Brain–Computer Interfacing Based on Cognitive Control

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Objective: Brain–computer interfaces (BCIs) translate deliberate intentions and associated changes in brain activity into action, thereby offering patients with severe paralysis an alternative means of communication with and control over their environment. Such systems are not available yet, partly due to the high performance standard that is required. A major challenge in the development of implantable BCIs is to identify cortical regions and related functions that an individual can reliably and consciously manipulate. Research predominantly focuses on the sensorimotor cortex, which can be activated by imagining motor actions. However, because this region may not provide an optimal solution to all patients, other neuronal networks need to be examined. Therefore, we investigated whether the cognitive control network can be used for BCI purposes. We also determined the feasibility of using functional magnetic resonance imaging (fMRI) for noninvasive localization of the cognitive control network.
Methods: Three patients with intractable epilepsy, who were temporarily implanted with subdural grid electrodes for diagnostic purposes, attempted to gain BCI control using the electrocorticographic (ECoG) signal of the left dorsolateral prefrontal cortex (DLPFC).
Results: All subjects quickly gained accurate BCI control by modulation of gamma-power of the left DLPFC. Prelocalization of the relevant region was performed with fMRI and was confirmed using the ECoG signals obtained during mental calculation localizer tasks.
Interpretation: The results indicate that the cognitive control network is a suitable source of signals for BCI applications. They also demonstrate the feasibility of translating understanding about cognitive networks derived from functional neuroimaging into clinical applications.

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Each year, a large number of people are struck by paralysis, as a result of brain trauma, intracerebral hematoma, neuromuscular disease, spinal cord injury, or stroke. In severe cases, paralysis prohibits any control over, or communication with, the environment, effectively locking people in their own body. Despite extensive research in the areas of neural repair, pharmacology, and rehabilitation strategies,[1–3] no successful treatment or cure is available to these patients.

In an effort to provide severely paralyzed patients with some form of functional restoration, researchers have been working on the development of brain–computer interfaces (BCIs). These systems aim to bypass the peripheral nerves and muscles and directly convert brain signals that are under conscious control into control signals for electronic devices, such as a computer, spelling device, or robotic arm. For example, a BCI can enable patients to operate devices such as a television, lights, or curtains by controlling a cursor in a computer program. In addition, a BCI allows the patient to conduct social interaction via the computer, without having to depend on the immediate presence and assistance of a caregiver.

BCI systems in humans have predominantly used electroencephalography (EEG). EEG-based BCI systems

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have been developed over the past 2 decades, but have not yet seen widespread clinical adoption. In principle, the systems can provide patients with 1- or 2-dimensional cursor control,[4,5] but there are remaining problems with system robustness and necessary expert supervision. Performance of these systems depends highly on precise positioning of electrodes on the scalp and careful calibration of hardware and software components. Recently, BCI systems using intracranial electrocorticographic (ECoG) electrodes have attracted interest. ECoG-based BCIs use signals acquired directly from the surface of the cortex. Because ECoG signals have much higher fidelity than EEG signals, it is possible to exploit the functional-topographical organization of the brain. Many brain functions are regulated by areas at the cortical surface, providing signals that are typically very specific in time and space. Accessing the neocortex directly allows one to select a specific brain function for a patient to apply for cursor control.

ECoG-based BCIs are invasive and cannot be tested in healthy volunteers. However, testing can be conducted in patients who have electrodes implanted subdurally for other reasons, such as for presurgical evaluation of medically intractable focal epilepsy. Several studies have been published showing that these patients can control a cursor, by using motor or auditory imagery.[6–10] Electrodes used in these studies were selected based on signal properties obtained after implantation of a high number of electrodes in so-called subdural grids. In paralyzed patients, such an extensive, permanent grid implantation is impractical and increases the risk to the patient. Preferably, the exact location of a brain region serving a particular function should be determined before implantation. This would allow minimal surgery involving only a small burr hole in the skull (rather than a full craniotomy) to accommodate 1 electrode or a small electrode array. As anatomical and functional brain topography varies considerably across individuals, such a presurgical localization requires accurate functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI). To date, it has not been investigated whether fMRI is sufficient to prelocalize the relevant regions for BCI purposes in individual subjects. In the current study, we take a first step in addressing this issue by combining fMRI activation patterns and the spatial distribution of responsive ECoG electrodes for electrode selection.

