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Somatotopic mapping of natural upper- and lower-extremity movements and speech production with high gamma electrocorticography

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ABSTRACT

Precise delineation of pathological and eloquent cortices is essential in pre-neurosurgical diagnostics of epilepsy. A limitation of existing experimental procedures, however, is that they critically require active cooperation of the patient, which is not always achievable, particularly in infants and in patients with insufficient cognitive abilities. In the present study, we evaluated the potential of electrocorticographic recordings of high gamma activity during natural, non-experimental behavior of epilepsy patients to localize upper- and lower-extremity motor and language functions, and compared the results with those obtained using electrocortical stimulation. The observed effects were highly significant and functionally specific, and agreed well with the somatotopic organization of the motor cortex, both on the lateral convexity and in the supplementary motor area. Our approach showed a similar specificity and sensitivity for extremity movements as previously obtained from experimental data. We were able to quantify, for the first time, sensitivity and specificity of high gamma underlying non-experimental lower-extremity movements in four patients, and observed values in the same range as for upper extremities (analyzed in six patients). Speech-related responses in the three investigated patients, however, exhibited only a very low sensitivity. The present findings indicate that localization of not only upper- but also lower-extremity movements congruent with electrocortical stimulation mapping is possible based on event-related high gamma responses that can be observed during natural behavior. Thus, non-experimental mapping may be usefully applied as adjunct to established clinical procedures for identification of both upper- and lower-extremity motor functions.

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Introduction

An important challenge in pre-neurosurgical diagnostics of pharmacoresistant focal epilepsy is exact delineation of eloquent cortex which needs to be spared from resection in order to prevent post-operative deficits such as permanent paresis or aphasia. Eloquent cortex is commonly identified using electrocortical stimulation mapping (ESM) by applying electric currents through the same subdural electrodes as used to determine the seizure onset zone in electrocorticographic (ECoG) signals. ESM is a necessary procedure, since eloquent brain areas cannot be defined solely based on macroanatomical landmarks due to the large inter-individual variability of the position and extent of functional areas (Amunts et al., 1999; Ojemann and Whitaker, 1978; Steinmetz et al., 1990). This variability may be even greater in epilepsy patients than in healthy subjects as a consequence of epilepsy-related brain reorganization (Borchers et al., 2012).

However, there are a number of practical constraints on ESM implementation. First, it is time-consuming and usually takes several hours per day over several days since a large number of electrode contacts have to be tested individually, and requires compliance and active patient cooperation. Thus, ESM may be not feasible in patients who lack cooperation or cognitive abilities required to perform experimental tasks, such as infants and young children or patients with mental impairments, e.g., related to postictal disturbances. Second, it may induce after-discharges and trigger epileptic seizures, which may preclude further testing (Blume et al., 2004; Lesser et al., 1984; Pouratian et al., 2004; Sinai et al., 2005), especially in infants and young children, in whom stimulation thresholds for localization of the motor cortex are generally higher but after-discharge thresholds are lower than in adults (Chitoku et al., 2001; Jayakar et al., 1992). Thus, there is a strong interest in complementary and/ or alternative methods for functional mapping (Bauer et al., in press; Breshears et al.,

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2010; Brunner et al., 2009; Lachaux et al., 2007a; Leuthardt et al., 2007; Miller et al., 2007a; Roland et al., 2010; Schalk et al., 2004, 2008; Sinai et al., 2005; Towle et al., 2008; Vansteensel et al., in press; Wray et al., 2012).

Mounting evidence exists that event-related changes in the high gamma (HG) frequency range (>60 Hz) constitute a spatially, temporally, and functionally-specific index of cortical processing in ECoG (Crone et al., 1998, 2001a,b; Leuthardt et al., 2012; Miller et al., 2007a; Pfurtscheller et al., 2003), electroencephalography (EEG; Ball et al., 2008), and magnetoencephalography (MEG; Cheyne et al., 2008).

Spectral power modulations in the HG range of the human ECoG have the advantage of carrying physiological information about cortical function in contrast to ESM, which is perturbation-based (Brunner et al., 2009; Miller et al., 2007b). Early research that compared ESM and high gamma mapping (HGM) observed overall agreement between the functional maps that can be derived with these two methods, and proposed HGM as a complement to established clinical procedures for localizing eloquent cortex (Crone et al., 1998, 2001a,b; Pfurtscheller et al., 2003). Later studies confirmed these observations by evaluating response sensitivity and specificity in HGM relative to ESM (Brunner et al., 2009; Leuthardt et al., 2007; Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010).

The view currently prevails that HGM cannot entirely replace ESM as a standard diagnostic procedure due to its moderate sensitivity (e.g., Brunner et al., 2009; Crone et al., 2006; Sinai et al., 2005, but see Kojima et al., 2012). Nevertheless, HGM is a conceivable alternative when ESM is not feasible due to after-discharges, seizure induction, pain, or similar side effects. Furthermore, HGM is useful for localization of high-priority sites for electrocortical stimulation-based testing (Brunner et al., 2009; Cervenka et al., 2011; Leuthardt et al., 2007; Roland et al., 2010; Sinai et al., 2005; Towle et al., 2008; Wray et al., 2012; Wu et al., 2010).

Yet a limitation of the HGM approach applied in previous experimental studies is that, like ESM, it crucially relies on active patient cooperation and compliance over an extended time period. This may be difficult to achieve in infants, small children, and in cognitively impaired individuals, or if electrodes need to be removed earlier than planned, e.g., due to such common implantation-related complications as hematoma or brain swelling (Lee et al., 2000). Non-experimental mapping, however, may still be possible in such cases. Another motivation for performing non-experimental mapping is the fact that experimental paradigms may not elicit the same brain activity as naturalistic behavior (Jackson et al., 2007; Vanin et al., 2012). For these reasons, there is a recent interest in using non-experimental ECoG recordings in pre-neurosurgical diagnostics of epilepsy to map essential upper-extremity motor (Vansteensel et al., in press; Wray et al., 2012) and communication-related functions (Bauer et al., in press; Cho-Hisamoto et al., 2012; Towle et al., 2008), as well as to investigate neural mechanisms underlying natural human cognition (Derix et al., 2012).

Previous ECoG studies comparing HGM and ESM in the context of pre-neurosurgical diagnostics of epilepsy, however, were mostly restricted to investigations of hand, arm, tongue, and speech functions (Crone et al., 1998, 2001a,b; Leuthardt et al., 2007; Sinai et al., 2005), and only few data on gamma alterations related to leg and foot movements are currently available (Miller et al., 2007b). This earlier study reported somatotopically atypical cortical responses related to movements of lower extremities, and additional investigations are needed to clarify whether signals in the HG range can reliably identify cortical locations that support lower-extremity movements.

Our aim in the present study was to map the whole somatotopic extent of the motor cortex using HG (60–400 Hz) power modulations in ECoG data related to spontaneous, everyday upper- as well as lower-extremity movements and speech production that can be obtained without active patient cooperation and without placing additional burden on epilepsy patients, and to perform a detailed *post hoc* analysis of the resulting functional maps with those obtained using ESM.

Material and methods

Patients

Data from six patients (P1–P6) were analyzed (Table 1). The patients were all adults and spoke German as a native language. Prior to the start of the study, all patients gave their written informed consent that the data recorded during electrode implantation might be used for scientific purposes.

Data acquisition

ECoG was recorded with a clinical AC EEG-System (IT-Med, Germany) at a 5-s time constant corresponding to a high-pass filter with a cutoff frequency of 0.032 Hz, and digitized at a sampling rate of 1024 Hz using an anti-aliasing digital low-pass filter with a cutoff frequency at around 400 Hz. All subjects were continuously monitored in digital video (25-Hz sampling rate and a 640 × 480 pixel resolution) and with 2 channels of audio recordings, both synchronized to the ECoG. In two patients (P2 and P3), electromyography (EMG) of the upper and lower extremities over the left and right deltoid and quadriceps muscles was continuously recorded together with the ECoG as a part of the diagnostic procedure. These synchronized ECoG-EMG data were utilized to validate our video-based approach to identification of extremity movements (see below). A post-implantation T1-weighted magnetization-prepared rapid-acquisition gradient-echo (MPRAGE) data set for every subject was acquired at an isotropic resolution of 1 mm in a 1.5-T magnetic resonance imaging (MRI) scanner (Vision, Siemens, Erlangen, Germany). These data were further used for anatomical assignment of electrodes to individual cortical areas (described below).

Selection of natural movements and natural speech production events

In the following, we refer to the non-experimental, everyday motor behavior and overt expressive speech as "natural movements" and "natural speech production." Movement/ speech onsets in all patients were determined based on the digital video/ audio recordings. Trials were included in the analysis if they had a sufficiently long baseline period (described below) to allow for investigation of spectral power changes relative to neural activity preceding the respective onset (Brown et al., 2012; Kojima et al., 2012; Miller et al., 2011; Sinai et al., 2005).

