Mapping the fine structure of cortical activity with different micro-ECoG electrode array geometries

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Abstract

\textbf{Objective.} Innovations in micro-electrocorticography (μECoG) electrode array manufacturing now allow for intricate designs with smaller contact diameters and/or pitch (i.e. inter-contact distance) down to the sub-mm range. The aims of the present study were: (i) to investigate whether frequency ranges up to 400 Hz can be reproducibly observed in μECoG recordings and (ii) to examine how differences in topographical substructure between these frequency bands and electrode array geometries can be quantified. We also investigated, for the first time, the influence of blood vessels on signal properties and assessed the influence of cortical vasculature on topographic mapping. \textbf{Approach.} The present study employed two μECoG electrode arrays with different contact diameters and inter-contact distances, which were used to characterize neural activity from the somatosensory cortex of minipigs in a broad frequency range up to 400 Hz. The analysed neural data were recorded in acute experiments under anaesthesia during peripheral electrical stimulation. \textbf{Main results.} We observed that μECoG recordings reliably revealed multi-focal cortical somatosensory response patterns, in
which response peaks were often less than 1 cm apart and would thus not have been resolvable with conventional ECoG. The response patterns differed by stimulation site and intensity, they were distinct for different frequency bands, and the results of functional mapping proved independent of cortical vascular. Our analysis of different frequency bands exhibited differences in the number of activation peaks in topographical substructures. Notably, signal strength and signal-to-noise ratios differed between the two electrode arrays, possibly due to their different sensitivity for variations in spatial patterns and signal strengths. Significance. Our findings that the geometry of \( \mu \text{ECoG} \) electrode arrays can strongly influence their recording performance can help to make informed decisions that maybe important in number of clinical contexts, including high-resolution brain mapping, advanced epilepsy diagnostics or brain–machine interfacing.

Keywords: \( \mu \text{ECoG} \) array size, topographic mapping, somatosensory cortex, cortical vascular, minipig

(Some figures may appear in colour only in the online journal)

List of abbreviations

| Abbreviation | Complete term |
|--------------|---------------|
| AEP          | auditory-evoked potential |
| BBB          | blood–brain barrier |
| BMI          | brain–machine interfacing |
| BW           | body weight |
| CAD          | computer-aided design |
| ECG          | electrocorticogram |
| FDR          | false discovery rate |
| FR           | fast ripple |
| HFO          | high frequency oscillation |
| IMTEK        | Institute of Microsystems Engineering, University of Freiburg, Freiburg, Germany |
| iqr          | interquartile range |
| LFP          | local field potential |
| MEMS         | micro-electromechanical systems |
| MRI          | magnetic resonance imaging |
| MUA          | multi-unit activity |
| PSP          | post-synaptic potential |
| relSP        | relative spectral power |
| relSPSnr     | signal-to-noise ratio of the relative spectral power |
| SEP          | somatosensory evoked potential |
| SNR          | signal-to-noise ratio |
| SSLM         | significant spatial local maxima |
| SUA          | single-unit activity |
| TE           | time of echo |
| TR           | time of repetition |
| TTL          | transistor-transistor logic |
| VEP          | visual-evoked potential |
| 3D           | three-dimensional |
| (\( \mu \))ECoG | (micro-)electrocorticography |

1. Introduction

Electrocorticographic (ECoG) recordings can provide detailed spatio-temporal information on cortical population activity (Di and Barth 1993, Crone 2000, Ojemann et al. 2013), and they play an important role in pre-neurosurgical evaluation of pharmaco-resistant epilepsy (Ojemann et al. 1989, Engel 1996) and in general neuroscience research. ECoG has proven useful to study such dynamic neuronal processes as movement execution (Toro et al. 1994, Crone et al. 1998, Ball et al. 2009), speech perception and production (Ojemann et al. 1989, Crone et al. 2001a, 2001b, Derix et al. 2014) or naturalistic social interaction (Derix et al. 2012). The conventional ‘macro’-ECoG electrode arrays used in previous studies and in current epilepsy diagnostics (Engel et al. 1996, 2007) have contacts with a diameter of several mm and an inter-contact distance on the order of 1 cm. In recent decades, however, there has been growing interest in increasing the spatial resolution. To this aim, novel electrode arrays with smaller contacts and higher electrode densities have been developed and tested with different experimental paradigms and animal species (Hollenberg et al. 2006, Kim et al. 2007, Kitzmiller et al. 2007, Blakely et al. 2008, Hosp et al. 2008, Slutzky et al. 2008, 2010, 2011, Kellis et al. 2009, 2016, Leuthardt et al. 2009, Wang et al. 2009, Khodagholy et al. 2011, 2015, Viventi et al. 2011, Fukushima et al. 2012, Wang et al. 2016, Flint et al. 2017, Trumpis et al. 2017). These electrode arrays span a range of spatial scales of approximately two orders of magnitude, both with respect to electrode contact size and spacing. Electrode sizes range from 1 to 2 mm (Ruehn et al. 2009, Vinjamuri et al. 2009, Wang et al. 2009, 2016, Wilks et al. 2009) down to a few \( \mu \)m, e.g. 4 \( \mu \)m in Kellis et al. (2016), 10 and 20 \( \mu \)m in Khodagholy et al. (2011, 2015), 40 \( \mu \)m in Blanco et al. (2010), or 75 \( \mu \)m in Leuthardt et al. (2009). Electrode spacing ranges from 3 to 4 mm (Blakely et al. 2008, Vinjamuri et al. 2009, Wang et al. 2009, 2016) down to 30–150 \( \mu \)m (Kitzmiller et al. 2007, Khodagholy et al. 2011, 2015; see table A1 for details). While the terms used in the literature differ, all recording techniques with geometries smaller than conventional clinical electrode arrays may collectively be defined as ‘micro’-ECoG (\( \mu \text{ECoG} \)). In the present study we follow this definition (alternatively, the term \( \mu \text{ECoG} \) could be reserved from electrodes that are substantially smaller geometries, down to the \( \mu \)m scale, and the intermediate range could be distinguished as, e.g., meso-ECoG).
There are several potential advantages of μECoG. As the overall size of electrode arrays is a main risk factor for implantation-related complications (Hamer et al. 2002, Wong et al. 2009), complications can be expected to occur less frequently during μECoG than macro-ECoG implantations (Morrell and Epilepsy Study Group 2011). μECoG electrode arrays have also been used for spatially detailed functional mapping in animal models and in human subjects. For instance, the cortical underpinnings of auditory-evoked potentials (AEPs) and somatosensory-evoked potentials (SEPs) have been elucidated in rats (Barth and Di 1991), sheep (Giertmuhlen et al. 2014) and in human patients (Rembado et al. 2017). Event-related potentials in μECoG have been employed to study sleep spindles, visual processing, and electrographic seizures in cats (Viventi et al. 2011). Event-related potential studies employing μECoG have also been conducted in humans to detect cortical sites for phoneme- (Blakely et al. 2008) and word-specific (Kellis et al. 2010) processing, as well as to localize cortical motor functions via movement-related potentials or changes in the spectral magnitude (Kellis et al. 2009, Leuthardt et al. 2009, Vinjamuri et al. 2009, Wang et al. 2009, Rouse et al. 2013, 2016, Hotson et al. 2015, Wang et al. 2016, Flint et al. 2017). The spatially and temporally localized neuronal effects observed in these studies suggest that μECoG electrode arrays have a high capability to differentiate signals within small cortical regions. In addition to basic neuroscience research, such characteristics can be useful for a number of clinical applications, such as high-detail functional mapping, presurgical epilepsy diagnostics and brain–machine interfacing (BMI), which all require source/control signals from small cortical regions.

Compared to other modalities used for functional mapping, such as those based on hemodynamic methods or conventional ECoG, μECoG research is not yet as widely used. Only several dozens of μECoG studies have been conducted, (see Appendix) and many open questions exist regarding the properties of this technique and its capacity to resolve topographic details. For example, invasive diagnostics of epilepsy requires high spatial precision to achieve seizure alleviation without compromising functional areas. Pre-neurosurgical monitoring with ECoG aims to delineate eloquent brain areas by neurostimulation on the one hand and to determine the seizure onset zone based on recordings of brain activity on the other hand. These data are used to decide (i) whether surgery is possible given the estimated risks of functional impairment, and (ii) whether surgery in the area identified based on (i) will suffice to achieve seizure freedom. The amount of spatial detail is important for these decisions, and increasing the spatial resolution of clinical procedures by using μECoG is expected to enhance the precision of pre-neurosurgical diagnostics (Kim et al. 2007, Stead et al. 2010, Kellis et al. 2016), but open questions remain on the impact of different μECoG geometries on the recorded data.