In the development of BCIs, researchers have traditionally focused on the use of signals from the sensorimotor cortex. Results from EEG and intracortical studies have been promising, showing that severely paralyzed patients are able to guide a cursor over a computer screen by imagining movement.[11,12] Brain regions subserving nonmotor functions are new emerging targets[9,13–15] for a number of reasons. First, the use of ECoG recordings enables targeting of higher cognitive functions. Second, motor cortex function can be impaired in paralyzed patients, especially after long-term paralysis[16–18] or trauma to the motor cortex. Third, to obtain full control over devices such as a robotic arm, wheelchair, or communication software, at least several independent channels are required, which can be achieved by additionally targeting systems other than motor circuits. Utilization of cognitive brain function has a particular intrinsic validity. As deliberate motor actions are typically preceded by mental planning, cognitive brain systems can be expected to display signals that may prove useful for the BCI purpose. The aim of the present study was to assess the feasibility of targeting 1 specific cognitive brain region for ECoG-BCI. This region, the left anterior dorsolateral prefrontal cortex (DLPFC), was selected based on previous neuroimaging and neurostimulation studies that showed a selective involvement in deliberate processing of information, and a close match in this region between fMRI and ECoG and between fMRI and neurostimulation.[14,19] The DLPFC is a critical region of the cognitive control (CC) network, which regulates the flow of information in the brain to plan actions and to solve problems.[20] Using a mental calculation paradigm that reliably and strongly activates the CC network,[14] we demonstrate here that the DLPFC is a highly suitable target region for BCI purposes.

Patients and Methods

Subjects in this study were 3 consecutive patients (see Supplementary Table 1) with intractable epilepsy, who were scheduled for subchronic ECoG using subdurally implanted electrode grids to localize the seizure focus and investigate the possibility of surgical removal of the epileptogenic tissue. The study was approved by the Medical Ethical Committee of the Utrecht University Medical Center. All patients gave written informed consent according to the Declaration of Helsinki.

Several weeks prior to grid implantation, patients underwent an fMRI scanning session, during which they performed several tasks to localize functionally relevant regions (see Supplementary Methods and Supplementary Table 2). For each patient, the set of tasks was based on clinical relevance, and included a mental calculation task for identification of the regions of the CC network. During grid implantation surgery, ECoG grid electrodes were implanted (between 120 and 136 contact points, 2.3mm exposed diameter, interelectrode distance 1cm, Ad-Tech, Racine, WI). Placement of grids was based entirely on clinical considerations. To coregister the ECoG and fMRI data, electrode locations were localized on a postoperative computed tomography scan that was registered to the anatomical MRI scan of the patient. The electrode locations were then projected to the cortical surface and visualized on a 3-dimensional rendering