Extremity movements were extracted during various everyday-life activities from an average of 5–13 h of recordings per patient at different times of the day over 2–3 days. Natural upper- and lower-extremity movements were analyzed only when no motion of trial-irrelevant body parts was observable in the video recordings from 2 s before until 2 s after movement onset. The investigated movements of the arm, hand, and fingers contralateral to the side of implantation comprised object-directed movements such as picking up an object, opening the drawer of the bedside table, opening a book or a magazine, or arranging a blanket (examples are shown in Fig. 1), as well as movements without any obvious goal or intention. The selected lower-extremity movements included movements of both legs as movements of individual legs were rare and could not be analyzed separately. Since the patients were not allowed, for safety reasons, to stand up and walk with the wired ECoG electrode connections, lower-extremity movements were mostly performed to change the body posture in the hospital bed, or without any obvious purpose.

We analyzed neural data for all conditions (i.e., speech production, upper-extremity movements, lower-extremity movements) if the number of trials in the respective category was at least 50. A sufficient number of trials for natural hand and arm motor behavior were obtained in all patients. Cortical activity underlying leg movements could be investigated in four patients (P1, P2, P4, and P5). For P3,

Table 1
Summary of patient data.

	Age	Sex	H./S. lat.	8 × 8-electrode grid location	Strip and depth electrode location	Lesion	Seizure onset	HGM con., № trials
P1	49	F	R*/B	Left fronto-temporo-parietal	1 × 4-contact strip left fronto-lateral; 1 × 6-contact strip left fronto-medial; 4 × 4-contact strips interhemispheric	Focal cortical dysplasia, left frontal	Left SMA	U.E., 160 L.E., 52 Speech, 110
P2	41	F	L/L	Left fronto-temporo-parietal	1 × 6-contact strip left fronto-polar, 1 × 6-contact strip left fronto-lateral; 4 × 4-contact strips interhemispheric	Focal cortical dysplasia, left fronto-central	Left precentral	U.E., 63 L.E., 97 Speech, 50
P3	27	M	R/L	Left fronto-parietal	3 × 4-contact strips interhemispheric; 2 × 10-contact depth electrodes to left insular cortex	Focal cortical dysplasia, left frontal	Left frontal	U.E., 106
P4	40	M	R/B	Left fronto-parietal	1 × 4-contact strip left fronto-medial; 4 × 4-contact strips interhemispheric	Focal cortical dysplasia, left frontal	Left frontal	U.E., 160 L.E., 52 Speech, 84
P5	21	F	R/L	Right fronto-temporo-parietal	–	Focal cortical dysplasia, right frontal	Right frontal	U.E., 51 L.E., 65
P6	41	M	R/L	Left fronto-temporo-parietal	–	Ganglio-gliom, left parietal cortex	Left parietal	U.E., 106

M: male, F: female, H./L. lat.: handedness/ language lateralization, R: right, L: left, B: bilateral, R*: right-handed converted from left, SMA: the supplementary motor area, con.: condition, U.E.: upper extremities; L.E.: lower extremities.

there were not enough trials to meet the inclusion criteria, and the leg motor cortex of P6 was not covered with electrodes.

HG power changes related to speech production were investigated in three patients (P1, P2, and P4) in whom ESM had revealed language sites. No speech functions were localized using ESM in P5, and the amount of speech-production trials in P3 and P6 was below the inclusion threshold. Trials were selected only when the patients did not move and there were no strong background noises (e.g., objects falling, the telephone ringing) or other people's speech throughout the period of at least 1 s before and at least 1 s after speech onset. Using these criteria, trials were extracted from 16–23 h of video material per patient, recorded at different times of the day within a period of 5–7 days. Many speech production events had to be discarded because they took place simultaneously with the patients' movements that could be observed in the video data, the most frequent of which were speech-accompanying gestures and head movements. All movement- and speech-production epochs were discarded when the patients were eating or drinking. See Table 1 for numbers of trials per patient and condition. A sufficient number of trials could be obtained in most cases. The limitation of the present approach that the minimal number of trials could not be reached in all cases may be overcome by automatized analysis of video and of additional motion capture data (see Discussion).

ECoG pre-processing and spectral analysis

The ECoG data were pre-processed by high-pass filtering at 0.3 Hz and re-referencing to a common average reference (Ball et al., 2008; Crone et al., 1998). Channels with artifacts such as due to broken wires or ongoing high-amplitude epileptic activity were excluded from the common average. We employed a multitaper method (Percival, 2000) with 200-ms sliding windows, 20-ms time steps, and 5 Slepian tapers to calculate time-resolved spectral power amplitudes in each trial. Relative power changes were computed against a baseline corresponding to the first 200 ms of the pre-event period (i.e., of the 2 s or 1 s before the onset of movements and speech production, respectively). The trial-averaged data were analyzed in a time window of the first 500 ms after speech/ movement onset. Our selection of this time window was motivated by the reproducible occurrence of robust HG responses around this latency in earlier studies, both relative to the onset of movement execution (Ball et al., 2009; Muthukumaraswamy, 2011) and overt speech production (Crone et al., 2001b; Kojima et al., 2012; Thampratankul et al., 2010; Towle et al., 2008).

For the consecutive analysis of event-related changes in the HG band, we calculated the median relative power over a broad range of frequencies from 60 to 400 Hz, as it had previously been suggested that broadband spectral power changes of the local field potential (LFP) are more closely related to neural spiking activity than narrowband signals (Manning et al., 2009). We analyzed HG responses up to the limit of 400 Hz, as it roughly corresponds to the cutoff frequency of the low-pass filter applied during acquisition, and because 400 Hz in our data corresponded to the so-called "Engineer's Nyquist frequency" at 2/5 times the sampling rate (Nunez and Srinivasan, 2006). We determined electrodes with significant HG power changes using a Wilcoxon sign test and applied the false discovery rate (FDR) approach for correlated p-values (Benjamini and Hochberg, 1995) to account for multiple

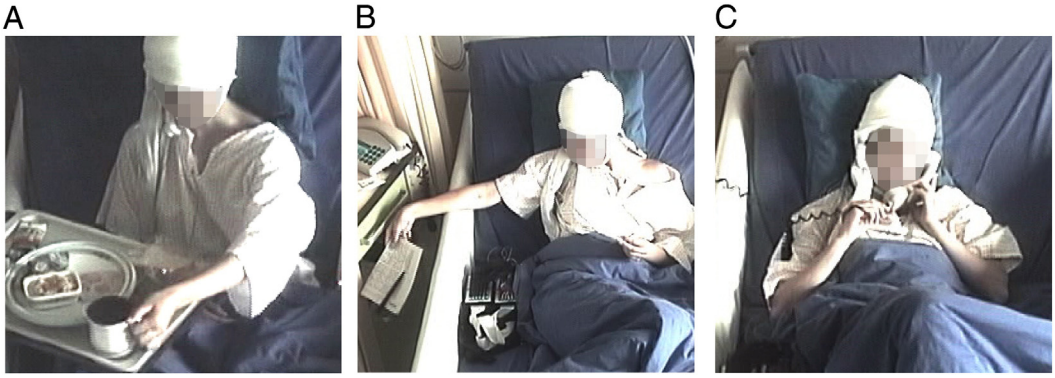

Fig. 1. Examples of natural movements analyzed to map the motor cortex. Frequent arm movements identified in the video recordings of P5 were object-directed movements such as grasping (A, B) and object manipulation such as holding the telephone cord (C). The images are cropped from the ECoG-synchronized video recordings used for the selection of natural movements and speech production events. The field of view of the video cameras encompassed the whole bed of the patients.

testing across channels. As the analysis was restricted to a single time window and frequency band, there was no other multiple testing than channels per patient. The significance threshold for the FDR correction was chosen depending on the number of trials per condition, and was $Q < 0.001$ for 50–150 trials and $Q < 10^{-6}$ for >150 trials.

Validation of video-based identification of natural movements

For validation of the video-based identification of natural movements, we analyzed concurrent EMG recordings of upper- and lower-extremity muscles in the patients in whom EMG data were available (P2 and P3). Trial-averaged time-frequency EMG spectra were calculated by the same procedure as applied on the ECoG data. The analysis of the EMG recorded at the deltoid muscles contralateral to the side of implantation and at the bilateral quadriceps muscles showed that there was increased lower- but not upper-extremity EMG in the lower-extremity trials (Fig. 2A, B). Conversely, while there was a pronounced increase in upper-extremity EMG in the upper-extremity trials, no substantial increase of lower-extremity EMG was observed (Fig. 2C, D). Thus, the video-based identification resulted in selective movements of either upper or lower extremities.