One open question concerns the role of μECoG electrode array geometry (i.e. contact diameter and inter-contact distance) in detection of high-frequency signal components. Most μECoG studies have investigated frequency bands up to ca. 250 Hz (Blakely et al. 2008, Wang et al. 2009, Khodagholy et al. 2011, Fukushima et al. 2012). Cortical activity in much higher frequencies (>250 Hz) has only rarely been reported (Jones and Barth 1999, Barth 2003, Leuthardt et al. 2009), and little is known about its spatio-temporal properties. Neuronal population activity in high-frequency frequencies (250 and 500 Hz, also termed ‘fast ripples’ (FRs; Bragin et al. 1999a, 1999b, Curio 2000, Staba et al. 2002, Cron et al. 2006), have been observed very locally. The spatial extent of brain areas generating FRs did not exceed 1 mm² in the rat hippocampus (Bragin et al. 2002), and μECoG arrays may be particularly useful to detect them. The capacity of μECoG to capture such high-frequency components of the neuronal signal, however, is currently controversial: While Worrell et al. (2008) showed that smaller electrode contacts matching the size of neuronal activity generators can detect FRs in the human amygdalo-hippocampal region, Chatillon et al. (2011) observed no influence of electrode size on FR detection in the rat hippocampus. Furthermore, Rouse et al. (2016) examined closed-loop BMI control with different inter-contact distances. Using signals in high frequencies (75–105 Hz), and they found that the performance was improved with smaller electrode arrays that obtained. Depending on the decoding strategy, however, the benefit of spatial resolution (inter-contact distance in the aforementioned study) may differ between the signal properties of neuronal recording and the implemented strategy of BMI control (Rouse et al. 2016). Thus, whether smaller electrode contacts and/ or smaller inter-contact distances are more efficient in detecting high-frequency cortical activity is yet not entirely clear, and one aim of the present study was to address this question.

A second and related question we address in this study is whether increasing the spatial detail of recordings will lead to a better spatial resolution of the functional organization of the cerebral cortex. This question is relevant with respect to the main motivations for using μECoG electrode arrays, namely, (i) to elucidate the characteristics of neuronal population activity and the functional organization of the cerebral cortex with high spatial detail and (ii) to increase the amount of meaningful information available for clinical neurotechnologies. For example, using a high-resolution 360-channel electrode array with a 500 μm electrode size, Viventi et al. (2011) were able to visualize previously unknown recurrent spiral waves during seizure propagation in the feline neocortex. Most previous μECoG studies, however, have focused on cortical response features at individual electrode contacts. Detailed topographical maps of very high-frequency neuronal effects have rarely been reported (Blakely et al. 2008, Hosp et al. 2008, Wang et al. 2009, Wang et al. 2016) and require further investigation.

The third open question addressed in this study concerns the influence of cortical blood vessels on μECoG recordings. Intracranial recordings are obtained from cortical tissue, which is perfused by vasculature. Blood vessels are separated from the brain by the blood–brain barrier (BBB), which is, among other functions, important for the precise control of the ionic environment of neural tissue (Daneman 2012). Endothelial cells, which are the main structure component in the BBB, enable a particularly high electrical resistance of the vessel walls in the brain (Crone and Olesen 1982, Fiederer et al. 2016). Since electrode contacts in subdural recordings often lie on blood vessels, i.e. between the source of neural activity and the recording site, they may impede or otherwise influence electrophysiological measurements. Only a couple
of studies so far have addressed the impact of blood vessels on neuronal recordings on macro-ECoG contacts located above cortical vasculature and excluded such contacts from further analyses. Bleichner et al. (2011) compared macro-ECoG recordings directly from the cortical surface with recordings obtained on blood vessels, observing an attenuation of the absolute spectral power at electrode contacts located above the vessels. This effect was most pronounced in the 30–70 Hz frequency range. These studies have been conducted with ‘macro’-ECoG, and, to our knowledge, no previous study has described the impact of blood vessels on micro-ECoG recordings. Since the aforementioned study by Bleichner et al. (2011) investigated the influence on absolute power values only up to the 70–115 Hz frequency range, it is also unclear whether and to what extent activity in higher frequency bands is affected.

The present study addressed these questions by employing two custom 4 × 12-contact micro-ECoG electrode arrays with different electrode contact sizes and contact-to-contact distances. We recorded neural responses elicited by peripheral electrical stimulation in the somatosensory cortex in a minipig animal model. The resulting SEP data obtained from the same cortical patch at a lower and higher spatial resolutions were transformed into spatial maps of frequency bands up to 400 Hz. This mapping procedure show, among other findings, that the geometry of the micro-ECoG electrode array can have a considerable influence on different signal features, and that it therefore needs to be taken into consideration for clinical and research applications.

2. Methods

2.1. Animals and implantation procedure

Four Goettingen minipigs of 20–26 kg body weight (BW) were intramuscularly premedicated with midazolam (0.5 mg/kg BW) and ketamine (20 mg/kg BW) and intravenously anesthetized with propofol (2–4 mg/kg BW). Following endotracheal intubation, 12–15 breaths min⁻¹ were provided by a volume-controlled ventilator (Servo 900C, Siemens Elema, Solna/Sweden) at a 10–15 ml/kg BW tidal volume, 5 mbar positive end-expiratory pressures, and normalized oxygen and carbon dioxide tension and pH values. Anaesthesia was maintained through an ear-vein with propofol (15–18 mg/kg BW/h), fentanyl (2–3 μg/kg BW/h) and pancuronium (0.2–0.4 mg/kg BW/h). Fluid requirements were substituted with ringer solution (10 mg/kg BW/h). The electrocardiogram (ECG), body-temperature and oxygen saturation were monitored continuously. It was possible to maintain this anaesthesia for up to 12 h. The study was approved by the Regierungspräsidium Baden–Württemberg and the Animal Committee of the University of Freiburg. The ‘Principles of laboratory animal care’ (NIH publication no. 86–53 23, revised 1996) were followed for all experiments.

The left somatosensory cortex was approached as previously described (Gierthmuehlen et al. 2011), and the electrode arrays were placed on the exposed surface of the somatosensory cortex parallel to the central sulcus (Craner and Ray 1991).

2.2. micro-ECoG electrode arrays

Two novel micro-ECoG electrode arrays in a hexagonal arrangement (figure 1(a)), both with 48 (4 × 12) contacts but of different sizes, were sequentially implanted subdurally to record SEPs. The electrodes were all designed and manufactured by the Laboratory for Biomedical Micro-technology at the Institute of Microsystems Engineering (IMTEK), University of Freiburg, Germany (Henle et al. 2009). The novelty of the electrode arrays is based in the high-purity platinum foil embedded in medical grade silicone rubber (Schuettler et al. 2005), which is well accepted by the body in long-term implantations manufactured using an automatic and flexible laser-structured fabrication process.

The larger electrode array (implanted first, figure 1(a), left) had a size of 37.8 mm × 15.4 mm, a thickness of 0.31 mm, an electrode contact diameter of 1.81 mm, and a centre-to-centre inter-contact distance of 3.5 mm. The smaller electrode array (implanted second, figure 1(a), right) had a size of 18 mm × 7.5 mm, a thickness of 0.23 mm, an electrode contact diameter of 0.87 mm, and a inter-contact distance of 1.68 mm. Electrode contacts and connecting tracks were made of platinum (12.5 μm thick layer of platinum) in a silicone substrate. The metal tracks were designed to be meander-shaped to facilitate...
Figure 2. Somatosensory-evoked potentials (SEPs) recorded with $\mu$ECoG. (a) and (c) Topographic maps of SEP amplitude changes upon contralateral stimulation (1.0 mA stimulation intensity, larger $\mu$ECoG electrode array) at two different stimulation sites. The stimulation sites corresponding to panels (a) and (c) are shown in (b). The maps show the trial- and time-averaged potential change in a time window from 14 to 23 ms after stimulation onset. The electrode contacts with significant positive and negative potential changes are marked by larger filled black and white circles, respectively (sign test, FDR-corrected at $q < 0.01$). The white and black dots in the centre of electrodes indicate the contacts with the maximum positive and negative amplitude changes, respectively. Among the remaining electrode contacts, which did not reach significance after FDR correction, those with $p \leq 0.5$ (sign test) are marked by larger filled gray circles, and those with $p > 0.3$ (sign test) are marked by the smaller filled black circles. (d) and (e) Topographic maps at the same stimulation site and within the same time window as in (c) but from a different minipig stimulated at 1.0 mA (d) and 8.0 mA (e). The signals were recorded with the larger $\mu$ECoG electrode array. (f) SEP amplitudes were proportional to the stimulation intensity. The black dots between the horizontal black error bars indicate the maximum positive amplitude values at different stimulation intensities from the same minipig at the same stimulation site within the same time window as in (d) and (e). The error bars indicate the corresponding standard errors across trials. The SEPs were significant (\*: sign test, FDR-corrected at $q < 0.01$); the black line is the polynomial fit to the data (see section 2).

bending and stretching of the electrode array (Schuettler et al 2009). Wires (bundled in silicone tubing) are welded to the metal tracks (Schuettler et al 2008). Silicone adhesive was used to electrically seal the welding spots against body liquids. All 48 electrode contacts were used to record cortical responses. Two extra metal wires with needle electrodes were directly connected to the amplifier; one was inserted into the contra-lateral (right) hemisphere as the reference, and the other was inserted at the posterior edge of the wound as electrical grounding. As an electrical shielding, an aluminium-cover was placed over the whole wound and connected to the common ground.

2.3. Recording, stimulation and online analysis

The $\mu$ECoG electrode arrays were connected to four 16-channel amplifiers (gUSB amp, g.tec, Schiedlberg, Austria) via a switchbox. We used 12 channels on each amplifier for equal distribution and one channel for the TTL trigger pulse to synchronize the stimulation and recordings. For data acquisition, we used the BCI2000 system (Schalk et al 2004). The signals from each channel were digitized at a sampling rate of 4800 Hz, amplified ($\times3000$ gain) and bandpass filtered between 0.1 Hz and 2000 Hz (8th order Butterworth bandpass filter).

Stimulation was performed with single isolated constant current pulses generated using an ML180 stimulator. This stimulator was connected to the PowerLab 8/30 controller (both AD-Instruments, Spechbach, Germany) with a BNC cable and activated by a TTL pulse. As the rostrum of the minipig is represented on a relatively large area of the cortex, we chose the appropriate area of the minipig’s noses for stimulation and the nasal somatosensory area for the recording of SEPs (Craner and Ray 1991, figure 1(b)). The minipig’s noses were marked with a regular grid of 10 dots (approximately 2.5 mm diameter, 7 mm inter-contact distance) around the right nostrils in order to insert the monopolar stimulation electrodes at equal distances (Gierthmuellen et al 2011).