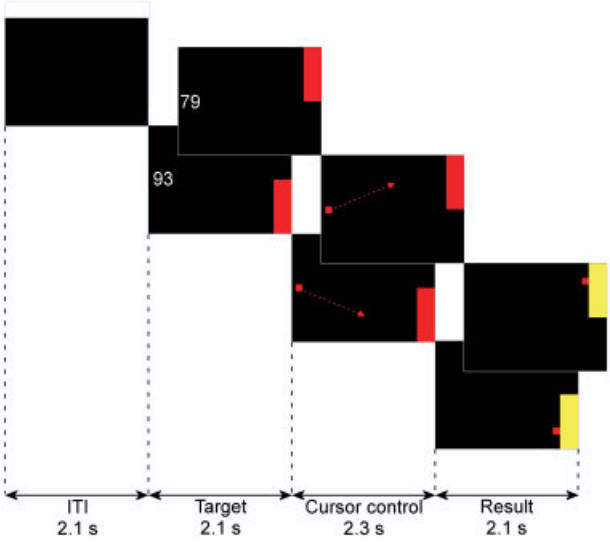

FIGURE 1: Cursor control task. Each trial of this task lasted 8.5 seconds and started with an intertrial interval (ITI) of 2.1 seconds, followed by the appearance of a target in the upper-right or lower-right corner of the computer screen (Target, vertical size = 50% of screen height, horizontal size = 10% of screen width), and a number on the left side. Next, a cursor appeared (2.1 seconds after the target) and traveled from left to right at a set pace (Cursor control, fixed travel-time of 2.3 seconds). The subject's task was to modulate electrocorticographic (ECoG) activity such that the cursor hit the target when it reached the right edge. ECoG activity was modulated by performing serial subtraction starting from the number on the left side of the screen (to send the cursor up) or by relaxing (to send the cursor down). Correct hits were indicated by a color change of the target (Result); incorrect hits by an absence of color change.

of the gray matter.[21] To confirm the involvement of the sites identified by fMRI, patients performed CC network localizer tasks during ECoG recording (see Supplementary Methods and Supplementary Table 2). Based on the data of fMRI and ECoG CC localizer tasks, a single electrode and frequency band was selected for use in subsequent 1-dimensional 2-target cursor control tasks (Fig 1 and see Supplementary Methods), in which patients voluntarily modulated ECoG activity (γ-power) of the selected CC electrode to control the vertical movement of a cursor on a computer screen. Patients controlled the cursor by performing serial subtraction (to send the cursor up) or by relaxing (to send the cursor down). The amount of data that could be obtained depended on the condition of the patients.

Results

Localizer Tasks

FMRI. Presurgical MRI scanning during a mental calculation task identified the key regions of the CC system in every subject (Fig 2, single subject analysis, significance threshold $p < 0.05$, family wise error [FWE]-corrected), including the DLPFC and parietal cortex near the intraparietal sulcus. In the remainder of this article, we focus on the DLPFC.

ECOG RECORDINGS. For each patient, fMRI-activated regions in the left DLPFC were at least partly covered by the electrode grids (see Fig 2). Performance of a mental calculation or serial subtraction localizer task during ECoG recording induced a significant increase in γ-power ($p <$ 0.05, Bonferroni corrected, see Fig 2) in 1 to 4 electrodes covering the left DLPFC. For every subject, the electrodes with significant γ-power changes were located on subregions showing the strongest fMRI activation (Fig 3). The electrode showing the strongest increase in γ-power in this region (highest mean R^2) was selected for use in the subsequent cursor control task.

Cursor Control Task

Each patient conducted 1 or more runs vocally to allow monitoring of correct understanding of the instruction and performance. All patients quickly obtained a high degree of cursor control (Fig 4); during the first vocal run, all subjects reached a performance score of >80% (with 50% correct being chance level). Performance during silent runs was initially <80% in 2 of 3 patients, but levels >80% were obtained within 6 and 12 silent runs, respectively. The maximum obtained bitrate[22] was 0.64, 0.52, and 0.42 bits per trial, for Patients 1, 2, and 3, respectively. Offline analysis of the cursor control tasks confirmed that the signal of the selected electrode of each patient exhibited a large difference in γ-power between up trials and down trials in runs with high performance scores (Fig 5). These changes in γ-power occurred quickly after presentation of the target, and were clearly visible at the single-trial level (Fig 6).

To assess whether the choice of fMRI sites provided the best electrode locations for BCI purposes, the ECoG signal of all electrodes was examined offline, by computing, per electrode, the average of the R^2 values of all (ie, vocal and silent) cursor control runs. For all patients, the selected electrode had the highest average (±standard error of the mean) R^2 value across runs (ie, 0.66 ± 0.05 [n = 4], 0.29 ± 0.04 [n = 27], 0.40 ± 0.07 [n = 7], for Patients 1, 2, and 3, respectively; ranges for R^2 values of other electrodes were −0.37 to +0.60, −0.10 to +0.21, and −0.13 to +0.31, respectively). This suggests that the selected electrode was the electrode of choice for optimal cursor control for each of the patients.

