Contents lists available at SciVerse ScienceDirect

NeuroImage

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

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ARTICLE INFO

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 pharmaco-resistant 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.,

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,