First, the larger electrode array (electrode contact diameter = 1.81 mm, inter-contact distance = 3.5 mm) was placed on the contralateral somatosensory cortex. Current pulses were applied to two stimulation sites on opposing sides of the nostril (figure 2(b)). The pulses had durations of 100 $\mu$s, and inter-stimulus intervals of 495 ms and were delivered in 3 min sessions, yielding approximately 360 trials. To determine the minimum stimulation intensity at which clear SEPs could be elicited, consecutive sessions with 0.5 mA, 1.0 mA, 2.0 mA, 4.0 mA and 8.0 mA were conducted at two stimulation sites, one after another. The data of each recording session was transferred to a workstation computer and was immediately analysed. This online analysis consisted of common average re-referencing, software high-pass filtering (4th order Butterworth, cut-off frequency 1 Hz) to remove offsets that impeded online visualization, and trial averaging. The online analysis performed during the experiment revealed that with the larger electrode array, clear SEPs were obtained with stimulation intensities between 1.0 and 8.0 mA, while 0.5 mA was too low to elicit clear measurable SEPs. We therefore chose the 1.0 and 8.0 mA intensities for the following position test (also conducted with the larger electrode array), where we stimulated all of the 10 marked stimulation sites around the nostril. The pulses were again delivered with durations of 100 $\mu$s, inter-stimulus intervals of 495 ms, and sessions of 3 min, yielding approximately 360 trials for each combination.
of the two stimulation intensities and the 10 stimulation sites. Online analysis of the SEP data obtained from this position test was performed as described previously. The position of the contact on the nasal somatosensory cortex that showed SEPs with the largest amplitudes was marked with the spot of a laser pointer. The larger electrode array was then carefully removed and the smaller electrode array was placed such that its centre was aligned to the laser point. The same stimulation protocol as for the large electrode array was again run for the smaller electrode array (electrode contact diameter = 0.87 mm, inter-contact distance = 1.68 mm). All the tests were performed within 5–6 h following the surgery, and the minipigs were sacrificed after the experiments.

2.4. MRI and electrode visualization

To visualize the electrode contacts on the cortex (figure 1(b)), a 3D brain model was created by segmenting a post-mortem isotropic (0.4 mm × 0.4 mm × 0.4 mm) T1-weighted magnetic resonance image (MRI) of the minipig’s brain obtained on a Bruker 3T Machine, Bruker Corporation, MA, Siemens, Germany. The image was obtained with the following parameters: maximum gradient strength 40 mT m⁻¹, TR = 1900 ms, TE = 900 ms, 32-channel receiver coil, section thickness = 0.4 mm, field of view 100 × 100 mm, interpolated to a 256 × 256 matrix. As the brain was fixed in formalin before the MRI was performed, the tissue contrasts were changed and the segmentation of the cortical grey matter was performed by performing the following steps. First, the brain was extracted from the background using the BET tool (Smith 2002) provided in the FSL-toolbox (Smith et al 2004, Woolrich et al 2009). The extracted brain volume still had many segmentation faults, likely due to (i) the high signal amplitude of the background formalin and; (ii) the fact that the algorithm was originally designed to extract brain tissue from whole head scans, preferentially using T1 and T2 data simultaneously (Smith 2002). Then, segmentation errors were corrected using custom MATLAB scripts (version R2012b, The MathWorks Inc., Natick, MA) with a semi-automatic grey-value threshold algorithm based on 26-direction 3D flood filling, taking into account the faulty extraction to impose local constraints/flexibilities (Zhang et al 2001). Lastly, the (partially resected) dura mater was modelled using the mesh_shrinkwrap algorithm implementation for MATLAB by Darren Weber (freely available at http://eeg.sourceforge.net/ as part of the BioelectromagnetismMatlab Toolbox).

2.5. μECoG data analysis

2.5.1. SEP analysis. The SEP data were analysed using custom MATLAB programs in the following way: (i) A 1 Hz high-pass filter (4th order Butterworth, cut-off frequency 1 Hz) was applied to the raw data to eliminate the low-frequency drifts due to hardware noise, and the data were re-referenced to a common average reference across all functioning electrode contacts. (ii) Data in a time period of −41 ms to −125 ms relative to stimulation onset were cut out for each trial for all recording sessions. These data will be referred to as ‘short-trial data’ in the rest of the manuscript. Approximately 360 trials for each recording session were acquired and averaged to a single SEP trace for each electrode contact and each individual session. (iii) Each trial of these data was further divided into 16 non-overlapping time windows of approximately 9 ms, and the mean SEP amplitudes for each of these time windows were calculated. Then, median SEP amplitudes across trials were calculated separately for each time window, electrode contact and session. Baseline correction was performed by subtracting the median SEP values over the first two time windows from the SEP amplitude in each of the following time windows. Then, a sign test was employed to detect significant SEP amplitude changes, and the obtained p-values were corrected for multiple comparisons across 48 contacts and 16 time windows using the false discovery rate (FDR) correction approach (Benjamini and Yekutieli 2001) at a q-level of 0.01. These steps were performed separately for each recording session. Significant contacts which recorded the maximum positive SEP amplitude changes will be referred to as ‘positive maxima contacts’ hereafter. As shown in figure 2(f), we used a polynomial fit to the data to visualize the relation between stimulation intensities and the amplitudes of positive maxima contacts in each time window. Among the contacts that showed no significant effects after FDR correction, some had large p-values > 0.3, clearly showing no effects. The remaining contacts that were neither clearly significant nor very large (p < 0.3, but above significance level) fell into an intermediate range of values. The distinction between these three cases (significant after FDR-corrected at q < 0.01, clearly no effect with p > 0.3, and intermediate cases) was important for the evaluation of spatial response patterns (see below). (iv) Topographic maps of the SEP amplitude changes were computed for all time windows and sessions using a linear interpolation method for smoother visualization. Different symbols were used to visualize the results of the statistical analyses in these maps (see captions of figure 2 for details). Additionally, as an alternative data set for the spectral analysis described in section 2.5.2, data within a longer period of −133 ms to 495 ms relative to stimulation onset were analysed and processed in the same way as described above. These data will be referred to as ‘long-trial data’ hereafter.

2.5.2. Analysis of relative spectral power changes. The spectral analysis was performed using a time-resolved fast Fourier transform (FFT) for all trials; the data were pre-whitened to ensure that all frequency components contributed equally for the next analysis steps). Two versions with different time-frequency resolution were computed. First, short-trial data were analysed with a sliding window of 20.8 ms and a window step of 2.0 ms in order to have a sufficient number of time- and frequency bins given the limited trial length, resulting in 51 frequency bins (0–2400 Hz in steps of 48 Hz). These data will be referred to as ‘low-frequency-resolution data’ (48 Hz frequency resolution). Logarithmic relative power changes were computed using the mean over the first 10 time bins as a baseline, by which all absolute power values were divided. We analysed four frequency bands in this case: 24–72 Hz (high-gamma band), 72–168 Hz (very high-gamma band 1), 168–264 Hz (very high-gamma band 2) and 264–408 Hz (very high-gamma band 3). Second, the long-trial data were analysed with a sliding window of 100 ms and a window step of 27.5 ms in order to obtain a higher frequency resolution compared with the
low-frequency-resolution data’, yielding 241 frequency bins (0–2400 Hz in steps of 10 Hz). These data will be referred to as ‘high-frequency-resolution data’ (10 Hz frequency resolution). In this case, the logarithmic relative spectral power changes were calculated as described above but using the first two time bins as a baseline period. The analysed frequency bands were as follows: 0–15 Hz (alpha band), 15–25 Hz (beta band), 25–45 Hz (gamma band), 45–85 Hz (high-gamma band), 85–155 Hz (very high-gamma band 1), 155–255 Hz (very high-gamma band 2) and 255–405 Hz (very high-gamma band 3).

The 16 time windows for the low-frequency-resolution data and 20 for the high-frequency-resolution data were computed as for the SEP data and visualized as interpolated topographic maps. The same statistical procedure as used for the SEP data was applied after baseline correction. The coding of electrode contacts for significance and the polynomial function for visualizing the relationship between the relative spectral power changes and the stimulation intensities (as shown in figure 3(f)) were implemented in the same way as for the SEP data.

Figure 3. Somatosensory-evoked relative spectral power changes recorded with μECoG. The results were from the very high-gamma band 2 (168–264 Hz) at different stimulation sites and intensities. The relative spectral power changes are shown for the same data sessions as in figure 2. All of the conventions are described as in figure 2.