ESM

Extraoperative bipolar and monopolar ESM was performed in all patients using an INOMED NS 60 stimulator (INOMED, Germany). The patients were awake and sat in their hospital beds during the procedure. First, the bipolar stimulation was conducted in a non-overlapping fashion to identify pairs of contacts with motor or language functions. The monopolar stimulation was performed to further explore the functional relevance of the individual contact(s) of the bipolar pairs. Trains of 10-s duration were used which consisted of 50-Hz pulses of alternating-polarity 250-μs square waves. Stimulation intensity was gradually increased up to 15 mA (up to 18 mA for the monopolar language mapping) or until the induction of stimulation effects. These were either sensory (tactile sensations reported by the patients), speech-related (transient stimulation-induced impairment of expressive and/ or receptive language functions), or motor-related (positive, when stimulation provoked movements of one or several body parts, or negative, when ESM elicited a transient inability to move). Electrodes for upper extremities comprise hand-, arm-, shoulder-, and finger-related motor responses together, those for lower extremities comprise leg and foot motor responses, and speech areas involve expressive and receptive language functions. Electrodes identified in the bipolar stimulation as not carrying motor or language functions were used as a reference for the monopolar stimulation. Language loci were tested using a battery of six tasks (reading, counting, naming everyday objects, execution of body commands, Token Test, and repetition of sentences) described in Wellmer et al. (2009), but we applied a combination of the bipolar and the monopolar ESM, while Wellmer et al. employed only bipolar stimulation, and, more conservatively than Wellmer and colleagues, we classified contacts that could not be stimulated because of after-discharges as "not assessable" and not as "noneloquent," and contacts with both speech impairments and after-discharges in all trials upon stimulation as "not assessable" and not as "eloquent."

Analysis of specificity and sensitivity of HGM

To quantify the specificity and sensitivity of HGM relative to ESM, we used all available information from both bipolar and monopolar stimulation. Thus, ESM-positive electrodes for the upper-extremity movement condition were defined as electrodes with upper-extremity motor responses to the monopolar stimulation. If the bipolar stimulation of two adjacent electrodes and the monopolar stimulation of both electrodes elicited the same type of response, both electrodes were considered ESM-positive for the respective category. Whenever a monopolar-elicited response was different from that provoked by the bipolar stimulation, the electrode was assigned according to its monopolar response. If only bipolar stimulation was performed, the response was assigned to both electrodes of the pair. As in the study by Sinai et al. (2005), electrodes at which ESM was not performed were excluded from the analysis. For our three categories of interest, electrodes with significant HG power changes were compared with the ESM results. To this end, we identified, for each condition, the number of:

i. True positive (t_p) electrodes with a significant HG power increase in the given condition and with a corresponding function revealed by ESM;

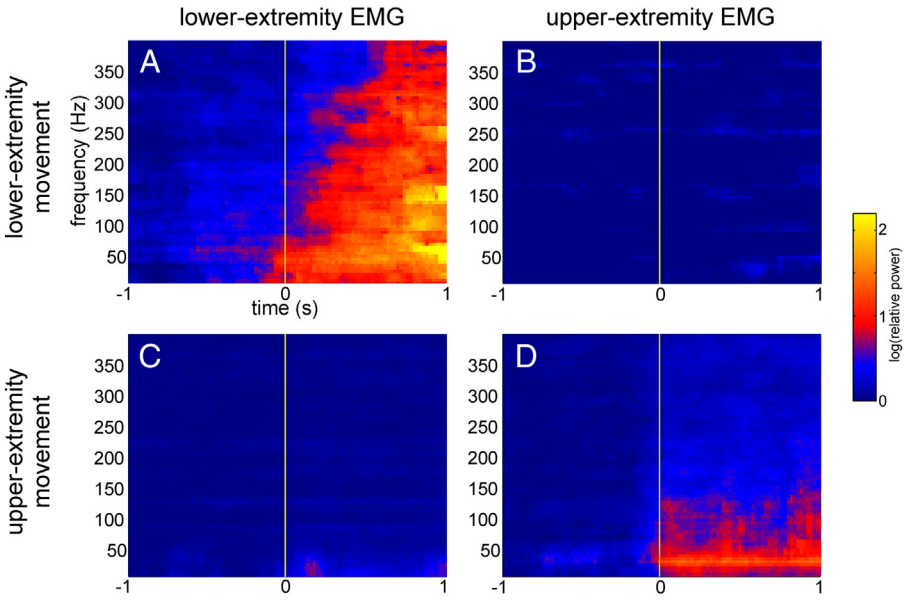

Fig. 2. Validation of video-based identification of natural movements. Trial-averaged relative power spectra of the (A) lower-extremity EMG (quadriceps muscle) but not (B) upper-extremity EMG (deltoid muscle) showed a clear power increase during lower-extremity movements. (C) and (D) same as (A) and (B) but for upper-extremity trials. The vertical line at 0 s corresponds to the movement onset identified in the video data.

ii. True negative (t_n) electrodes with no significant HG power increase in the given condition and with no function revealed by ESM in this condition;
iii. False positive (f_p) electrodes with a significant HG power increase in the given condition but with no corresponding function revealed by ESM;
iv. False negative (f_n) electrodes with no significant HG power increase in the given condition but with a function revealed by ESM in this condition.

Using these electrode classifications, sensitivity and specificity were calculated (Sheskin, 2007):

$$\text{Sensitivity (true positive rate)}: \quad P = t_p/\left(t_p + f_n\right)$$

$$\text{Specificity (true negative rate)}: \quad P = t_n/\left(t_n + f_p\right).$$

Anatomical electrode assignment

We applied a hierarchical method to assign electrode positions to anatomical areas of the cortex (Pistohl et al., 2012). An advantage of this method is that it combines individual topographic information from the patients' MRI with probabilistic anatomical information. The post-operative T1 magnetic resonance images (MRIs) were normalized to a standard brain in Montreal Neurological Institute (MNI) space using SPM5 (Friston et al., 1993). Using in-house-developed Matlab-based software for MRI visualization, electrode void artifacts, as well as the central and lateral sulci were identified and marked manually. In a next step, the individual positions of these sulci were used to assign electrodes to the frontal, parietal, and temporal lobes. A further assignment to anatomical areas within these lobes was performed using a probabilistic atlas system (Toga et al., 2006) based on the MNI coordinates of the individual electrodes. The frontal contacts were assigned to the primary motor cortex (M1; Brodmann area (BA) 4), the premotor cortex (lateral part of BA6), or to Broca's area and its non-dominant homologue (BA44 and BA45). Electrodes were assigned to the supplementary motor area (SMA) when they were either interhemispheric or lay within a 10-mm distance from the midline (Wise et al., 1996) and if they were at the same time probabilistically assigned to BA6. Frontal electrodes on the lateral convexity that remained unassigned in the procedure as described so far were classified as belonging to the prefrontal cortex. Parietal electrodes were probabilistically assigned to the primary sensory cortex (BA1), the superior parietal cortex (BA5 and BA7), and the inferior parietal cortex (BA40 and BA39). For each patient, we projected individual positions of the grids on a standard brain surface from SPM5. To visualize the somatotopy of group-averaged results in each condition, we show all electrodes with significant HG increases assigned to M1, PM, and Broca's area or its contralateral homologue, as well as those located on the CS on the same standard brain. Visualization of the individual and group-averaged electrode locations was performed in MNI space.

Results

ESM results

The topography of movement- and speech-related responses to ESM in all patients concurred well with the basic somatotopy of the human motor cortex (Penfield and Boldrey, 1937), e.g., Figs. 3A, 4A, and 5A. However, there were some additional observations unpredicted by this basic somatotopy, such as prefrontal leg motor responses upon stimulation of an electrode in P3 or focal hand motor responses in the ventral precentral cortex of P1 and P3 (light blue arrows in Figs. 4A and 3A, respectively). We also observed several examples of discrepancy between the mono- and the bipolar stimulation. For instance, while monopolar stimulation of two adjacent perisylvian electrodes in P1 provoked mouth sensory responses, a mouth motor response was observed upon bipolar stimulation (orange arrow in Fig. 4A). Similarly, a hand motor response and a hand sensory response at neighboring dorsal premotor-cortical electrodes of P3 were observed upon monopolar, but a leg motor response upon bipolar stimulation (orange arrow in Fig. 3A; note that both electrodes were adjacent to electrodes with a leg motor function). Such functional discordance may be due to the different effects of mono- and bipolar stimulation on the cortical motor system (Kombos and Süss, 2009). In most cases, however, the mono- and the bipolar stimulations elicited concordant results.

HGM results on the lateral cortical surface

In all patients, there were significant HG effects in all conditions. HGM and ESM of extremity movements were in overall good agreement. Fig. 3B shows a left-hemispheric example of an activation map with significant upper-extremity movement-related HG responses on the lateral cortical surface of P3, which were found in the premotor cortex and on the central sulcus. Activation related to upper-extremity movements in these anatomically-defined locations was reproducible across patients (e.g., compare Figs. 3B and 4B) and hemispheres (e.g., compare Figs. 3B, 4B, and 5B). Upper-extremity movement-related activity in the primary somatosensory cortex (S1) was observed in all patients (see Figs. 4B and 5B for examples from P1 and P5, respectively) except P3, in whom the largest part of the dorsal S1 was not covered by electrodes (Fig. 3B).