Discussion

We demonstrate here that the DLPFC is suitable for use in ECoG-BCI applications. The DLPFC is part of a neuronal network that coordinates mental processes in the

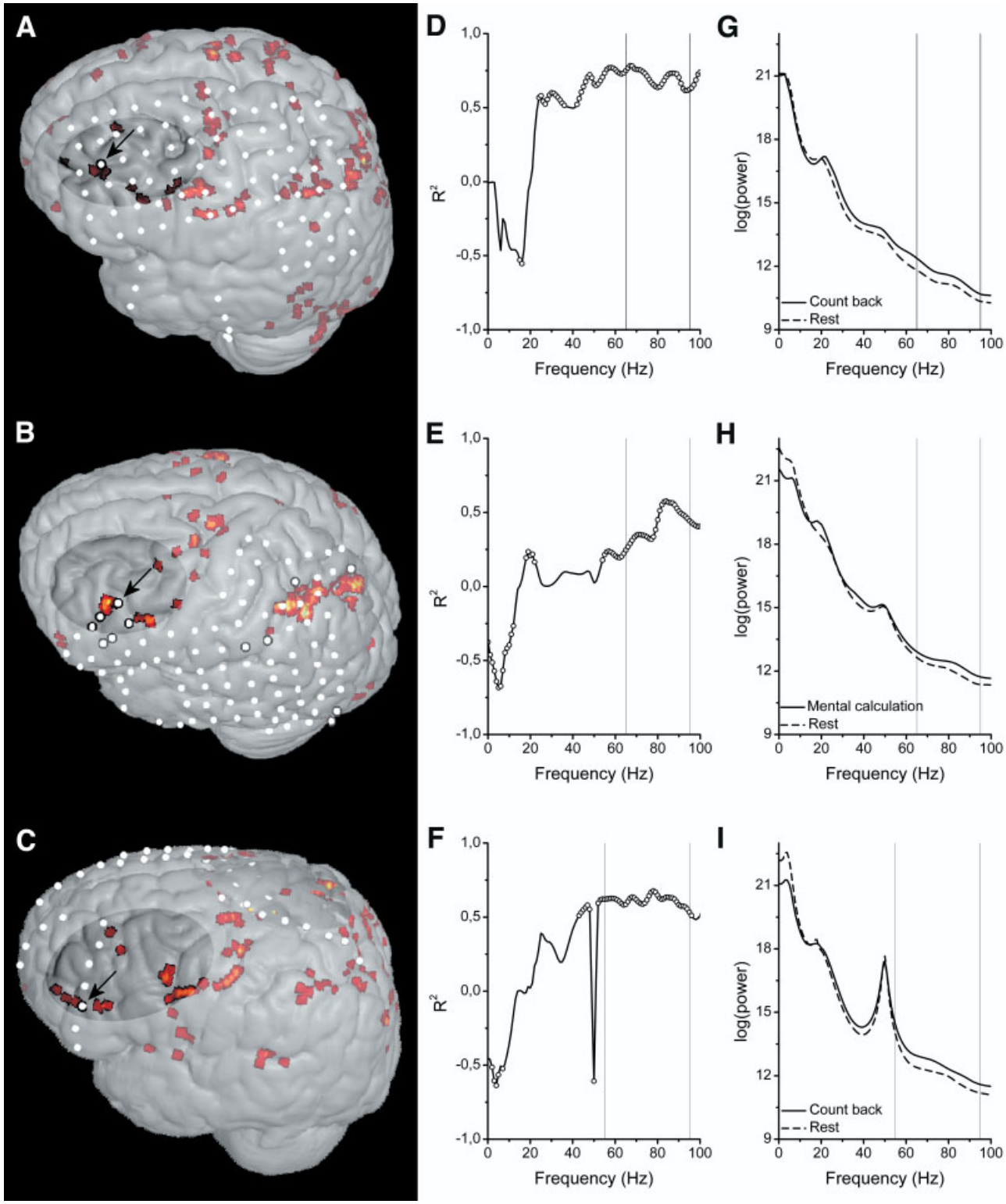

FIGURE 2: Prelocalization of optimal cortical region for cognitive control brain–computer interface. (A–C) Three-dimensional renderings of the brains of Patients 1, 2, and 3, respectively. The left prefrontal cortex is indicated by darker shading and contains several areas with significant ($p < 0.05$, FWE corrected) functional magnetic resonance imaging activation ($T > 8.5$, 8.5, and 5, respectively, mental calculation versus rest, red and yellow voxels). Subdurally implanted electrodes are represented by white dots. Black circles indicate electrodes that showed significant ($p < 0.05$, Bonferroni corrected) γ-power changes as a result of mental calculation/serial subtraction localizer tasks during electrocorticographic recording after grid implantation. Black arrows point at the electrode in the left prefrontal cortex with the strongest γ response (ie, largest average R^2; average R^2 values = 0.79, 0.53, and 0.65; $p_{Bonferroni\text{-}corrected} = 1.61^{e-5}$, 2.55^{e-12}, and 2.23^{e-3} for Patients 1, 2, and 3, respectively) in each patient. (D–I) R^2 distributions (D–F, significant values indicated by *open circles*, $p < 0.05$, Bonferroni corrected) and (G–I) log(power) plots of the appointed electrodes. Note that the power in the γ frequency range (indicated by *vertical lines*) is higher during mental arithmetic (counting backwards/mental calculation, *solid line*) than during rest (*dashed line*), corresponding to high R^2 values in this frequency range. The large deflection at 50Hz in parts F and I is caused by mains power interference.

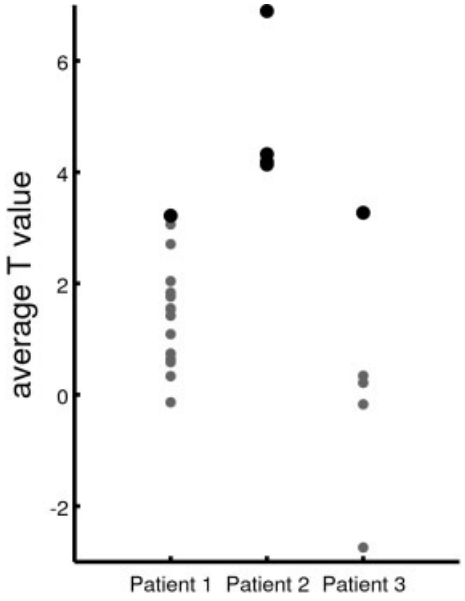

FIGURE 3: Functional magnetic resonance imaging (fMRI) prelocalization. For each electrode on the dorsolateral prefrontal cortex (see selection in Fig 2), the average fMRI t value (8mm radius in the gray matter) is indicated as a dot. The electrodes that showed significant changes in γ-power during the electrocorticographic localizer task are indicated in black. Note that these electrodes are those located in regions showing the highest fMRI t values.