Figure 4. Comparison of recording properties using μECoG electrode arrays with different geometries. (a) Topographic maps of relative spectral power changes recorded with the larger electrode array (left) and the smaller electrode array (right), both showing very high-gamma band 2 (168–264 Hz) responses in a time window of 5–14 ms after stimulation onset and at 1.0 mA. The same stimulation site and the same minipig were used for these recordings. Topographic maps in (b) show the relative spectral power changes in very high-gamma band 3 (264–408 Hz) from another minipig recorded in the same time window as in (a) with the larger electrode array (left) and the smaller electrode array (right), at 8.0 mA stimulation intensity. Black boxes in the left panel in (a) and (b): approximate position of the smaller electrode array relative to the position of the larger electrode array on the cortex. The conventions for significance are as described in figure 2. (c) Statistical comparison of relative spectral power changes and SNR for the positive responses across all sessions (sign test, FDR-corrected, $q < 0.01$). Blue and cyan bars: relative spectral power (relSP) responses recorded with the larger and smaller electrode arrays, respectively. Red and magenta bars: SNR of relative spectral power responses (relSPSnr) recorded with the larger and smaller electrode arrays. ** and *: significant differences between the results obtained with larger and smaller electrode array (sign test, FDR-corrected) at $q < 0.0001$ and $q < 0.01$, respectively.
2.5.3. Analysis of \( \mu \)ECoG signal quality depending on electrode array geometry. To assess the impact of the electrode array geometry on the quality of \( \mu \)ECoG recordings, we compared both the relative spectral power changes and the signal-to-noise ratio (SNR) at positive maxima contacts for the larger and the smaller electrode arrays (figure 4). To this end, we pair-matched all recording sessions obtained in each minipig using the same stimulation parameters for the larger and the smaller arrays, resulting in a total of 85 stimulation sessions with identical stimulation conditions for each electrode array. For all of these sessions, the medians of the relative spectral power changes in each time window and the frequency band across all trials were computed as described above. In the SNR analysis, we defined the noise as the interquartile range (iqr) as a measure of the variability (noise) across trials of the relative spectral power changes in each session. SNRs for the positive maxima contacts were calculated as the trial-averaged (median) spectral power values divided by the noise level in each frequency band and time window. We then applied a sign test (\( q < 0.01 \), FDR-corrected) for each frequency band and time window to test the positive maxima contacts of the larger and smaller electrode arrays for differences in relative spectral power changes and SNRs.

2.5.4. Comparison of response map complexity depending on electrode array geometry. To compare the spatial complexity of responses between larger and smaller electrode arrays, we detected the number of positive significant peaks (referred to as significant spatial local maxima (SSLM)) in each topographic map. For this analysis, matched sessions were used as in section 2.5.1. Positive significant peaks were identified as responses with positive significant relative spectral power changes higher than those of all of their direct neighbours (\( q < 0.01 \), FDR-corrected; as marked in figures 5 and 6). For this analysis, contacts were required to have at least three neighbouring contacts with a distance equal to the inter-contact distance of the respective electrode array. This was not the case for some contacts at the edge of the electrode arrays, precluding an assessment of the neuronal responses in the adjacent area (not covered by electrode contacts). The number of SSLMs was calculated for each time window, frequency band, and session, for the larger and the smaller electrode arrays, respectively. Pie charts, as shown in figure 6, were used to illustrate the distribution of specific numbers of positive significant peaks across all sessions in selected frequency bands and time windows.

2.5.5. Analysis of \( \mu \)ECoG signal quality depending on electrode contact position relative to cortical vasculature. We initially tried to determine the exact locations of individual electrode contacts relative to cortical vasculature manually like in previous study (Miller et al 2009, Bleichner et al 2011). In our experience, however, this method proved to be tedious and too subjective, and we abandoned this method in favour of custom semi-automatic approach that can be described as follows. First, we acquired intra-operative photographs of the somatosensory cortex with and without the implanted electrode arrays. The photographs with and without electrodes were then co-registered based on the positions of cortical vessels using the MATLAB program Image Registration. The colour images (figure 1(b)) were then converted to gray-scale photos (Adobe Photoshop CS3, Adobe Systems Incorporated, CA). The cortex in these images had a light gray colour and the blood vessels were dark gray (figures 7(a) and (b), and background image). The electrode contact centres were determined in the photographs with the implanted electrode contact positions on the cortex. The mean gray values of the area underneath each contact were computed based on the photographs of the cortex without implanted electrode arrays. The mean gray values were high if an electrode contact was positioned on the cortex and low if it lay above a vessel. Accordingly, we defined contacts as ‘cortex contacts’ if the mean gray values were above the 75th percentile of all mean gray values across contacts, and contacts with mean gray values below the 25th percentile were defined as ‘vessel contacts’. Contacts between the 25th and 75th percentiles were excluded from this analysis because the assignment to either cortex or blood vessels was not always unambiguous in this group. The median values of relative spectral power changes for the ‘cortex contacts’ and ‘vessel contacts’ groups were calculated for each frequency...
Figure 6. Topographic complexity of $\mu$ECoG responses observed with different electrode array geometries. (a) Top row: topographic maps of SEPs recorded with the larger (left) and the smaller (right) electrode arrays (5–14 ms time window, 1.0 mA stimulation intensity). The black box in the left panel indicates the position of the smaller electrode array relative to the larger electrode array. The pie charts colour-code the number of distinct peaks found across recording sessions, with the whole pie chart representing all 188 recording sessions from all minipigs. (b) The same figure components as in (a) but in a different minipig and in a different time window (14–23 ms). (c) The number of SSLM averaged across sessions for the larger and smaller electrode arrays. The symbol colours indicate the time windows relative to the onset of stimulation. Symbol shape: triangles indicate highly significant differences between the number of SSLM obtained with the larger and smaller electrode arrays ($p < 0.005$, Wilcoxon rank sum test), squares: $0.005 < p < 0.05$, circles: non-significant differences ($p \geq 0.05$). The symbols above and below the dotted diagonal indicate cases with more SSLM with the larger and smaller electrode array, respectively. (d)–(o): the same results for different gamma frequency components; all of the conventions are as described in (a)–(c). The topographic maps in each column of the figure show the neuronal effects that were observed in different frequency bands simultaneously during the same stimulation session. The larger electrode array yielded more SSLM in the SEP time domain (c), especially in the later time windows. With increasing frequency, the number of SSLM observed with the smaller electrode array increased compared with the larger electrode array, particularly in the earlier time windows.

3. Results

3.1. $\mu$ECoG responses dependent on stimulation site and intensity

Using the novel $\mu$ECoG electrode arrays, we were able to reliably record spatially fine-grained cortical activity patterns. Figures 2 and 3 depict representative topographic maps of SEPs, each time window and each session separately. To determine whether there was a significant response difference between the contacts on the vessels and those on the cortex, a statistical comparison of the median relative spectral power changes was performed between these two contact groups across all sessions for each frequency band and each time window (Wilcoxon rank sum test, $q < 0.01$, FDR-corrected).
the corresponding logarithmic relative spectral power changes for the same minipig, and the stimulation parameters obtained with the larger electrode array. These data indicate that SEP and spectral power changes exhibited a strongly overlapping topography (figures 2(a), (c), (d), (e) and 3(a), (c), (d), (e)). Both site-specific and intensity-related topographically focalized SEPs and gamma responses were reproducibly observed. For instance, changes of the stimulation sites caused a spatial shift of the main response (figures 2(a), (c) and 3(a), (c)), while all other stimulation parameters were kept constant. Changes of stimulation intensity also influenced the spatial extent of stimulation-related neuronal effects. Figures 2(d), (e) and 3(d), (e) show the topographical maps with stimulation intensities at 1.0 mA (figures 2(d) and 3(d)) and 8.0 mA (figures 2(e) and 3(e)), demonstrating that the SEP amplitude (figures 2(d) and (e)), the relative power changes (figures 3(d) and (e)) and the number of contacts with significant effects were modulated by stimulation intensity. Additionally, for SEPs, when the number of electrode contacts with significant effects increased with higher intensity, the significant effects were observable in two distinct areas and not spread to all of the other contacts in between. Analysis of the relation between stimulation intensity and the amplitude of the neuronal responses for both SEPs (figure 2(f)) and relative power changes (figure 3(f)) indicated that the response amplitude increased with the intensity of stimulation, as expected. High spatial specificity of neuronal effects and their dependence on stimulation intensity were also observed with the smaller electrode array.
3.2. Influence of electrode array geometry on the amount of spatial detail and the quality of neuronal recordings

In the present study, two different µECoG electrode arrays were utilized, with 3.5 mm and 1.68 mm inter-contact distances and 1.81 mm and 0.87 mm contact diameters, respectively. Neuronal responses elicited by peripheral electrical stimulation and recorded with the smaller electrode array revealed more topographical details than those obtained with the larger electrode array in the same cortical region (figures 4(a) and (b)). In the examples in figures 4(a) and (b), activity in the very high-gamma bands 2 and 3 recorded with the larger electrode array (figures 4(a) and (b), left panel) revealed a single, spatially extended response pattern. Using the smaller electrode array placed on the same area, however, several spatially segregated peaks could be clearly distinguished (figures 4(a) and (b), right panel). These peaks were separated by electrode contacts with non-significant responses (marked by larger filled-gray circles and smaller filled-black circles, see section 2).

To investigate whether the geometry of the electrode arrays affected signal quality, we compared the SNR and the maximum amplitudes of spectral power changes observed with the larger and the smaller electrode arrays. This analysis shows that the maximum amplitudes (see section 2), especially for very high-gamma responses, were significantly higher (sign test, FDR-corrected) in recordings with the smaller electrode array, while the SNR was better in recordings with the larger electrode array (figure 4(c)).