An example of lower-extremity motor effects can be seen in Fig. 4C (P1). The HG effects underlying movements of lower extremities in this patient were located in the ESM-positive leg motor cortex, and at one electrode close to the lateral sulcus (Fig. 4C). Reproducible lower-extremity motor responses in HG were observed in the dorsomedial premotor cortex (P5, Fig. 5C; P2, not shown). The analyzed HG responses during natural upper- and lower-extremity movements mostly showed a clear somatotopic arrangement (Fig. 7A and B, respectively): lower-extremity movement-related effects were observed closer to the midline, while activity underlying movements of upper extremities took place more laterally (e.g., Figs. 4B, C and 5B, C).

As overt expressive speech has both motor and cognitive aspects, we expected a correspondence of speech HGM to ESM identifications of both mouth motor and higher-order language functions. The observed HG effects underlying natural speech production, however, mostly showed only moderate spatial correspondence to ESM (Fig. 4D), and were less localized than the HGM of extremity motor functions. Some speech-related HG power increases did not reach significance despite their relatively high amplitudes, as is indicated for one example by a white star in the lower left quadrant of the electrode grid in Fig. 4D. Reproducible speech-related HG effects were observed in Broca's area and on the central sulcus (P1, P2), as well as in the premotor cortex (P1, P4). The cortical sites with underlying speech and mouth motor functions according to ESM were mostly, but not necessarily, located in all of these regions (compare Figs. 3A and 4A).

HGM results for interhemispheric electrodes

Four patients (P1–P4) were implanted with interhemispheric strip electrodes (Table 1), which partially covered the SMA, the M1, the S1, and the cingulate cortex. We found a good correspondence between HGM and ESM in upper- and lower-extremity movement-related maps and for speech production in these interhemispheric areas (see Fig. 6 and Supplementary Fig. 1).

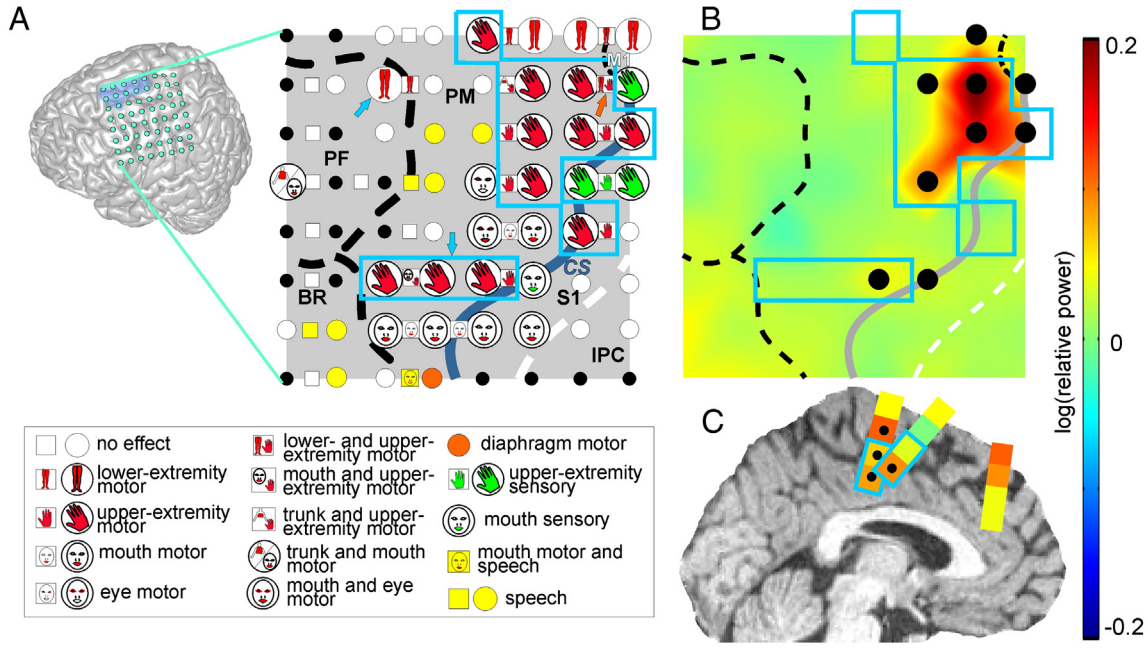

Fig. 3. Results of ESM and upper-extremity movement-related HGM (P3). (A) Position of the 8 × 8 electrode grid visualized on a standard brain (left) and a functional map of the anatomically-assigned electrode locations (right). The planned resection area is indicated in transparent blue in the left panel. Right panel: solid blue line: the central sulcus (CS). Dashed black lines: probabilistically-defined borders within the frontal cortex. M1: primary motor cortex, PM: premotor cortex, PF: prefrontal cortex, BR: Broca's area. Dashed white line: probabilistically-defined border between the primary sensory cortex (S1) and the inferior parietal cortex (IPC). Square symbols between neighboring electrodes indicate results of the bipolar and round symbols of the monopolar ESM, respectively. Black dots mark electrodes that were either not stimulated or not assessable using the monopolar ESM (see Material and methods). Upper-extremity motor areas identified using ESM are outlined in light blue. The light blue arrows in the upper and lower left quadrants indicate ESM results unpredicted from the basic somatotopy (Penfield and Boldrey, 1937). An example of a contradictory mono- and bipolar ESM result is marked with an orange arrow in the upper right quadrant. (B) Interpolated HG activity map of contralateral upper-extremity movements. Significant responses (sign test, $Q < 0.001$, FDR-corrected) are marked with black dots. Solid gray line: the CS, other lines are the same as in (A). (C) HG activity during natural movements of the upper extremity in three interhemispheric electrode strips is shown on an individual parasagittal MRI of the patient. Color scale and other conventions as in (B).

Somatotopy of HGM effects across patients

The topographic distribution of motor-cortical HGM effects across patients is visualized for each of the three conditions on the surface of a standard brain in SPM5 (Fig. 7; see Material and methods). The lower-extremity movement-related responses predominate over the dorsal premotor cortex, responses underlying movements of upper extremities extend more laterally and ventrally along the central sulcus, and responses related to speech production can be observed along the inferior part of the central sulcus and in Broca's area.

Sensitivity and specificity of HGM results relative to ESM

Sensitivity and specificity values of HGM relative to ESM are summarized in Table 2 for both lateral and interhemispheric brain regions. Like in previous HGM studies (e.g., Sinai et al., 2005), we calculated the specificity and sensitivity values for speech production in a group of electrodes with either ESM-localized language or mouth motor functions, as both are likely contributors to overt speech production. Language functions were tested for both receptive and expressive speech (see Material and methods). The number of electrodes with ESM-positive receptive speech functions was smaller than the number of electrodes with expressive speech functions, and all "receptive" electrodes in our sample of patients overlapped with some of the "expressive" electrodes. Thus, these ESM findings were not treated separately. Separate values for the sensitivity and specificity of electrodes with either speech or mouth ESM responses are summarized in Table 3. The sensitivity for the SMA when analyzed separately was: 50.7% for upper extremities, 47.2% for lower extremities, and 25% for speech. The specificity in the SMA was respectively 72.9%, 92.6%, and 100%.

Postoperative motor and language deficits

The consequences of neurosurgical intervention could be, in most cases, equally well predicted from ESM and HGM results. The postoperative outcomes are summarized below for a period of 3–12 months. In P1, a large portion of the left frontal precentral cortex was resected, and multiple subpial transsections (MSTs) were performed on the cortical area which comprised some of the electrodes with upper-extremity functions according to ESM (Fig. 4A). As could be expected, P1 suffered from a transient postoperative SMA syndrome. Uni- and bilateral hand motor coordination was reduced up to 12 months postoperative, but hand/ arm paresis was no longer observed. As the resection area comprised one fronto-medial electrode with an upper-extremity-related response in HG, this motor deficit was predictable from HGM. A further transient postoperative deficit in P1 was mild hemiparesis of the left leg, which could not have been expected based on either ESM or HGM. MSTs on the left superior precentral cortex were performed in P2, causing hemiparesis of the right foot, which was still detectable 12 months postoperative, as was predicable based on both ESM and HGM (Fig. 6B). In P3, postoperative deficits after 3 months were a transient SMA syndrome, right hemiparesis, a disorder of speech initiation as symptom of the predictable SMA syndrome in this case, and an additional spastic component of the right lower extremity. The observed postoperative upper-extremity motor deficits could be predicted using both ESM and HGM. Since lower-extremity and speech functions could not be tested by means of HGM (see Material and methods), it is unclear whether HG in this case would have been an equally good predictor. In P4, a partial resection of the left superior frontal gyrus resulted in a transient SMA syndrome, and bimanual coordination was reduced 12 months postoperative. The observed motor deficit was not predicted by ESM. In HGM, however, one interhemispheric electrode showed