service of explicit intentions or tasks, referred to as the CC network.[20,23–25] It responds to the amount of information that needs to be processed in the context of cognitive tasks, which can be imposed externally or internally, and as such is highly under voluntary control. The CC network can be activated by various tasks, including mental calculation,[14] which requires manipulation of information and holding information online for the different steps of addition and subtraction. The specific region targeted in the present study is strongly associated with CC,[26] as evidenced by the selective deficits upon electrocortical stimulation of ECoG electrodes and upon surgical removal.[19]

Our data show that the left anterior DLPFC is consistently activated by mental calculation, as evidenced by fMRI activation and a significant increase of ECoG γ-power. Using this region, all 3 patients acquired good BCI control (>80% correct hits) within 1 vocal 4-minute BCI control run and within 1 to 12 silent runs, demonstrating that the accuracy of cognition-based ECoG-BCI is at least as high as that of 1-dimensional ECoG systems using the well-studied motor cortex.[6–9] The initial difference in performance score between vocal and silent runs may be explained by a more optimal task execution during the vocal runs, possibly related to psychological factors, such as the experimenter listening, or increased focused attention due to autofeedback. The increase in performance over silent runs may be attributed to a training effect or a general improvement of alertness in the course of days after electrode implant surgery. It should be noted that our performance results are an underestimation of what can be achieved, because most patients suffer from (fluctuating) reduced alertness and sometimes headache and nausea caused by the surgical procedure in the brief period of seizure registration (1 week), which is usually too short for full recovery.

Accurate prelocalization of functionally relevant brain areas is essential for the application of ECoG-BCI systems in paralyzed patients. Cognitive systems are composed mainly of association cortex, and are not as clearly defined in terms of function and topography as primary regions such as the motor cortex. Although a number of cortical regions have consistently been associated with the CC network,[27] exact locations vary across subjects much like other associative cortex systems. Targeting cognitive systems therefore depends heavily on knowledge obtained with functional neuroimaging. In the current study, we used fMRI for presurgical localization. fMRI localizes brain activity on the basis of vascular parameters, notably changes in oxygenation that follow changes in neural activity.[28] Our data show that the location of electrodes with significant ECoG γ-power changes corresponded with subregions showing the largest fMRI activation, suggesting that accurate fMRI prelocalization of the CC re-

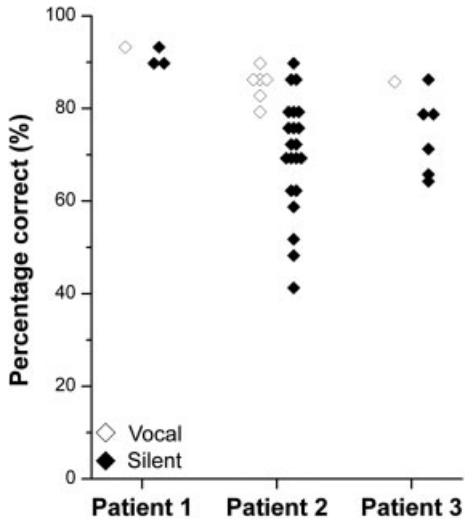

FIGURE 4: Brain–computer interface performance (% correct) of the patients during individual 4-minute cursor control runs, performed vocally *(open diamonds)* and silently *(solid diamonds)*. Performance during vocal runs was >80% in the first run for all patients. Although performance was initially lower during silent runs, all patients quickly reached accurate silent control as well. The average (±standard error of the mean) performance of all silent runs (n = 3, 21, and 6, for Patients 1, 2, and 3) was 91 ± 1 (range, 89.7–93.1%), 70 ± 3 (range, 41.4–89.7%), and 74 ± 3% (range, 64.3–86.2%).