3.3. Topographic complexity of µECoG responses observed with different electrode array geometries

As shown in section 3.2, the spatial structures of µECoG response maps likely reflect different cortical activation patterns in different spatial scales. Given this finding, an examination of the role of µECoG electrode array geometry on the topographic complexity of the µECoG responses was the next reasonable analysis step. To this end, we used the number of SSLM in the µECoG response maps as an index of topographic complexity. To obtain a comprehensive overview of topographical complexity, the number of SSLM was determined for both electrode array types and each session individually for averaged frequency bands and time windows. These values were used as the basis for the results presented in this section. For example, in the very high frequency maps shown in figure 5(e), the number of SSLM ranged from 1 to 3. The larger electrode array yielded more SSLM in the SEP response maps (figures 6(a)–(c)), at least in the later time windows. However, with increasing frequency of the analysed µECoG signal component, the number of SSLM observed with the small electrode array increased compared with the larger electrode array (figures 6(d)–(o)). Particularly in the earlier time windows, this difference between the larger and smaller electrode array was highly significant (rank sum test, p < 0.005, triangles in figures 6(f), (i), (l) and (o)).

3.4. Influence of cortical vasculature on the µECoG signal

The results in sections 3.2 and 3.3 show that µECoG can capture cortical responses with fine-grained spatial detail. Are these spatial patterns a genuine property of cortical activation, or are they possibly artefacts caused by cortical vasculature? For example, the µECoG response map in figure 7(a) shows two distinct regions with significant responses that are separated by a ‘valley’ with no significant responses (yellow box in figure 7(a)). Was the cortex in this region truly silent, or was a blood vessel running between the electrode contacts and the cortex, possibly preventing responses from being detected? We used intraoperative photographs, both with the electrode arrays in place (figure 7(b), left-most panels in figures 7(c) and (d)) and of the same region of exposed cortex without electrode arrays (figures 7(e) and (d), remaining panels) to address this question.

In many examples, comparison of response and vascular patterns showed spatial response structures that could not be explained by vascular effects (figures 7(a)–(d)). Furthermore, we found that the location of electrode contacts, i.e. on the cortex or on blood vessels, generally did not significantly impact the neuronal responses (figure 7(e)). The only exception was the level of beta band (15–25 Hz) responses, which were significantly higher at electrode contacts lying directly on the cortex than on the vessels. These results suggest that at least the level of gamma band activity is not distorted by the presence of cortical blood vessels.

4. Discussion

4.1. Suitability of µECoG electrode arrays for cortical recordings

The spatially and functionally specific patterns of cortical activity in the present study demonstrate that µECoG is well suited to obtain high-quality neuronal recordings of cortical activity. Our recordings had high signal-to-noise ratios and were sensitive to spatially and temporally very local changes in the neural signal. The high amount of spatial detail that can be seen in our functional maps may be attributed to the innovative procedures implemented to fabricate the electrode arrays.

Customized non-penetrating flexible µECoG electrode arrays from IMTEK, University of Freiburg, were used to record brain activity in the somatosensory cortex of the minipig. Compared to other techniques that use polyimide and manufacturing with MEMS technology (Rubhn et al 2009), the electrode fabrication technology applied in this study permits a shorter design-to-prototype time. This benefit is gained because the actual geometry is designed as a computer-aided design (CAD) file and transferred to a laser that ablates silicone and metal in a highly automated process (Henle et al 2012). In contrast to most commercially available silicone rubber-based electrode arrays, which are predominantly handmade and therefore restricted in feature sizes to the millimeter range (Stieglitz et al 2009), this process allows for electrode arrays in the sub-millimeter range. In this work, we show that the designed electrode arrays have great potential for reliable and robust recording of neuronal assembly activity on millimeter (larger electrode array, contact Ø 1.81 mm, inter-contact distance 3.5 mm) and sub-millimeter (smaller electrode array, contact Ø 0.87 mm, centre-to-centre inter-contact distance 1.68 mm) scales up to very high frequency bands. Medical grade silicone rubber and high-purity platinum foil are known to
be stable and well accepted by the body in long-term implantations (several decades), allowing for electrode arrays designed for animal studies to be used in human clinical trials with minimal legislative hurdles. In addition, electrode arrays covering a smaller cortical area may reduce clinical surgical risks and complications, such as subclinical seizures or trauma, which can arise due to decreased pressure over the cortical surface (Wong et al. 2009). These features of the designed μECoG electrode arrays, namely, enhanced signal detection, material properties and reduced clinical risk, make them promising candidates for long-term implantation in human clinical applications.

4.2. The role of electrode array geometry in μECoG signal quality

The first primary question addressed in this study concerns the role of electrode array size (contact diameter and inter-contact distance) in neuronal μECoG recordings and, in particular, its impact on the detection of high-frequency signal components. Optimal contact diameters for subdural electrode arrays were suggested to be 0.7 mm for rats and 1.25 mm for humans based on finite element modelling and spatial spectral analysis (Freeman et al. 2000, Slutzky et al. 2008). An experimental study by Worrell et al. (2008) compared contact areas between 9.4 mm² (Ø 1.73 mm) and 0.012 mm² (Ø 40 μm, micro-wires) in humans, with the former being larger than the stated optimal diameter for humans and the latter much smaller. This previous study found that high frequency oscillations (HFOs) were more frequently recorded using micro-wires, suggesting that small contacts are more suitable to detect the sub-millimeter activity pattern that is supposed to be investigated, rather than the optimal electrode contact diameter for the minipig might be between 0.7 and 1.25 mm (the proposed diameters for rats and humans), but presumably closer to 1.25 mm. The findings presented here support this range of proposed optimal electrode contact diameter given that the smaller electrode array with a diameter of 0.87 mm is nearer to the proposed optimal diameter for humans. Based on the results of the present study, given the comparability of the minipig’s gyrencephalic brain to the human brain in terms of general anatomy, growth and development (Jelsing et al. 2006), the optimal electrode contact diameter for the minipig might be between 0.7 and 1.25 mm (the proposed diameters for rats and humans), but presumably closer to 1.25 mm. The findings presented here support this range of proposed optimal electrode contact diameter given that the smaller electrode array with a diameter of 0.87 mm is nearer to the proposed optimal diameter for humans than the larger electrode array with a diameter of 1.81 mm. Moreover, the electrode array with the smaller diameter (0.87 mm) recorded significantly higher relative spectral power changes (especially in the very high-gamma 3 frequency band, up to 408 Hz, figure 4(c)) in the cortex area with the main neuronal responses. This result is similar to that observed in Worrell’s study (Worrell et al. 2008). Although, we were able to detect differences in recording performance using different electrode contact sizes (figures 4(a), (b) and 7), and the results presented here tend to support the findings of Worrell et al. (2008) and thus suggest an impact of electrode contact size on cortical recordings, the optimal electrode contact size for minipigs and humans were only estimated, and still remain unclear. Even the question arises, whether there are several optimal electrode contact sizes, depending on the area and the activity pattern that is supposed to be investigated, rather than a universal size that can be applied to arbitrary areas and patterns. For instance, HFO generators (especially FR generators) were found to be less than 1 mm³ (Bragin et al. 2000, 2002). If the electrode contact size exceeds the area of interest, a larger electrode contact might record events in a larger area, i.e. more neuronal populations, leading to a blurred recording and to a reduction in total recorded signal strength. Such behaviour was observed in the study by Worrell et al. (2008) as well as in the present study. However, for non-HFO activity or other types of general activity, electrode contact size might be chosen differently in order to achieve an optimal spatial sampling.

In a BMI study with monkeys performing closed-loop BMI control tasks, Rouse and his colleague (Rouse et al. 2016) suggested optimal inter-contact distances to be 3 mm for independent epidural recordings. For humans, this distance might be larger due to the thicker dura mater (Bundy et al. 2014, Rouse et al. 2016). However, a better signal quality can be obtained if the μECoG electrode array is implanted subdurally (Bundy et al. 2014). Furthermore, the influence of inter-contact distance was found to be different between BMI control tasks and normal neuronal recordings (Rouse et al. 2016). Specifically, for normal neuronal recordings, the signal from each contact site represents the activity directly under the contact and is minimally distributed between the electrodes. However, in the BMI control task, the signal might be distributed depending on the utilized decoding strategy. Thus, the practical limit for normal neuronal recordings using μECoG is likely smaller than 3 mm. Ours is the first study to probe the impact of inter-contact distance in normal neuronal recording. It is clear that more spatial details can be obtained with electrode arrays that have smaller inter-contact distances (1.68 mm; topographic mappings in figures 4 and 7). We can also conclude based on the present results that the smaller electrode array does not provide the same data as a macro-electrode array; rather, each contact can record neuronal activity independently. Thus, it is worth seeking the practical limit for normal neuronal recording if the technical conditions permit.

A related question arising from electrode contact miniaturization is how the impedance increase associated with electrode contact miniaturization impacts neural recordings and whether the described reduction in SNR might be due to these impedance changes. Usually, the ratio between the electrode contact impedance and applied amplifier impedance (rather than the contact impedance alone) is the main factor for assessing the quality of neuronal recordings. If this ratio is <1%, the electrode contact size appears to have no effect on impedance-related signal attenuation (Chatillon et al. 2011). In previous reports as well as in the present study, the observed ratio was consistently near this limit (electrode contact impedance <5 kΩ and amplifier input impedance >10 GΩ in the present study), excluding the possibility of neuronal signal distortion.
due to impedance. Thus, cortical volume, i.e. the neuronal populations beneath the electrode contact, was the main factor for the observed reduction in signal strength. However, a difference between smaller and larger contact impedances exists in the sense that smaller contacts usually have higher impedances (Stieglitz 2009). This could be the reason why signals recorded with larger contacts had a better SNR as shown in figure 4(c).

4.3. Assessment of topographic complexity captured with µECoG electrode arrays of different geometries

The second main objective of the present study was to investigate not only whether µECoG electrode arrays can record spatially segregated activity peaks (such as in the studies by Hosp et al. (2008), Wang et al. (2009) and Wang et al. (2016)) but also whether different electrode array geometries affect the representation of topographical complexity in terms of both the number of SSLM and their respective frequency bands.