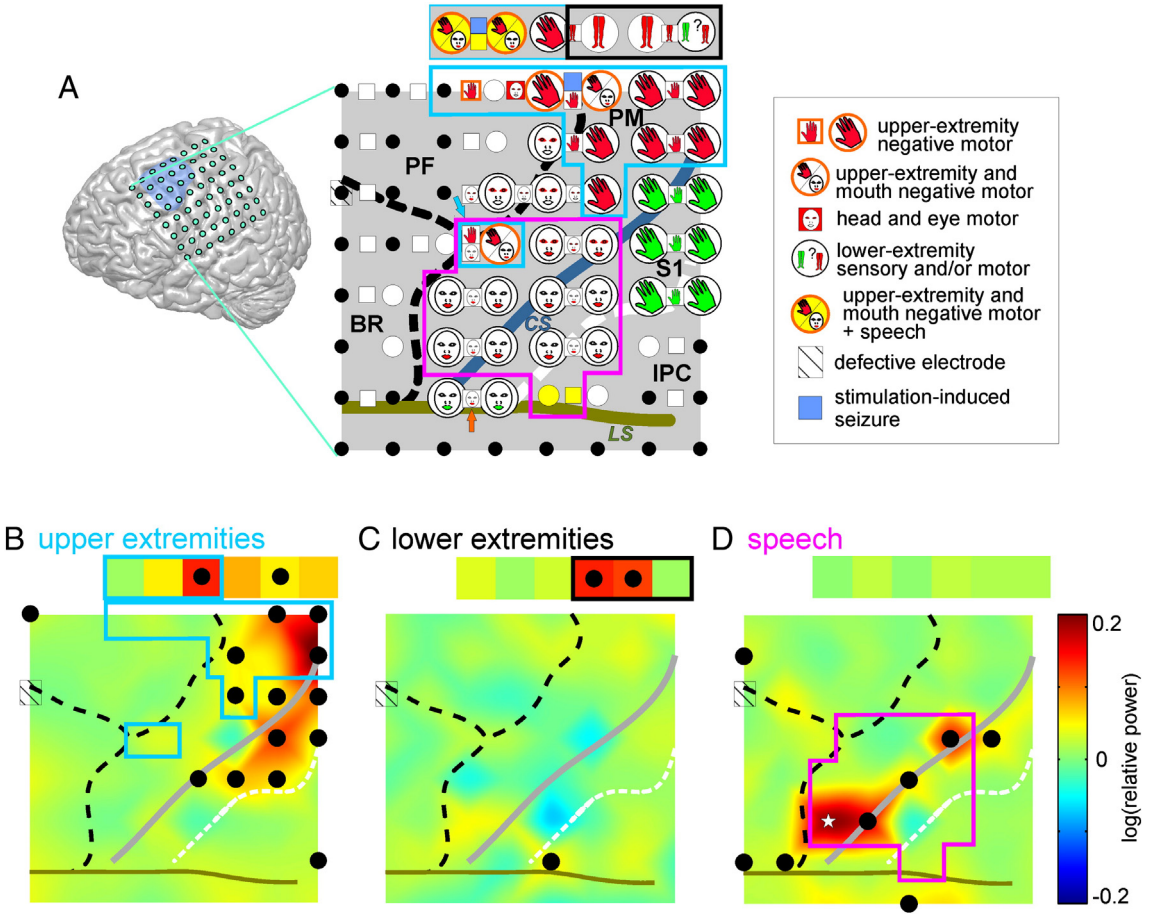

Fig. 4. HGM and ESM on the lateral convexity of the left hemisphere (P1). (A) Solid green line: the lateral sulcus (LS), all other conventions as in Fig. 3. (B) HG activity map of contralateral upper-extremity movements in the 1 × 6 fronto-medial electrode strip (upper panel) and in the 8 × 8 electrode grid (lower panel). (C) Same as (B) but for lower-extremity movements. HG effects were observed in the leg motor area identified using ESM (black box) and at one electrode close to the LS. (D) Same as (C) but for speech production. The white star in the lower left quadrant of the grid indicates an electrode at which a potentially speech-relevant HG power increase did not reach significance, in spite of its high relative amplitude.

upper-extremity movement-related effects. Thus, this postoperative deficit could have been predicted using HGM. P5 suffered from very mild and transient postoperative deficits after partial resection of the right frontal lobe (Fig. 5A), namely, a mild impairment of the fine motor skills of the left hand, and localized numbness of the right part of the head. According to ESM, the former impairment was not

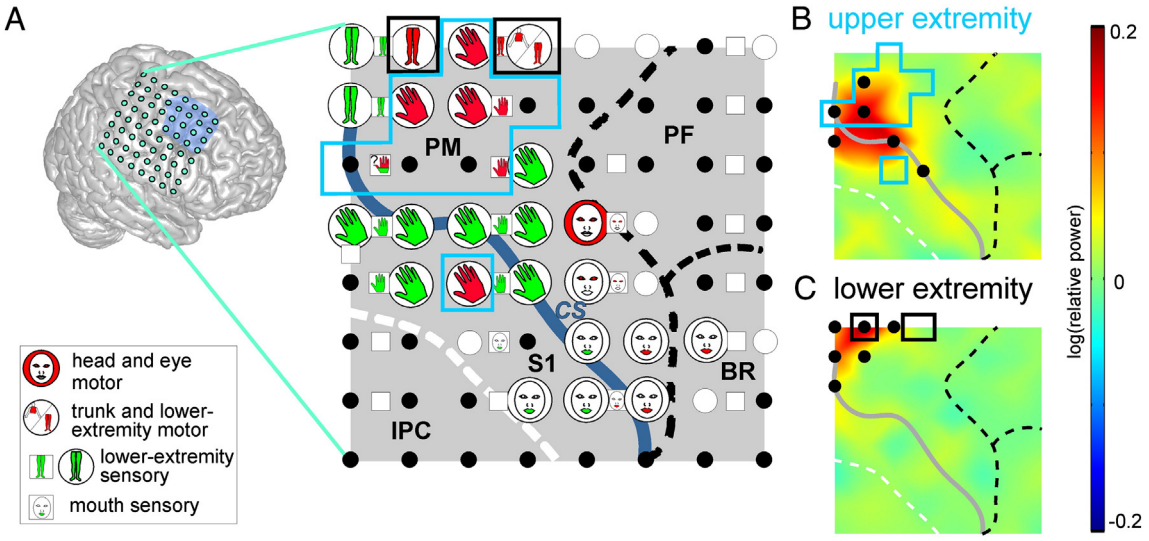

Fig. 5. HGM and ESM on the lateral convexity of the right hemisphere (P5). All conventions as in Figs. 3 and 4.

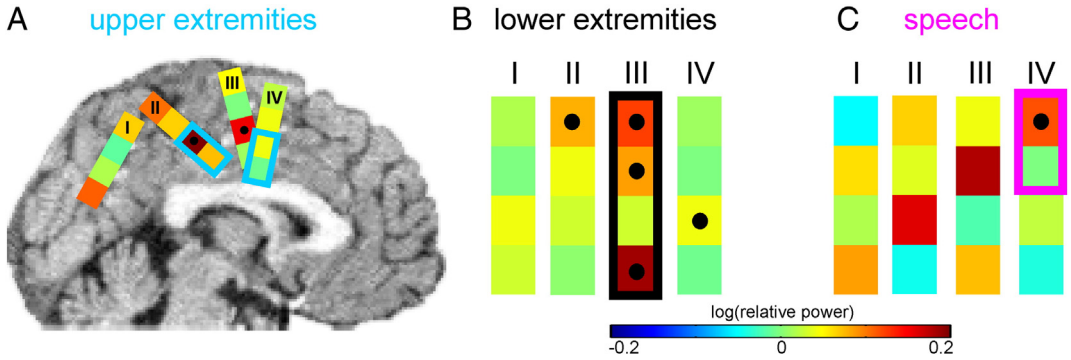

Fig. 6. Correspondence between HGM and ESM for extremity movements and speech production in interhemispheric electrodes (P2). HG activity on an individual parasagittal MRI of the patient is shown in four interhemispheric electrode strips for natural (A) upper-extremity movements; (B) lower-extremity movements; (C) speech production. Electrode strips are labeled with Roman numbers. All other conventions as in Figs. 3–5.

unexpected, since the resection area bordered on some locations with hand sensory and motor functions, and the latter deficit was also predictable. HGM of upper extremities, however, did not predict the observed deficit in this patient. In P6, the resection of a region in the fronto-parietal cortex resulted in right brachiofacial hemiparesis that could have be expected according to ESM and in a bucco-facial apraxia and aphasia without comprehension or reading problems. Speech production was not tested using HGM in this patient (see Material and methods). After surgery, at least partial seizure freedom was achieved in all patients.

As can be seen from this summary, the two methods elicited mostly concordant results. In one case (P5), however, ESM was a better predictor, and in P4 it was the other way round. Thus, a combination of these methods may be beneficial in clinical diagnostics. Still, note that neither ESM and HGM alone nor their combination elicited 100% correct predictions, and additional methods, such as mapping based on functional magnetic resonance imaging (fMRI) or somatosensory-evoked potentials may be useful to increase the sensitivity for postoperative functional deficits (Wray et al., 2012). Note that the resection boundaries in the patients included in the present study were planned taking ESM but not HGM findings into account. Further reports on the functional deficits after neurosurgical intervention based on ESM and both experimental and non-experimental HGM will be necessary to further assess the clinical usefulness of these procedures.

Discussion

Event-related activity in the gamma frequencies of ECoG is an established neural marker for movement (Aoki et al., 2001; Crone et al., 1998; Pfurtscheller et al., 2003) and speech (Crone et al., 2001a,b; Sinai et al., 2005) in humans. Recently, ECoG-based tools have been developed which allow for fast, accurate, and robust HGM of eloquent cortex (Lachaux et al., 2007a; Miller et al., 2007a; Schalk et al., 2004, 2008) and are under evaluation in a growing number of epilepsy centers (Ritaccio et al., 2010, 2011).

HGM has several main advantages over ESM. It allows inferring physiological information which cannot be obtained with ESM (Hamberger, 2007; Ritaccio et al., 2011). HGM is a more patient-friendly procedure and it does not require interference with cortical function. HGM can be used as adjunct to ESM for pre-selection of priority sites, and it may potentially replace ESM in cases where stimulation is not feasible due to after-discharges or other side effects (Brunner et al., 2009; Cervenka et al., 2011, 2013; Leuthardt et al., 2007; Roland et al., 2010; Sinai et al., 2005; Towle et al., 2008; Wray et al., 2012; Wu et al., 2010). In the present study, we aimed to develop and test an HGM procedure which would permit localization of eloquent cortex and its specializations for upper-, lower-extremity motor and language functions in patients who cannot be tested experimentally. To this end, we evaluated HG power increases related to natural movements of upper and lower extremities and natural overt speech, and assessed the sensitivity and specificity of HGM relative to ESM.

HGM of upper-extremity motor functions based on ongoing ECoG recordings has recently been proposed as a valuable addition to experimental testing (Vansteensel et al., in press; Wray et al., 2012), but the potential of non-experimental HGM to localize lower-extremity and speech-related functions was unclear. Here we demonstrate that non-experimental identification of both upper- and lower-extremity motor functions is possible. HGM in these natural movement conditions

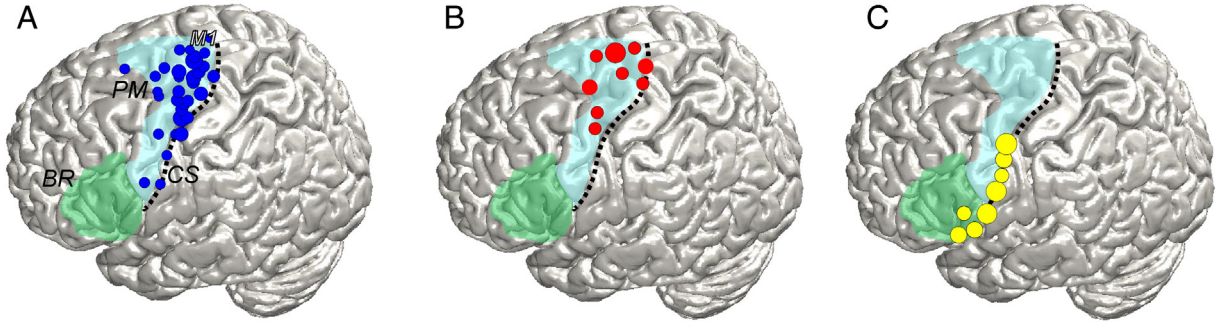

Fig. 7. Somatotopy of HGM effects across patients. Significant results are visualized on a standard brain for all electrodes on the lateral convexity assigned by a hierarchical anatomical assignment procedure to the PM and the M1 (BA 6 and 4, outlined in transparent blue) or to BR (Broca's area and its non-dominant homologue, BA44 and BA45, transparent green), and located directly on the CS (dotted black line). (A) HG effects during upper-extremity movements in all patients (blue dots). Each dot indicates the position of an electrode at which a significant response was detected; dot size indicates relative HG power amplitude in arbitrary units. All electrodes are illustrated on the left hemisphere; electrodes from the right hemisphere (P5) are mirrored. (B) as (A), red dots depict results for lower-extremity movements. (C) as (B), yellow dots depict results for speech production. Note that, as expected, the average position of the CS in the investigated patients is not exactly identical to the course of the CS on the standard brain.

Table 2
Specificity and sensitivity of HGM compared with ESM.

	Condition	Electrodes included in the analysis	Condition-related ESM responses	tp	tn	fp	fn	Specificity (%)	Sensitivity (%)
P1	U.E.	75	17	8	46	12	9	79.3	47.1
	L.E.	75	7	5	66	2	2	97.1	71.4
	Speech	75	15	3	54	6	12	90	20
P2	U.E.	73	23	10	46	4	13	92	43.5
	L.E.	73	11	5	57	5	6	91.9	45.5
	Speech	73	15	4	58	0	11	100	26.7
P3	U.E.	70	15	9	51	4	6	92.7	60
P4	U.E.	58	9	7	37	12	2	75.5	77.8
	L.E.	58	6	0	52	0	6	100	0
	Speech	58	10	1	48	0	9	100	10
P5	U.E.	54	7	3	43	4	4	91.5	42.9
	L.E.	54	2	1	47	5	1	90.4	50
P6	U.E.	62	3	2	50	9	1	84.8	66.7
Mean	**U.E.**	**65.3**	**12.3**	**6.5**	**45.5**	**7.5**	**5.8**	**85.9**	**56.3**
	L.E.	**65**	**6.5**	**2.8**	**55.5**	**3**	**3.8**	**94.9**	**41.7**
	Speech	**68.7**	**13.3**	**2.7**	**53.3**	**2**	**10.7**	**96.7**	**18.9**

"Electrodes included in the analysis" provides the total number of stimulated lateral and interhemispheric electrodes which were used to compare the sensitivity of HGM relative to ESM (see Material ans methods). "Condition-related ESM responses" provides the number of electrodes where a positive ESM response was observed in the respective condition. tp: true positive; tn: true negative; fp: false positive; fn: false negative. Other conventions as in Table 1.

exhibited both sensitivity and specificity values (Table 2) that fit well with previous observations reported for experimental HGM of upper-extremity movements in humans (Leuthardt et al., 2007). The mapping of natural speech production, however, showed only a very low sensitivity (Tables 2, 3) compared to previous experimental HGM (Miller et al., 2011; Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010). Thus, the present method can be of value for pre-operative mapping of upper- as well as lower-extremity movements, but is not suitable in its current form for identification of cortical locations supporting expressive speech.

HGM of natural upper- and lower-extremity movements

In the analysis of HGM during natural contralateral movements of upper extremities, we observed a sensitivity of 56.3% and a specificity of 85.9% relative to ESM (Table 2). A similar single-electrode analysis by Leuthardt et al. (2007) revealed comparable sensitivity (42.9%) and specificity (89.5%) during experimentally-obtained, visually-cued contralateral hand movements. (Note that the present values and the previous results by Leuthardt et al. were obtained for HGM-ESM correspondence at one and the same electrode, and they cannot directly be compared with the respective HGM measures by Brunner et al. (2009), which were obtained in a "next-neighbor" analysis.)

Observations of gamma-range activity underlying movements of lower extremities are quite rare at present (Miller et al., 2007b), and the potential of HGM to map the cortex supporting movements of lower extremities was hence unclear. We investigated HGM during natural movements of lower extremities and found a mean sensitivity of 41.7% and a specificity of 94.9% (Table 2). In general, these results are comparable with those for upper-extremity movements in the present study and in an earlier report by Leuthardt et al. (2007). Non-experimental HGM of lower extremities was successful in all patients who had lateral electrodes with lower-extremity motor functions revealed using ESM (P1, P2, P5; see Figs. 4C and 5C for examples from P1 and P5, respectively), and in two out of three patients with interhemispheric lower-extremity motor contacts (P1 and P2, Figs. 4C and 6B, respectively). In one patient (P4, data not shown) in whom ESM revealed lower-extremity motor functions only at interhemispheric contacts, there was increased HG activity at these contacts, but it did not reach significance (Table 2), possibly due to a large inter-trial variability of responses and a relatively small number of trials that could be obtained in this patient (Table 1).