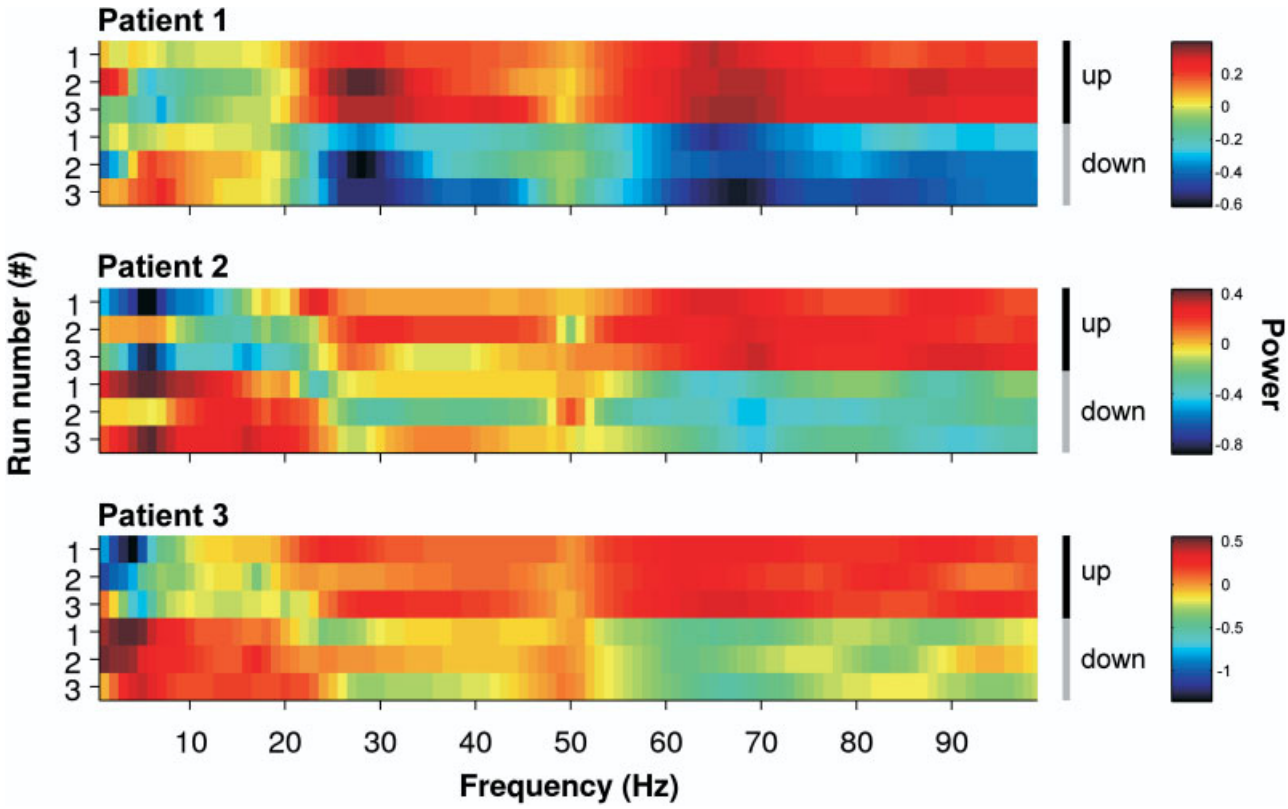

FIGURE 5: Offline signal analysis. Normalized average power is shown of up trials (serial subtraction, marked by *black vertical line* on the right) and down trials (relaxation, marked by *gray vertical line*) of the 3 best cursor control runs performed by Patients 1, 2, and 3, respectively. Frequency in hertz is indicated on the x axis. Scaling on the color bar is logarithmic for plotting purposes. Note that these runs with high performance scores are characterized by large differences in γ-power between up trials and down trials.

gion in the left anterior DLPFC is feasible. Although the correspondence between γ-power changes and fMRI blood oxygen level-dependent (BOLD) signal changes has been shown earlier[29] and seems a robust phenomenon, it should be noted that the fMRI activity maps in our study tended to indicate a larger number of active regions than ECoG. Indeed, the full relationship between the fMRI BOLD signal and electrophysiological processes is far from being understood, and is under investigation by us and by other research groups.[29–31] We believe that a growing insight into the correlation between these 2 types of signals will only strengthen the predictive value of fMRI activation patterns for optimal implantation sites, especially when this information is combined with detailed anatomical knowledge about the targeted networks, as was done in the present study.

For more complex BCI applications, more than one control channel is required, and neural signals need to be obtained from multiple electrodes. The CC system consists of several cortical regions across the frontal and parietal cortex and could enable a multichannel BCI, provided that activation patterns differ for different specific cognitive functions. Functional imaging studies in humans have shown that regions within the CC network can indeed be dissociated, lending support to this expectation.[20] Nonhuman primate studies have shown that there may be a topographical diversity of modality and process-specific CC functions within the DLPFC,[32–35] raising the possibility of obtaining multiple, highly function-specific signals from this region. When high-density surface electrode grids become available for chronic implantation in humans, it will be possible to determine whether multiple specific mental processes can be distinguished from each other within a small grid covering the DLPFC. This would open the possibility of obtaining multichannel BCI from a small patch of prefrontal cortex using specific self-generated mental actions.