As mentioned in the Introduction, topographic maps presented in previous studies often contained only one activated area, representing the main response. However, topographic maps with two or multiple segregated, respondent areas were rarely reported. These results raise the question of whether the observation of a single activation peak reflects the actual activation pattern or rather results from the summation of larger (or multiple) neuronal populations. Such sources would be distinguishable when using electrode arrays with smaller inter-contact distance and electrode contact diameters, respectively. For instance, using microelectrodes with a sub-millimeter scale, Hosp et al. (2008) showed that the spatial representation of the SEP P1-N1 amplitude evoked in the hindlimb area of the rat was separated into two activity foci, a medial and a lateral field, in three of five rats. Spectral power maps of finger movement-related activity in humans were obtained from electrode arrays with 4 mm inter-contact distances. These data showed multiple segregated areas around micro-scale activation peaks (Wang et al. 2009, 2016), similar to the outcomes reported for a larger electrode array (3.5 mm inter-contact distance) in this study. Furthermore, the present results show that compared to the larger electrode array, the smaller electrode array (1.68 mm inter-contact distance) can robustly detect a higher number of separate activation areas in the same cortical location (figure 6). We found a quantitative measure (SSLM) to address these topics by comparing two electrode arrays with different spatial resolutions; specifically, these electrode arrays were used to record activity elicited by unvarying stimuli in the same area of the cortex. We were able to show that especially in the high-frequency domain, the geometric properties of electrode arrays influence the mapped topographic complexity (figure 6), a difference that can be expressed in terms the number of SSLM quantity. The number of SSLM recorded with the smaller electrode array was higher than for the larger electrode array, especially in very high frequency bands. We also found very high-gamma frequency oscillations (up to 408 Hz) coexisting with low- or classical gamma frequency oscillations in overlapping, partially overlapping and spatially segregated cortical locations in the minipig’s somatosensory cortex. A similar coexistence of low- and high-gamma frequency oscillations was also observed and described for the visual cortex in cats (Siegel and König 2003) rats (Oke et al. 2010) and humans (Tallon-Baudry et al. 2005, Chaumont et al. 2009). Such overlapping patterns have been proposed to indicate different aspects of information processing.

Whether the increased complexity observed in this and the aforementioned studies reflects the actual activity in the underlying tissue and how it can be reconciled with findings from studies investigating single- and multi-unit activity (SUA and MUA) remains unclear. µECoG signals reflect the contributions of electrical field variations (postsynaptic potentials, PSPs) arising at different cortical layers. The larger and more numerous pyramidal cells have somata residing primarily in cortical layer V and dendritic arbors in more superficial layers, i.e. closer to the µECoG contacts on the brain surface (Zanos 2009). This arrangement was demonstrated by Barth and Di (Barth and Di 1990) in the rat auditory cortex using a micro-electrode array of cortex-penetrating depth electrodes to record local field potentials (LFPs). In this study, the first component of the auditory evoked potential arose from layer II and the second component from layer IV and V. In addition, the rates of excitatory and inhibitory PSPs generated at the dendrites of pyramidal cells differ from the respective cell’s firing rate, which can differ even between neighbouring pyramidal cells. A previous study suggested that coexisting low- and high-gamma oscillations may originate from different cortical layers due to the cross-layer arborisation of both excitatory and inhibitory axons, especially for responses in the higher frequency bands (Watts and Thomson 2005).

Siegel and König (2003) proposed that the high-gamma cortical oscillations reflect an emergent property of local networks rather than activity driven by fast thalamic oscillations, as has been previously proposed and that these oscillations are little affected by inputs from other networks. There are also studies investigating the somatosensory cortex of monkeys showing that 600 Hz oscillations are modulated by somatosensory stimuli that reflect the timing of cortical spike bursts (Baker et al. 2003) and that multi-unit activity usually reflects the spiking outputs of neurons in an area.

Taking all of this into account, it can be assumed that cortical recordings reflect a substantial temporal and spatial summation of overlapping activity, both within and between neighbouring neuron populations, due to the different firing rates and PSP rates. The responses at each electrode contact site would therefore be the result of asynchronous contributions from sub-populations of cells in different lamina, and (very) high-gamma frequency oscillations recorded in the somatosensory cortex of the minipig may be due to emergent properties of local networks. This arrangement could generate the multiple activation peaks observed in the topographic maps presented here.

4.4. Impact of cortical blood vessels on µECoG signals

The third main question addressed in this study was the role of cortical blood vessels in µECoG recordings and whether they influence signal components. A previous study by Bleichner et al. (2011) investigated the effect of blood vessels in macro-ECoG recordings, showing that the absolute power spectral density in the frequency band from 30 to 70 Hz was clearly attenuated
for electrode contacts located on blood vessels (Bleichner et al 2011). In the present study, we compared relative spectral power changes. We assume that these values are more robust than measures of absolute power given that baseline variation-corrected values better reflect differences between cortex and blood vessel electrode contact groups in spectral powers of different frequency bands (Leuchter et al 1987, Leuchter and Walter 1989). In addition, we used a different approach to define the electrode contact position compared to the method of (Bleichner et al 2011) where electrode contact positions were defined based on the opinions of two independent observers. To be more objective regarding electrode contact assignment (i.e. cortex or vessel), we used the 25 percentile and 75 percentile of all electrode contact gray values as an assignment threshold rather than the median. Electrode contacts with gray values falling between this range were excluded from further analysis (white circles in 2nd columns of figures 7(a) and (b)). Although this objective approach reduces the amount of information available for the analysis, this processing step ensured that we compared signals that certainly came from electrode contacts either on the cortex or on vessels. Using this method, we show that if all investigated parameters (i.e. data from both electrode arrays with high-frequency-resolution data sets) are included in the analysis, there are no significant differences between the relative spectral power changes in the gamma frequency band as measured at the cortex and vessel electrode contacts, and there was a significant decrease for blood vessel electrode contacts in the beta band (15–25 Hz). Such a decrease in beta frequencies could be related to the properties of the cortical layer(s) in which this activity originates. High-frequency oscillations may come from more superficial cortical layers (Oke et al 2010). A contact lying on a vessel would lie farther from the source of cortical activity, resulting in a greater relative distance increase of generators in superficial cortical layers, possibly contributing to frequency-specific differences in the attenuation of responses. In fact, results might be more complicated than what we presented here, and they should be addressed in more detail in further study, for example, is the contact size plays a role in such kind of analysis, or if we focus on more specific time/frequency range, the tendency will also keep constant? However, at the very least, these data provide a general hint that significant effects might not be influenced by the contact location but rather by the source of the signal. That is, if the source is under the vessels, a significant effect can be detected even if the contacts lie above it.

4.5. Influence of anaesthesia on μECOg signals

As all of the results in this study were obtained under general anaesthesia (GA), an important question is whether there are differences in the brain responses that are evoked by external sensory stimuli in the awake and GA state.

In the present study, GA was induced by propofol and maintained with propofol, fentanyl and pancuronium (section 2.1). Pancuronium is a muscle relaxant or neuromuscular blocking agent, the latter of which has been reported to have no effect on SEPs (Sloan 1998, Bithal 2014) and is usually applied after the induction of anaesthesia to facilitate the surgical procedure. Fentanyl is an intravenous opioid agent that can suppress the activity of the central nervous system but has been proposed to be less reliable as an aesthetic and to have significant side effects (Philbin et al 1990, Streisand et al 1993). Therefore, fentanyl is frequently used in combination with other agents to maintain anaesthesia due to its primary action as an inhibitor of nociception (Miller 2005). It has been reported that opioids have little effect on spinal and subcortical SEP recordings (short-latency SEP) but result in a slight reduction in the amplitude of cortical responses (long-latency SEP) and longer latencies for late cortical responses (Bithal 2014). However, propofol was the primary aesthetic in the present study. Most studies investigating SEPs under GA merely induced using propofol only suggest that it decreases the amplitude of the cortical responses (Kumar et al 2000, Bithal 2014). However, in combination with opioids, propofol reduces the amplitude of evoked potentials less than other GA agents (Schwartz et al 1997) and thus is the most common option for monitoring cortical SEPs (Calancie et al 1998).

However, the reported influence of GA on the functional state of the cortex varies depending on the used agent, dose and network studied. Even the subject’s age, race, or body temperature may influence the obtained results. Thus, the agent’s utilization or its influence needs to be considered for each case individually. It has been suggested from studies on auditory or visual evoked potentials (AEPs, VEPs) that external stimulus-evoked brain responses are suppressed in cortical regions of higher-order information processing under GA; however, such suppression is not observed in the primary sensory cortices, which engage in low-order information processing (Kerssens et al 2005, AEP/sevoflurane; Dueck et al 2005, AEP/propofol; Ramani et al 2007, VEP/sevoflurane; Boveroux et al 2010, AEP. VEP(propofol). In contrast, studies on SEPs elicited by tactile or painful stimuli showed stronger suppression in the primary somatosensory cortex (Antognini et al 1997, Kumar et al 2000, Bonhomme et al 2001, Bithal 2014). This effect that may be due to the inhibition of ascending sensory information (stimuli input) in the spinal cord, which is absent in AEP or VEP recordings. Therefore, one can presume that if the somatosensory stimulation is applied at sites that are innervated independently of the spinal cord, e.g. facial nerves, activations in lower-order cortical areas might persist, such as was proposed to be the case for AEPs and VEPs.

