Fabrication and validation of reference structures for the localization of subdural standard- and micro-electrodes in MRI

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Abstract

Objective. