiting the analysis to data from sensorimotor cortex hand regions. These correlations were significant (p < 0.05; Table 5). For the LFB, the overall relation between BOLD and LFB was negative, but not significant. For the acute unipolar dataset, the correlation between LFB and BOLD showed a negative trend (p = 0.051). Despite heterogeneity between participants, individual trend lines for the BOLD - HFB ECoG data (except for UNP5 acute unipolar data) indicate a positive trend, consistent with the correlation based on the pooled sensorimotor data.

3.3. Predicting optimal control pairs

Interestingly, we observed that BOLD held some predictive value for the selection of BCI control pairs. Evaluation of weighted BOLD surrounding electrodes comprising electrode pairs (Table 6) revealed that for UNP1 and UNP4, the electrode pairs selected for BCI control were also the ones showing the highest BOLD values. For UNP5, the BCI control pair had the second highest BOLD values.

3.4. Prediction of BCI proficiency (Question 2)

Our approach to investigating the relation between BOLD and BCI proficiency was threefold.

First, we looked at differences between participants in overall BOLD and ECoG r² to investigate whether a participant’s BOLD level could predict the strength of the ECoG response in the LFB and HFB during the attempt-rest task on the sensorimotor cortex. The three
**Fig. 3. BOLD and ECoG Data Relation Figure.** Blood-oxygenation-level-dependent (BOLD) and electrocorticography (ECoG) data for all electrodes and electrode pairs of all participants (see Table 3 for details). Weighted BOLD-values (x-axis) plotted against ECoG $r^2$ values for each unipolar or bipolar electrode (individual markers) and for each of the three ECoG datasets (plotted across the rows) separately for high and low frequency band (columns). Participants are denoted by different marker shapes and line types (see legend). Trend lines are plotted for individual participants. The thicker solid line indicates the trend line based on datapoints of all participants together.

**Table 4**
BOLD and ECoG Data Relation Table. Correlations (Pearson’s r or Kendall’s tau-b) between the electrocorticography (ECoG) $r^2$ values (datatype indicated in the upper two rows) and the corresponding weighted-t values (based on the blood-oxygenation-level-dependent signal). Bottom row shows average correlation values for rows.

<table>
<thead>
<tr>
<th></th>
<th>Acute Unipolar Data</th>
<th>Acute Bipolar Data</th>
<th>Chronic Bipolar Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HFB</td>
<td>LFB</td>
<td>HFB</td>
</tr>
<tr>
<td>UNP1</td>
<td>Correlation</td>
<td>0.444 ** (t&lt;sub&gt;6&lt;/sub&gt;)</td>
<td>-0.367 * (t&lt;sub&gt;6&lt;/sub&gt;)</td>
</tr>
<tr>
<td></td>
<td>Significance (p)</td>
<td>0.008</td>
<td>0.024</td>
</tr>
<tr>
<td>UNP4</td>
<td>Correlation</td>
<td>0.583 *</td>
<td>-0.754 **</td>
</tr>
<tr>
<td></td>
<td>Significance (p)</td>
<td>0.023</td>
<td>0.002</td>
</tr>
<tr>
<td>UNP5</td>
<td>Correlation</td>
<td>0.478 *</td>
<td>-0.575 **</td>
</tr>
<tr>
<td></td>
<td>Significance (p)</td>
<td>0.031</td>
<td>0.010</td>
</tr>
<tr>
<td>Average across participants</td>
<td>0.502</td>
<td>-0.565</td>
<td>0.329</td>
</tr>
</tbody>
</table>

* Correlation is significant at the 0.05 level (1-tailed).
** Correlation is significant at the 0.01 level (1-tailed).
HFB = High Frequency Band; LFB = Low Frequency Band; UNP = Utrecht NeuroProsthesis.
Fig. 4. **BOLD and ECoG Data Relation on Sensorimotor Cortex Hand Region.** Z-scored blood-oxygenation-level-dependent (BOLD) and electrocorticography (ECoG) data for all electrodes and electrode pairs on the sensorimotor cortex hand region of all participants (see Table 3 for details). Z-scored weighted BOLD-values (x-axis) plotted against z-scored ECoG $r^2$ values for each unipolar or bipolar electrode (individual markers) and for each of the three ECoG datasets (plotted across the rows) separately for high and low frequency band (columns). Participants are denoted by different marker shapes and line types. Trend lines are plotted for individual participants. The thicker solid line indicates the trend line based on datapoints of all participants together.
participants showed relatively large differences in the averages and variance of the task-related BOLD and ECoG modulation (i.e., BOLD values and ECoG $r^2$ values) taken across all sensorimotor hand cortex electrode pairs (Fig. 5; note that values were z-transformed across participants to evaluate interindividual differences). Based on visual inspection, there seems to be a relation between a participant’s task-related BOLD modulation and ECoG signal modulation, i.e.: high BOLD was associated with stronger ECoG task modulation, and lower BOLD with weaker ECoG modulation. Overall, UNP1 had the strongest BOLD, HFB and LFB values, and UNP4 the weakest. Statistically significant differences between participants based on one-way ANOVA (post hoc Bonferroni-corrected) are indicated in Fig. 5. Linear regression analyses with BOLD values as the predictor and the average LFB and HFB $r^2$ values per electrode as the dependent variables were significant for all three datasets (Table 7), indicating BOLD explained significant portions of the observed variance in ECoG modulation across the participants. Relations were strongest for the chronic data (explained variance > 0.6).

Next, we looked at the electrode pair that was recorded regularly during the attempt-rest task for longitudinal assessment of signals. We plotted the z-scored (again across participants) weighted BOLD values of those electrode pairs against the z-scored HFB and LFB $r^2$ values (Fig. 6, top panel). Statistically significant differences based on one-way ANOVA (Bonferroni-corrected) are indicated by horizontal lines. All 3 metrics were highest for UNP1. UNP4 had the lowest BOLD value (single value; no statistics applied) and the lowest LFB values (compared to UNP1 and UNP5: $p < 0.001$), but higher HFB values than UNP5 ($p < 0.001$), indicating that the relation between BOLD and ECoG across participants is not clear for a single electrode pair.

Finally, to investigate a potential direct link between BOLD and BCI performance, we compared BOLD with the average BCI performance per participant. BOLD and BCI performance were z-scored across participants for easy visual comparison. Although results in Fig. 6 (bottom panel) show that UNP1’s BOLD and BCI performance (one-way ANOVA, Bonferroni-corrected: $p < 0.001$) were highest, when considering data from UNP4 and UNP5 there is no direct relation between BOLD and BCI performance across participants.

### 4. Discussion

We investigated in three people with LIS and an implanted ECoG-based BCI system whether pre-surgical fMRI matches spatially with ECoG, and whether BOLD can predict BCI proficiency. Briefly, we observed that BOLD and ECoG match spatially in people with LIS, that BOLD may be useful for the selection of BCI control electrodes, and that BOLD may be used as a proxy of an individual’s ability to volitionally produce signal changes as measured by ECoG.

#### 4.1. Question 1: Spatial match between BOLD and ECoG

First, regarding the spatial match between presurgical fMRI and ECoG, we found that BOLD correlates positively with HFB ECoG and negatively with LFB ECoG signals in all participants when considering all implanted electrodes over sensorimotor cortex and the DLPFC. Two out of the nine correlation analyses using all electrodes did not reach statistical significance (UNP4’s acute bipolar HFB correlation and UNP5’s chronic HFB correlation) although they did show positive correlations (0.255 and 0.398).

Limiting the analysis to data from the sensorimotor cortex hand region only, the correlations between BOLD and HFB ECoG remained significant when pooling data from the three participants. These results indicate that the mechanisms underlying neurovascular coupling in the sensorimotor cortex do not seem to be affected in people with LIS and that pre-localization of useful BCI target regions with fMRI is possible in people with LIS. The positive correlations we observed between BOLD and ECoG HFB power on the sensorimotor hand region correspond with earlier findings in able-bodied volunteers comparing 3 T fMRI and ECoG data recorded with similar electrodes (Hermes et al., 2012; Piantoni et al., 2021). In the current manuscript, the $r^2$ between BOLD and HFB ECoG data averaged across the three datasets is 0.38. The $r^2$ values obtained in the aforementioned studies were 0.39 (Piantoni et al., 2021) and 0.46 (Hermes et al., 2012).

The most prominent correlation with BOLD was found for the ECoG data acquired with the implanted device (see tables 4 and 5; average $r^2$ value from sensorimotor data 0.54). This might be explained by the fact that those ECoG values were computed by averaging over more datasets than the values based on acute data. Averaging results from more ECoG datasets may provide a better estimate of the underlying task-related brain activity. At the same time, it needs to be acknowledged that the BOLD dataset to which the ECoG data are compared is based on a single repetition of the task per participant. An alternative explanation for weaker correlations between BOLD and acute ECoG data may be that the participants performed the task sub optimally during the first days after
Fig. 5. Inter-Subject Differences in the Relation between BOLD and Sensorimotor ECoG Electrodes. Inter-subject differences based on sensorimotor blood-oxygenation-level-dependent (BOLD) and electrocorticography (ECoG) data (from datasets in which all electrode/electrode pairs were recorded, see Table 3 for more info). Boxplots of the three participants (x-axis; labels on bottom), separately for the three different ECoG datasets (rows; labels on right side). Data was z-scored across participants instead of within. For each participant's electrode (pair), low and high frequency band (LFB and HFB) $r^2$ values were averaged across runs. For each participant, left bars indicate BOLD, and middle and right bars show HFB and LFB ECoG results, respectively. In boxplots, black horizontal lines indicate the median; colored boxes the interquartile range; and whiskers minimum and maximum values, excluding outliers (circles; interquartile edge +/- 1.5 x interquartile range, default SPSS method) and extreme values (asterisks; interquartile edge +/- 3 x interquartile range, default SPSS method). For easier comparison, the LFB $r^2$ values have been inverted (high values indicate a strong, negative correlation). Connecting lines above each graph show which variables differ significantly ($\alpha = 0.05$; Bonferroni corrected).
were done on z-scored data, the intercept of the model was always 0 and is not reported. Variables (same data as plotted in Fig. 5). Data from all available electrodes and electrode pairs from sensorimotor regions was used (more info in Table 3). Because these analyses were done on z-scored data, the intercept of the model was always 0 and is not reported.

Since BOLD and ECoG matched spatially, implanting more electrodes than strictly necessary were implanted to ensure full coverage that was used. From the sensorimotor LFB results, it seems that the spatial match with BOLD - although not statistically significant - is stronger in the unipolar data than in the bipolar data (Table 5). One explanation for this could be that LFB changes - generally occurring over larger patches of cortex than HFB changes - partially cancel each other out in bipolar referencing over the sensorimotor cortex. This would imply that the phase of low frequency band power (24–30 Hz) to HFB power only increased the r² values for high and low frequency band (HFB and LFB) from the attempt-rest task, z-scored separately across participants. Only data from selected electrode pairs for UNP1 and UNP4 were the electrodes selected for BCI control and longitudinal signal assessment. For UNP5, the selected electrode pair had the second-highest BOLD values. This finding might have important implications for future implanted BCI work. Considering the experimental nature of the UNP study, more electrodes than strictly necessary were implanted to ensure full coverage of relevant areas. All electrodes required testing during the acute measurements to select the optimal electrode strips. Implantation of the system was therefore spread over two surgeries. Since BOLD and ECoG matched spatially, implanting more electrodes than strictly required to ensure optimal coverage may not be necessary for future ECoG-BCI systems. After confirmation in more participants with LIS, future studies may skip the acute recordings and rely entirely on fMRI results to implant a BCI system with only few electrodes or a small electrode array, resulting in shorter hospital stay and lower surgery-related risks. In addition, our results indicate that BOLD can be used to pre-select promising control channels in ECoG-based BCI systems and thereby speed up the post-implant feature selection phase.

4.2. Question 2: Prediction of BCI proficiency

To investigate the predictive value of BOLD for BCI proficiency, we ran three comparisons. First, we looked at attempt-rest data from all sensorimotor electrodes and electrode pairs and the associated ECoG LFB and HFB r² values, assuming these are proxies of BCI performance. We observed that a participant’s ability to modulate their BOLD signal seems closely related to how well they can modulate their ECoG LFB and HFB signals.

This relation was observed for all three datasets and strongest in the chronic dataset. Concerning the differences between individuals in the level of BOLD and ECoG activity (as shown in Fig. 5): these may relate to differences in the ability of each participant to mentally perform the attempted movement strategy and thereby recruit the sensorimotor cortex. Alternatively, there may be differences in the overall functioning or activity of the sensorimotor cortex between participants, in the effect of the underlying etiology on the sensorimotor cortex (e.g. Freudenburg et al. 2019)). Further investigation of this topic may benefit from the use of somatosensory tasks, which are independent of a participant’s ability to perform the attempted movement strategy. As more people are implanted with ECoG-BCI systems in the coming years, this topic can be further investigated. If the relation between the overall task-related BOLD and ECoG activity is consistent across many participants, BOLD might be used as a general predictor of the strength of ECoG signal changes.

Second, we looked at the relation between BOLD and ECoG for the control electrode pairs. For UNP1, BOLD and ECoG LFB and HFB values were highest across the three participants. For UNP4, BOLD and LFB values were lower than for UNP5, but HFB values higher. This indicates that the relation between BOLD and ECoG
is less clear when investigated at finer spatial detail (at the level of a single electrode pair). UNP5’s weaker HFB response may be due to age- and/or disease related atrophy, mostly affecting HFB signals. It is also noteworthy that we have shown UNP4’s LFB signals are weak compared to UNP1 and able-bodied people, potentially caused by her brainstem stroke (Freudenburg et al., 2019).

The second observation corresponded to findings from the third comparison: BCI performance - which was based on a combination of LFB and HFB from one (or two in UNP4) electrode pairs - did not show a clear match with each participant’s BOLD. Even though task-related BOLD signal changes on the sensorimotor hand region predicted the overall level of task-related ECoG signal changes on the sensorimotor hand region (i.e., r² values in LFB and HFB across all channels; Fig. 5 and Table 7), the predictive value of BOLD may not be strong enough to predict an individual’s BCI performance based on one or two electrode pairs. It is noteworthy that UNP1’s BOLD and BCI performance were highest, but that BOLD did not match with performance in UNP4 and UNP5. This might be explained by the fact that BCI performance was in the same range for all three participants (85.8, 78.1, and 76.7%); with only UNP1’s performance scores significantly different from the others, which may have yielded limited predictive power of BOLD especially in UNP4 and UNP5. The BCI performance distribution across participants (Fig. 6, bottom panel) seems more related to the ECoG HFB results from the control pair (Fig. 6, top panel) than to BOLD. An explanation for this is that transient signal changes in HFB power during attempted movement might be more important for good performance on scanning-based, timing-dependent tasks than the slower LFB response (Crone et al., 1998b, 1998a). BCI control not only depends on the ability to activate the control regions, but also to activate them at the appropriate time. The latter may be more difficult for some participants.

The main limitations of this study are the limited number of participants and the limited number of implanted electrodes for each participant. Also, because we used electrode strips with 4 electrodes spaced 10 mm apart, coverage was sparse. The small number of electrodes unfortunately prevented single-subject analyses when limiting the analysis to the sensorimotor cortex electrodes. ECoG-based BCI systems with more degrees of freedom and correspondingly more coverage (e.g. (Benabid et al., 2019)) will be informative in further elucidating the spatial match between BOLD and ECoG in people with locked-in syndrome.

5. Conclusions

Taken together, we found significant spatial correlations between BOLD and HFB and LFB ECoG activity in people with locked-in syndrome. The relationship between BOLD and ECoG LFB power seemed less straightforward when analysis was focused on the sensorimotor cortex, potentially explainable by a spatially widespread LFB response to the task. We conclude that pre-surgical fMRI is a useful method for localizing electrode target regions for an ECoG-based BCI. Our results also suggest that fMRI may contribute to the post-implant electrode selection phase, in cases of more extended coverage with ECoG electrodes. Moreover, if our results are confirmed in more participants, future studies might use fMRI exclusively for electrode placement, without the need for acute measurements or coverage extending beyond the fMRI hotspots, thereby decreasing participant burden and surgery related risks, and potentially improving acceptance. Finally, the weak relation between BOLD and BCI proficiency across participants suggests that BOLD cannot predict relatively small differences in individual’s BCI performance based on a single electrode pair but might be used as a proxy for an individual’s ability to activate the target regions. Whereas all findings need to be validated with more participants, we recommend the use of pre-surgical fMRI for localization of BCI target regions.

Acknowledgements

The authors thank Max van den Boom and Benny van der Vlijgh for their work on research task software used in this study; Maxime Verwoert for her help with fMRI data acquisition and analysis; Vincent Kersten for maintaining our file server; UMCU ICU and radiology staff for their help during the fMRI session and in the week of implantation; UMCU clinical neurophysiology staff for their help with signal quality checks in the OR during the implantation and for their help with ECoG measurements in the days after implantation. The authors thank the participants and family and caregivers for their hard work, hospitality, and their courage.

Funding

This work was funded by grants from the Dutch Organization for Scientific Research (NWO; Intense Project EU, work package 3), the Dutch Technology Foundation STW (STW 12803), and the National Institute for Deafness and other Communication Disorders (U01DC016686; U.S. NIH Grant/Contract). Medtronic provided implanted hardware as an in-kind contribution and provided technical support.

Declaration of Interest

NFR is co-founder and director at Braincarta, which specializes in off-the-shelf fMRI software for clinical assessment of brain anatomy and functioning. Braincarta software was not used for the analyses described in this manuscript. The authors report no other competing interests.

References