HGM of natural speech production

HGM of non-experimental speech production revealed a sensitivity of 18.9% and a specificity of 96.7%, compared with the group of electrodes with either mouth motor or language functions detected by ESM (Table 2). In general, these values are respectively lower and higher than those reported in experimental research (cf. in a picture-naming task in Sinai et al. (2005) respectively 43% and 84%; in word-repetition tasks in the studies by Towle et al. (2008) 63% and 57% and by Wu et al. (2010) 71.0% and 59.9%; in noun reading 89% and 66% and in verb generation 74% and 48% in Miller et al. (2011)), and they agree well with the recent non-experimental findings by Bauer et al., in press (respectively 22% and 82% for speech production). Separation of the ESM speech-relevant electrodes (see

Table 3
Specificity and sensitivity of speech HGM compared with mouth motor and speech ESM.

	Mouth ESM	tp	tn	fp	fn	Spec. (%)	Sens. (%)	Speech ESM	tp	tn	fp	fn	Spec. (%)	Sens. (%)
P1	15	3	54	6	12	90.0%	20.0%	1	0	65	9	1	87.8%	0%
P2	13	4	60	0	9	100%	30.8%	1	0	69	3	1	95.8%	0%
P4	8	1	50	0	7	100%	12.5%	2	0	55	1	2	98.2%	0%
Mean	**12**	**2.7**	**54.7**	**2**	**9.3**	**96.7%**	**21.1%**	**1.3**	**0**	**63**	**4.3**	**1.3**	**94.0%**	**0%**

"Mouth ESM" refers to the number of lateral and interhemispheric electrodes where mouth motor responses were observed during ESM. "Speech ESM" provides the number of electrodes with the speech-essential locations identified using ESM. Spec.: specificity; Sens.: sensitivity. Other conventions as in Table 2. Note that the high specificity close to a 100% combined with a very low or 0% sensitivity indicates that the procedure is not usable for clinical language mapping.

Material and methods) into two groups with only mouth-motor or only speech functions resulted in higher ESM-HGM correspondence in the former (21.1% sensitivity) and in 0% sensitivity in the latter group (Table 3). Thus, only a small portion of the electrodes with mouth-motor ESM exhibited speech-related changes in HG, and no ESM-positive contacts with cognitive language functions could be revealed using HGM.

As HG constitutes a robust marker of cortical activity and it was observed using ECoG in relation to such higher-order language functions as covert speech repetition (Pei et al., 2011b) and semantic processing (Wang et al., 2011), it is unlikely that cognitive language functions in our study were "HG-silent". Human speech, however, is a complex phenomenon that involves multiple levels of abstraction (Hickok, 2012; Price, 2012), and a linguistically fine-grained approach is most likely required to achieve a better sensitivity of HGM for natural expressive language functions. For instance, since the processing of lexis, grammar, and phonology is manifested in intracranial signals from Broca's area at different timing (Sahin et al., 2009), a time-resolved analysis may be needed to capture these distinctive phenomena. Furthermore, as robust articulation-related HG ECoG responses can be observed in the ventral sensorimotor cortex prior to the onset of speech production (Bouchard et al., 2013), exploration of the early preparatory activity in addition to post-onset signals may be useful to increase the sensitivity of HGM.

There may be several explanations as to why the present non-experimental HGM approach revealed a considerably lower sensitivity compared to experimental studies. Previously, Miller et al. (2011) compared HGM of noun reading and verb generation to ESM during object naming, and found that both sensitivity and specificity in noun reading were higher than in verb generation. They proposed that this difference may be due to the greater semblance of noun reading to picture naming than to verb generation. Similarly, a better agreement of previous experimental HGM with ESM may be at least to some extent attributable to the difference between experimental tasks and natural speech production. Previous studies reporting on sensitivity and specificity of experimental speech HGM relative to ESM employed tasks that are more similar to stereotyped electrocortical stimulation protocols for language mapping than in natural, experimentally-unrestrained speech production. Thus, a greater difference between tasks in ESM vs. non-experimental HGM may be reflected in the low sensitivity of the latter method. Variability of HGM-ESM correspondence between this and earlier studies may also result from differences in electrode coverage. Notably, Wu et al. (2010) showed that HGM sensitivity for language is higher in Wernicke's than in Broca's area. Unlike in the patients evaluated in prior research (Miller et al., 2011; Sinai et al., 2005; Towle et al., 2008; Wu et al., 2010), however, no electrodes with speech ESM responses lay over the temporal cortex in the sample of patients in the present study.

Somatotopy of HGM responses

The primary motor cortex in humans extends along the central sulcus with a somatotopic arrangement of motor functions along its course. The lower extremities are represented medial-dorsally, mostly on the mesial surface. They are laterally followed by the upper extremities on the lateral convexities, and the oro-facial representation area is situated ventro-laterally. The human SMA also exhibits somatotopy, as the lower extremities are represented caudally, the head and the face rostrally, and the upper-extremity representation is between these two areas. This basic functional organization of the human motor cortex has been shown experimentally with a wide range of neurophysiology and neuroimaging techniques, including electrocortical stimulation (Fried et al., 1991; Lim et al., 1994; Penfield and Boldrey, 1937; Uematsu et al., 1992), fMRI (Alkadhi et al., 2002; Cauda et al., 2011; Mayer et al., 2001), positron emission tomography (PET) (Grafton et al., 1993; Matelli et al., 1993), magnetoencephalography (MEG) (Cheyne et al., 2008), and electroencephalography (EEG) (Pfurtscheller et al., 1994). While the somatotopic organization of upper-extremity and speech motor functions in HG ECoG is well established (Aoki et al., 2001; Crone et al., 1998, 2001b; Miller et al., 2007b; Pfurtscheller et al., 2003; Vansteensel et al., in press), the spatiotemporal characteristics of HG activity representing movements of lower extremities are far from being clear. To our knowledge, only one ECoG study in humans to date reports positive HGM of lower-extremity movements (Miller et al., 2007b). These authors, however, observed HG responses outside the anatomically-defined leg and foot motor cortex.

Previous experimental HG ECoG findings for upper extremities and speech production could be confirmed in the present study based on natural, non-experimental behavior (Figs. 7A and C, respectively), and HG responses underlying natural lower-extremity movements could be observed that were mostly in agreement with the somatotopy of the motor cortex (Fig. 7B), both on the lateral convexity (e.g., P1 in Fig. 4C, P5 in Fig. 5C) and in the interhemispheric areas (e.g., Fig. 6B for P2). Note, however, that two of the three frontal lower-extremity movement-related effects in one patient (P2) were more ventral than expected (the lowest two red dots in Fig. 7B) and, unlike the majority of lower-extremity-related responses, they lay outside the corresponding leg and foot motor area revealed using ESM. Importantly, the validity of trial selection in P2 was confirmed using both EMG of upper and lower extremities. It is thus possible that these atypical lower-extremity responses on the lateral convexity of P2, as well as the previous topographically atypical findings by Miller et al., 2007b, may reflect a larger degree of epilepsy-related motor-cortical re-organization than in the other patients in our sample. Nevertheless, since most of the present lower-extremity-related effects are consistent with the homuncular distribution of the motor cortex, some of the observed differences between this and the earlier study by Miller et al., 2007b may also be attributable to a lower degree of ecological validity of experimental tasks, as opposed to natural behavior (Jackson et al., 2007). It would be particularly interesting for future studies to compare within-subject results of lower-extremity HGM in experimental vs. non-experimental conditions.

The SMA

While it is unequivocally accepted that pre-neurosurgical diagnostics requires localization of "eloquent cortex," the literature offers different definitions of this term. According to Richardson (2003), it is "any cortical area in which injury produces symptomatic cognitive or motor deficit." Functional deficits after unilateral resections in the SMA are mostly transient in nature (Matz et al., 1999), partly due to the recruitment of the contralateral homologue (Krainik et al., 2004; Mandonnet et al., 2010). Nevertheless, some authors include the SMA in their definition of the eloquent cortex (González-Darder et al., 2010). To account for this discrepancy, we provide information on the SMA separately, albeit both sensitivity and specificity in this anatomically-defined area (see Material and methods) were in a range similar to that in the other motor and speech areas. Functional mapping of the SMA is clinically less relevant than that of the precentral motor cortex. Nevertheless, an important finding of the present study is that functional properties of this cortical region can be well captured non-experimentally. This opens up a new possibility of studying the functions of the SMA under natural, ecologically more valid conditions.