Furthermore, SEPs consist of both short- and long-latency components. The results from human clinical applications have indicated that GA has a stronger suppressive effect on long-latency than short-latency SEPs (Kumar et al 2000, Uhrig et al 2014). Huotari and his colleagues (Huotari et al 2004) found that short-latency SEPs evoked by painful stimuli at the median nerve showed no differences whether they were recorded in awake patients’ or those in propofol-induced GA. Zhang and his colleagues (Zhang et al 2014) compared the amplitude and latency differences of short- and long-latency SEPs elicited by whisker deflection in rats. The responses were recorded in various cortical areas in animals under GA induced by different propofol doses. Short-latency SEPs exhibited no dose-dependent differences, whereas long-latency SEPs were delayed and showed decreased amplitudes. This prolonged...
latency effect of late components were also found in other studies using different animal models and GA agents. For example, this effect was observed in cats for VEPs using pentobarbital (Robson 1967), in rats for SEPs and halothane (Chapin et al 1981), and in rats for VEPs with desflurane (Hudetz et al 2009). The reason why short-latency components are unaltered under GA is unclear, although it has been proposed that these responses emerge from the primary sensory cortices and that feed-forward projections might be more insusceptible to GA, such as for the abovementioned lower-order processing areas.

However, the previous studies mentioned here were primarily focused on evoked brain responses, amplitudes or latency alterations in the time domain. Only few studies have described alterations of responses between the awake and GA state in the spectral domain. Most of these studies investigated the results only with respect to an overall power alteration in the form of power-law plots that included quasi-continuous frequencies (Zhang et al 2014, Insanally et al 2016). There was one study from Mhuircheartaigh’s group (Mhuircheartaigh et al 2013) in which the results were presented in terms of different frequency bands. These data showed that there was a slow-activity (0.5–1.5 Hz) saturation after a specific dose of propofol in humans. In this study, however, the evoked responses were elicited by various stimulus modalities.

Taking the findings from all of these important studies into account, we conclude that propofol-induced GA in combination with opioids suppresses SEPs primarily due to the interruption of high-order information integration. Moreover, this effect primarily manifests as reduced amplitude and prolonged latency of the long-latency component. We further conclude that SEPs evoked by spine-independent facial electrical stimulation should be less affected by GA. This was the case for AEPs and VEPs, two modalities that are processed independently of the spinal cord. The results in the present study were primarily obtained from early SEP responses recorded from the lower-order primary somatosensory cortex and were elicited by electrical stimulation at the nostrils of minipigs. Moreover, these recordings were made when the animals were primarily under propofol-induced and -maintained GA. We therefore propose that the SEP results presented here should be largely uninfluenced by the GA. Unfortunately, with respect to our spectral domain analyses, we cannot reach such a firm conclusion. Nonetheless, we are confident that the results presented here provide important insights in the role of electrode array geometry. We note, however, that alterations between the awake and GA state in the spectral domain still need to be investigated more thoroughly.

5. Conclusions

We showed that for the somatosensory cortex of the minipig, the spatial information extent increases when using electrode arrays with finer spatial resolution in terms of both inter-contact distance and electrode contact diameter. This increase in information is observed especially in the low, high and very high-gamma band and can be quantified in terms of the number SSML. In addition, smaller contacts might perform better in detecting high-frequency signal components. We also showed that the presence of blood vessels subjacent to electrode array contacts only has a significant impact on beta-band power but not on gamma-band power. To further clarify the roles of spacing, size and spatial complexity in different frequency bands, suitable studies for investigating the smooth transition between SUA/MUA activity and μECoG signals must be conducted, such as the one recently published by Khodagholy et al (2015). In this previous analysis, a micro-electrode array was employed to record LFP signals as well as single spikes from the surface of the brain in epilepsy patients. Of special interest in this context is (i) how we can investigate the specific electrode array geometry that is suitable for different activity patterns and (ii) how micro- electrode arrays will advance our understanding of the complexity of spatial cortical activity and of the multiple separated areas around activation peaks. Lastly, new strategies must be developed to translate the outcomes of these basic questions to advanced BMIs, high-resolution cortical mapping and other therapeutic neurological and neuropsychological clinical applications. A previous study reports that infection rates as an implantation-related complication in patients with conventional ECoG recordings were increased with more than 100 electrode contacts, more than ten cables, more than one cable exit site, and more than 14 d of implantation (Wiggins et al 1999). Thus, also with μECoG implantation risks may be higher if a larger number of μECoG arrays need to be implanted at the same time. Alongside the surgical procedure per se, also other factors such as μECoG array geometries or the length of the implantation period may be relevant. We recognize that the amount of electrode grids, electrode geometries and the design of the implant are certainly factors that should not be neglected when planning μECoG procedures for clinical applications in humans. The exact choices related to these factors will depend on the goal of the project, and informed solutions need to be designed with caution to achieve an optimal balance in the trade-off between implantation risk and the desired spatial coverage.

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**Table A1. Overview of µECoG studies in recent decades.**

| Author                  | Subjects | Location | Task                                                                 | Electrode Results | Multiple peaks in topographic maps | Blood vessel infl. | High freq. focalization | Topographic map |
|-------------------------|----------|----------|----------------------------------------------------------------------|-------------------|-----------------------------------|--------------------|------------------------|------------------|
| Kaga et al (2000)       | 16 cats  | Left ACx | Subd. Acute & chronic MAEPs                                          |                   |                                   |                    |                        |                  |
| Barth and Di (1990)     | 4 rats   | Right PT | Epic. (subd.) Acute MAEPs                                            |                   |                                   |                    |                        |                  |
| Barth and Di (1991)     | 4 rats   | Right PT | Epic. (subd.) Acute MAEPs                                            |                   |                                   |                    |                        |                  |
| Di and Barth (1991)     | 4 rats   | Right PT | Epic. (subd.) Acute Vibrissa SEPs                                   |                   |                                   |                    |                        |                  |
| Barth and Di (1992)     | 4 rats   | Right SCx| Epic. (subd.) Acute MAEPs                                            |                   |                                   |                    |                        |                  |
| Di and Barth (1993)     | 5 rats   | Right PT | Epic. (subd.) Acute MAEPs                                            |                   |                                   |                    |                        |                  |
| Di et al (1994)         | 7 rats   | Right PT | Epic. (subd.) Acute AEPs, vibrissa SEPs, ASEPs                      |                   |                                   |                    |                        |                  |
| Franowicz and Barth (1995) | 15 rats | Right cNCx| Epip. Acute MAEPs, spontaneous activity                             |                   |                                   |                    |                        |                  |
| MacDonald and Barth (1995) | 4 rats   | Right ACx & SCx | Acute MAEPs, vibrisa MSEPs, spontaneous activity                  |                   |                                   |                    |                        |                  |
| Jones and Barth (1999)  | 7 rats   | Right PT | Epic. (subd.) Acute AEPs, vibrissa SEPs                             |                   |                                   |                    |                        |                  |
| Jones et al (2000)      | 4 rats   | Right PT | Epip. Acute Vibrissa SEPs                                          |                   |                                   |                    |                        |                  |
| Benison et al (2007)    | 11 rats  | Right S1S2, PV | Acute AEPs, vibrisa& electrical/ mechanical stimuli-related SEPs, VEPs |                   |                                   |                    |                        |                  |
| Hollenberg et al (2006) | 4 rats   | Right whisker barrels (SCx) | Acute Whisker-deflection-related SEPs, VEPs          |                   |                                   |                    |                        |                  |
| Kitzmüller et al (2006) | 1 pig    | Left OCCx near midline | Acute Whisker-deflection-related SEPs, VEPs |                   |                                   |                    |                        |                  |
|                         |          |          |                                                                      |                   |                                   |                    |                        |                  |