Understanding the exact brain function that is targeted for BCI may be essential for successful BCI application in that the selected brain region should not generate a BCI signal for mental processes other than that targeted (false-positive cursor signals). For instance, the presently selected region is active during tasks that require controlled mental processing in functional imaging studies, suggesting a general involvement in cognition. Inactivation of this region by electrocortical stimulation, how-

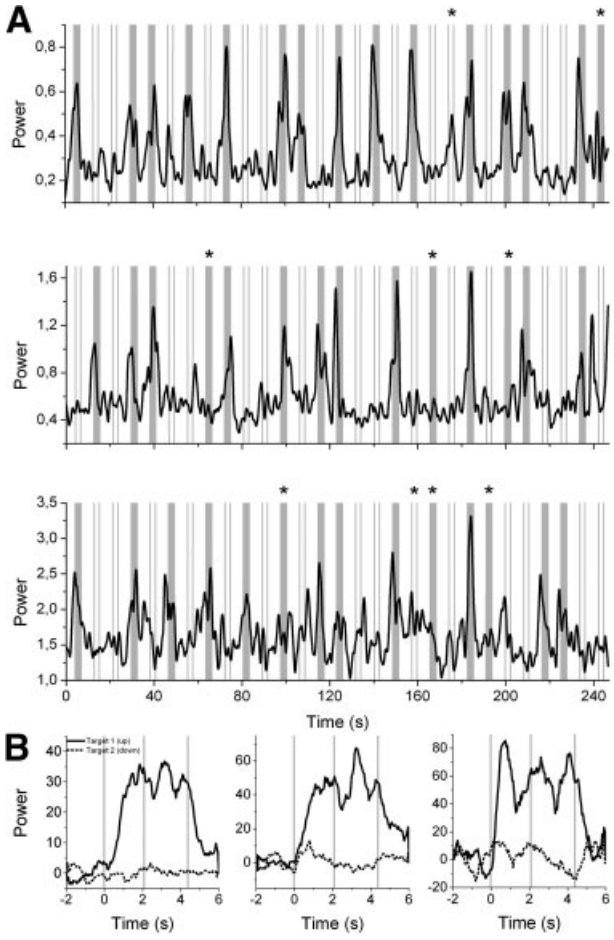

FIGURE 6: Time frequency analysis. (A) Top to bottom: Changes in average γ-power (smoothed) over time *(black line)* during a 4-minute brain–computer interface (BCI) control run for Patients 1, 2, and 3 (for each patient, the silent BCI control run with the highest performance was used for this figure). Vertical grey bars in the background indicate a target in the upper-right corner of the computer screen, requiring the patient to send the cursor upward by increasing γ-power using mental calculation. Vertical white bars indicate a target in the lower-right corner, requiring the patient to relax, thereby decreasing γ-power to send the cursor down. Misses are indicated by asterisks. (B) Left to right: Changes in average γ-power (corrected for baseline, smoothed) over time, averaged over correct hit trials of up targets *(solid line)* and down targets *(dashed line)* of the silent BCI control run with the highest performance for Patients 1, 2, and 3. Vertical lines indicate the appearance of the target, and the start and end of the feedback period, respectively.

ever, impairs only selective cognitive functions and not general cognition, as evidenced by a study of Kho and colleagues.[19] They showed that electrical stimulation disrupts the ability to repeat serially presented letters in reverse while preserving the ability to repeat them in the same order, as well as preserving picture naming, reading, and spontaneous speech. In the present study, the fMRI data showed that, besides mental calculation, language tasks with a mental search component activated the selected region (see Supplementary Methods and Supplementary Table 2). In contrast, the ECoG results clearly distinguished between mental calculation and language tasks, in that γ-power of the selected electrode was only affected by calculation and not by language processing. Hence, in the present study, the combination of regional and functional targeting together with the choice of a specific frequency band enabled patients to control the cursor with a selective mental process.

In conclusion, the current study introduces the value of the CC network for BCI applications. Once highly accurate, noninvasive prelocalization of individual functional subregions of the system has been accomplished, we foresee a major role for cognitive brain functions in implantable BCI systems that are likely to be clinically applied within the near future.

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Potential Conflicts of Interest

G.S. owns stock in the company Neurolutions.

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