Explanations for ESM-positive–HGM-negative cortical sites

In all patients, we found examples of ECoG channels that showed a specific function in ESM, but no corresponding significant HGM effects (Figs. 3–6). The sensitivity of HGM with respect to ESM was thus below 100% in all cases (Tables 2, 3). Some of the observed ESM-positive–HGM-negative cortical sites may be due to false-positive ESM, presumably caused by propagation of the

stimulation along axonal connections or through unwanted stimulation of adjacent cortical and even subcortical areas (Borchers et al., 2012; Mandonnet et al., 2010; Pouratian et al., 2004). Another likely explanation for ESM-positive–HGM-negative sites with respect to language function is that not all ESM-positive mouth motor locations in the present study are involved in speech production, and that some of them may be responsible for execution of non-speech mouth movements, e.g., during eating, mimicking, or smiling. Further research will be needed to explore these various possibilities.

Methodological aspects of data analysis, including definitions of tasks and frequency bands, may also have contributed to the present ESM-positive–HGM-negative observations. For instance, contralateral upper-extremity movements, as analyzed in the present study, may be insufficient to reveal cortical locations specialized for bimanual movements (Cramer et al., 1999; Hanakawa et al., 2005). Furthermore, previous reports on ECoG-based mapping of experimental movements (Leuthardt et al., 2007) and speech production (Wu et al., 2010) observed different sensitivity and specificity values for the low-frequency component (8–32 Hz) compared to gamma frequencies (75–100 Hz). Although the overall agreement of HGM with ESM in these previous studies was better than that of the low-frequency component, lower frequencies in the study by Wu et al. (2010) showed an increased sensitivity in localizing expressive speech than did gamma-band frequencies. A priori selection of the range of HG frequencies may hence account for some of our false-negative HGM effects. Furthermore, it has recently been suggested that a single broad range of gamma frequencies may not reflect the full extent of cortical activity and that exploration of more narrow sub-bands within this frequency range may be useful (Gaona et al., 2011; Leuthardt et al., 2012).

Explanations for ESM-negative–HGM-positive cortical sites

Alongside ESM-positive–HGM-negative, ESM-negative–HGM-positive electrodes were also found in all patients. This may be explained in part by false-negative ESM (Borchers et al., 2012; Cervenka et al., 2011, 2013; Mandonnet et al., 2010; Pouratian et al., 2004), due to the restricted range of functions that can be explored in a limited amount of time using experimental approaches (Lachaux et al., 2007b). In addition, HGM-positive contacts that revealed no function in ESM may reflect task-related involvement of cortical areas that are contributing but not crucial to a particular function (Leuthardt et al., 2007). Another explanation might be that subtle movements of task-irrelevant body parts were associated with our movements of interest. Such correlations, however, can be excluded for upper- vs. lower-extremity movements involving the deltoid and quadriceps muscles based on our analysis of EMG recordings from the respective muscles (Fig. 2).

Notably, several HGM-positive cortical sites in the present study were spatially remote from the locations with respective ESM effects. Thus, one electrode close to the lateral sulcus showed significant increase in HG activity during movements of lower extremities (Fig. 4C). This may reflect signals originating in the insular cortex, where an area with reproducible activation related to leg movements has recently been demonstrated in both humans (Mutschler et al., 2009) and monkeys (Jezzini et al., 2012). Other HG responses in ESM-negative areas, such as the prefrontal cortex, may reflect activity of extended cortical networks for speech and motor control which likely involve ESM-silent areas (Fogassi and Luppino, 2005; Rizzolatti et al., 1998).

The majority of false positives in HGM, however, were observed at electrodes immediately adjacent to the functional areas localized using ESM (Figs. 3B, 4B-D, 5B-C, 6). This is consistent with previous observations by Brunner et al. (2009) from a "next-neighbor" analysis. Such HGM-positive effects may be at least partly due to volume conduction of electrical fields beyond the cortical sites where gamma activity originates. Further investigation, such as using source analysis of ECoG signals (Dümpelmann et al., 2012), will be needed to address this issue.

Feasibility of using ECoG during natural behavior to study the motor and language systems

Converging evidence from human psychology and single-neuron research in animals suggests that experimental paradigms may elicit observations that are different from free, experimentally-unrestricted behavior. One reason is that experimental findings may be affected by unnaturally increased levels of attention even in simple tasks or by investigator bias (Gibson, 1950; Ray, 2000). Furthermore, stereotyped experimental procedures may not reflect the full extent of brain activity as it occurs during natural behavior (Evarts, 1965; Jackson et al., 2006, 2007; Mavoori et al., 2005; Vanin et al., 2012). For instance, a study in macaque monkeys (Jackson et al., 2007) found significant differences in activation of motor-cortical cells in an experimental vs. free movement paradigm. Neuron-muscle correlations for preferred directions in this earlier study exhibited substantial differences between the two conditions, and both maximum EMG levels and maximum firing rates of motor-cortical neurons were higher during natural motor behavior than in an experimental movement task. In humans, Bock and Hagemann (2010) analyzed force and kinematic aspects of prehension movements under laboratory compared to "everyday-like" conditions, and found that experimental motor tasks may not entirely reflect the properties of real-life movements. The present study provides a proof of principle that it is feasible to use ECoG recordings during natural behavior to study the motor and language systems. This opens new possibilities of exploring a wider range of scenarios than those that can be captured experimentally (Derix et al., 2012).

In spite of the several differences to previous experimental HGM findings that have been addressed above, the present data support the ecological validity of HG as an index of cortical motor function, and confirm that activation in this frequency range is a robust feature of everyday motor behavior (Fig. 7). Finally, our observation of somatotopically differential activation patterns in non-experimental motor and speech tasks advocates the feasibility of brain-machine interfaces (BMI) that exploit event-related HG alterations for movement (Ball et al., 2009; Leuthardt et al., 2006; Pistohl et al., 2012), as well as speech restoration (Blakely et al., 2008; Pei et al., 2011a) and which are currently being developed to make movements and expressive speech possible in the everyday life of paralyzed patients.

Conclusions and outlook

To our knowledge, this is the first study to investigate both natural motor and natural expressive speech behavior in humans, revealing robust, highly significant, and functionally and spatially specific HG ECoG responses. The present HGM approach may provide useful information about cortical representation of extremity movements, especially when the use of ESM or experimental HGM is not conceivable. Like experimental HGM, however, HGM during natural behavior cannot entirely replace ESM because of moderate sensitivity. Nevertheless, a non-experimental HGM approach may be applied as a complement to gain physiological information in addition to the perturbation-based localization of eloquent cortex via ESM. Non-experimental HGM may be particularly useful in infants or small children who lack cooperative or cognitive abilities required for experimental procedures (Brown et al., 2008; Cho-Hisamoto et al., 2012; Wray et al., 2012) and in patients for whom ESM is not feasible due to pain or seizures caused by electrical stimulation.

Analysis of non-experimental neural recordings for scientific purposes has several other advantages, compared to experimental research. First, it permits exploration of a wide range of behaviors and the associated neural processes that may not be captured in experimental tasks, e.g., processes supporting natural, synergistic motor control (Jackson et al., 2007). Second, such recordings are not unduly affected by unnatural experimental procedures and environments.

Third, while experimental time with ECoG-implanted patients is limited, investigation of non-experimental behavior can strongly benefit from the larger data sets of neural recordings that are obtained around the clock over the entire period of pre-neurosurgical diagnostics.

Over-optimization of analysis parameters may lead to the problem of "overfitting" and thus compromise the generalization of results to a larger population. For this reason, we set a priori fixed parameters for the variables of spectral and statistical analyses in the present study. However, several aspects of our HGM approach, including the selection criteria for events to be analyzed, neural signal components, frequency bands, time windows for analysis, and statistical thresholds, may be optimized in follow-up studies based on larger samples of patients to achieve maximal sensitivity and specificity in detection of the motor cortex. Like some previous experimental HGM approaches (e.g., Crone et al., 1998, 2001a,b; Pfurtscheller et al., 2003; Sinai et al., 2005), the present method relies on retrospective examination of neural recordings underlying movements of upper and lower extremities and speech production, and requires expert time for data acquisition and analysis (Roland et al., 2010; Schalk et al., 2008). Alternative analyses such as using regression methods instead of trial averaging may be useful to increase the sensitivity/ specificity of non-experimental mapping. One benefit of regression analysis, e.g., would be that partially confounded but orthogonal events/ regressors (such as due to overlapping upper-and lower-extremity movements) could be included in the analysis. Manual coding of multiple continuous, graded regressors, however, would be extremely time-consuming, and automated procedures are hence required (e.g., departing form approaches by Lachaux et al., 2007b; Miller et al., 2007a; Schalk et al., 2004; Wray et al., 2012). Automate procedures for mapping the eloquent cortex based on natural behavior may not only use video and EMG signals, but can benefit from additional motion capture data (Ziegler et al., 2011). This may substantially increase the number of trials for analysis, reduce the required time and effort, and open up new possibilities for data analysis such as using continuous regression instead of trial-based averaging. Thereby, a wider range of patients may benefit from the advantages of HGM methods, which are currently being evaluated in epilepsy centers worldwide.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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