(Continued)
| Author/et al. (Year) | Subjects | Location | Type | Task | electrodes | spacing (µm) | size | material | type | Analysis | Human application | multiple peaks in topographic maps | blood vessel infl | High frq. focalization | Topographic map |
|---------------------|----------|----------|------|------|------------|-------------|------|----------|-------|----------|------------------|----------------|----------------|----------------|----------------|
| Kitzmiller et al. (2007) | 1 pig | Left OCCx | Subd. | Acute | VEPs | 350 µm | 150 µm | 2 x 4 | Au within PI | Non-commercial | T | Suitable for human (cytotoxicity test) | # | # | # | # |
| Molina-Luna et al. (2007) | 27 rats | MCx | Epid. | Acute & chronic | Stimulation mapping | 100 µm | 640 µm medio-lateral, 750 µm antero-posterior | 72 contacts (64 + 8 (ref.)) | Tinitrite within PI | Commercial | T | Potentially for human | # | # | # | Motor cortical somatotopy with forelimb evoked movements |
| Molina-Luna et al. (2008) | 16 rats | Left cMCx | Epid. | Acute & chronic | Stimulation mapping and motor learning | 100 µm | 640 µm medio-lateral, 750 µm antero-posterior | 72 contacts (64 + 8 (ref.)) | Tinitrite within PI | Commercial | T | Potentially for human | # | # | # | Motor cortical somatotopy with forelimb evoked movements |
| Hosp et al. (2008) | 5 rats | Right cMCx | Epid. | Chronic | Electrical stimulation-related SEPs | 100 µm | 640 µm medio-lateral, 750 µm antero-posterior | 72 contacts | Ti within PI | Commercial | T | Potentially for human | 2 peaks in P1-N1 ampl. map | # | # | # | Limb-stimulation somatotopy & motor cortical somatotopy with forelimb evoked movements |
| Kim et al. (2007) | Monkeys | SMCx unilaterally | Epid. | Acute | Spontaneous brain activity | # | 1 mm | Pt within PI | Non-commercial | T & F | # | # | # | # | Up to 100 Hz, no foc. disc. | # |
| Kim et al. (2009) | Monkeys | # | Subd. | Acute | # | # | # | Pt within PDMS | Non-commercial | T | # | # | # | # | # | # |
| Blakely et al. (2008) | 1 female human patient | Left IFG | Subd. | Chronic | Pronunciation-related \( \mu \)ECOG | # | 3 mm | 8 x 8 | Pt | Commercial/Ad Tech Medical Instruments, Racine, WI | F | For human | # | # | # | Phonomotopy |
| Slutzky et al. (2008) | Rats | Right SMCx | Subd. & epid. | Acute & chronic | SSEP & motor-related potentials | 0.125 mm | 0.5 mm | 1 x 161 x 32 | Medical-grade silicone, Pt/Pt-Ir | Commercial | T & F | # | # | # | Up to 180 Hz, no foc. disc. |
| Slutzky et al. (2010) | Rats | Right SMCx | Subd. & epid. | Acute & chronic | SSEP & motor-related potentials | 0.125 mm | 0.5 mm | 1 x 161 x 32 | Medical-grade silicone, Pt/Pt-Ir | Commercial | T & F | # | # | # | Up to 180 Hz, no foc. disc. |
| Slutzky et al. (2011) | 3 rats | Right SMCx contralateral | Epid. | Chronic | Decoding with movement-related potentials | 100 µm/100 µm/150 µm | 500 µm/700 µm/400 µm | 1 x 16/4 x 16 x 4 | Pt within silicone / PI | # | T & F | # | # | # | Up to 170 Hz, no foc. disc. |
| Kellis et al. (2009) | 2 male human patients | M1 contralaterally | Epid. | Chronic | Movement-related ECoG | # | 2 mm | 32 contacts | # | Commercial (PMT Corp.) | F | For human | # | # | # | Up to 80 Hz, no foc. disc. Percentage of gamma band power distribution |
| Leuthardt et al. (2009) | 1 female human patient | Right M1 | Subd. | Chronic | Movement-related ECoG, EMG | 75 µm | 1 mm (4 x 4 mm²) | 4 x 4 | # | Non-commercial | F | For human | # | # | # | Up to 566 Hz, high gamma show more focal increase in ampl. Movement-related power distribution |

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(Continued)
Table A1. (Continued)

| Author          | Subjects | Location    | Task                            | Ø   | Spacing (covered area) | Size | Material | Type              | Analysis          | Human application | Multiple peaks in topographic maps | Blurred vessels infl | High freq. localization | Topographic maps |
|-----------------|----------|-------------|---------------------------------|-----|------------------------|------|----------|-------------------|-------------------|-------------------|----------------------|-------------------|------------------|-------------------|
| Rubehn et al. (2009) | 1 monkey | Large parts of left hemi. | Subd. Chronic VEPs | 1 mm | 35 × 60 mm² | 252 contacts | Pt within PI | Non-commercial | T&F               | #                | #                   | #                  | Up to 40 Hz, no foc. disc. | Coherence in high-freq. band (60–120 Hz) smaller |
| Wang et al. (2009)       | 1 female human patient | Left MCx anterior to central sulcus | Subd. Chronic Motor cortical activity | 1.5 mm | 4 mm | 16 contacts | #             | #                   | T&F               | For human | 2 peaks in finger-movement-related ampl. map | #                  | #                |
| Vinjamuri et al. (2009) | 1 female human patient | Left MCx anterior to central sulcus | Subd. Chronic Motor cortical activity | 1.5 mm | 4 mm | 16 contacts | #             | Commercial | T&F               | #                | #                   | #                  | T&F               | Finger-movement-related somatotopy (T&F) |
| Wilks et al. (2009)       | #Rat     | #           | Chronic Used for stimulation | 1.5 mm/150 µm | 300 µm/400 µm | 16 contacts | (4 × 4) | Pr-Ir               | Non-commercial | T                | #                   | #                  | #                |
| Blanco et al. (2010)      | 9 human patients | #           | Chronic Spontaneous brain activity | 0.5–1 mm | 16/12 contacts | #             | Commercial | Ad Tech Medical Instruments, Racine, WI | #                | T&F               | #                   | #                  | #                |
| Kim et al. (2010)         | #Cats    | #           | Acute VEPs | 500 µm | 2 mm | 6 × 5 | #             | Commercial | Ad Tech Medical Instruments, Racine, WI | T                | #                | #                   | #                  | #                |
| Viventi et al. (2011)     | 10 cats | #           | Acute Sleep spindles, VEPs, electrographic seizures | 300 µm | 500 µm | 360 contacts | Pt within PI | Non-commercial | T                | #                | #                   | #                  | Visual somatotopy, topographic maps of sleep&seizure components |
| Khodagholy et al. (2011)  | #Rats    | Right SCx | Subd. & epid. Acute SEPs | 20 µm square | 60 µm | 32 contacts | Au, PEDOT:PSS within parylene C | Non-commercial | T&F               | #                | #                   | #                  | #                |
| Thongung et al. (2011)    | #Monkeys | Right SMCx | Epid. Acute & chronic Stimulus-evoked/spontaneous epileptic activity | 300 µm | 1 mm | 32 contacts | Au within PI | Non-commercial | T&F               | #                | #                   | #                  | #                |
| Toda et al. (2011)        | 12 rats | VCx | Epid. Acute & chronic VEPs | 50 µm square | 1 mm (6 × 6 mm²) | #             | #             | T                | #                | #                   | #                  | #                |
| Rouse et al. (2013)       | 3 monkeys | Proximal arm area of M1 & PMd | Epid. Chronic Movement-related μECoG, BMI control | 300 µm | 3 mm | 28 contacts | Pr-Ir | Non-commercial | T                | #                | #                   | #                  | #                |
| Rouse et al. (2016)       | 3 monkeys | M1 & PMd | Epid. Chronic Movement-related μECoG, BMI control | 300 µm | 3 mm | 28 contacts | Pr-Ir | Non-commercial | T                | #                | #                   | #                  | #                |
| Houston et al. (2015)     | 1 male human patient | Left SMCx | Subd. Chronic Movement-related μECoG, BMI control | 1 mm | 3 mm | 8 × 16 | #             | Commercial (PMT Corp.) | T&F               | For human | #                   | #                  | Up to 160 Hz, no foc. disc. |
| Khodagholy et al. (2015)  | 13 rats and 2 human patients | Right hemi. in rats; | Subd. Chronic LFP&LFP-modulated spiking activity | 10 µm square | 30 µm | 256 contacts | Au, Pt within parylene C | Non-commercial | T&F               | #                | #                   | #                  | #                |

(Continued)
| Author          | Subjects          | Location       | Task        | Electrode | Results                                                                 |
|-----------------|-------------------|----------------|-------------|-----------|-------------------------------------------------------------------------|
| **Kellis et al** | 5 human patients  | Right temp. lobe | Subd.       | Acute     | SEPs                                                                    |
|                 |                   |                | Subd.       | SEPs      | 4 µm, 1.5 mm, 10 x 10 (96 used) Pt-zipped silicon, Commercial           |
| **Wang et al**  | 6 human patients  | M1             | Subd.       | Chronic   | Movement-related δECG, BMI control                                      |
|                 |                   |                | Subd.       | Movement-related δECG, BMI control                                    |
|                 |                   |                | Subd.       | δECG      | 2 mm, 4 mm, 8 x 8 Pt, Commercial                                       |
| **Flint et al** | 5 human patients  | M1             | Epid.       | Chronic   | Movement-related δECG, BMI control                                      |
|                 |                   |                | Epid.       | Movement-related δECG, BMI control                                    |
| **Trumps et al**| 3 rats            | ACx            | Epid.       | Chronic   | Movement-related δECG, BMI control                                      |
| **Current study**| 4 minipigs        | Left SCx       | Epid.       | SEPs      | 0.87 mm/1.81 mm, 1.68 mm/3.5 mm, 4 x 8 Medical-grade silicone rubber, Pt/Ir |
|                 |                   |                | SEPs        | δECG      | 200 µm, 3.25 x 3.25 mm², 8 x 8 Au, Non-commercial                      |

* Mean number of the subjects involved in is not specified in the respective study. infl. = influence; frq. = frequency; PT = parieto-temporal areas; SCx = somatosensory cortex; cINCl = caudolateral neocortex; hemi. = hemisphere; S1 = primary somatosensory areas; S2 = secondary somatosensory areas; PV = parieto-ventral areas; OCCx = occipital cortex; MCx = motor cortex; cMCx = caudal motor cortex; SMCx = sensorimotor cortex; IFG = inferior frontal gyrus; M1 = primary motor cortex; PCx = parietal cortex; VCx = visual cortex; PMd = premotor dorsal area; Epic. = epicortical; Epip. = epipial; Subd. = subdural; Epid. = epidural; MAEPs = middle-latency auditory evoked potentials; (S)SEP = somatosensory evoked potentials; AEPs = auditory evoked potentials; ASEP = auditory evoked potentials; VEPs = visual evoked potentials; EEG = electrocorticography; μECG = micro-electrocorticography; EMG = electromyography; BMI = brain–machine-interface; LFPs = local field potentials; Ag = silver; Cl = chlorine; Pt = platinum; Au = gold; Ti = titanium; Ir = iridium; P1 = p1; N1 = n1; P2 = p2; No = n0; IIS = interictal spikes; ampl. = amplitude; foc. = focalization; disc. = discussion; corp. = corporation; diff. = difference; Ø = diameter; # = not referred to in the respective study.
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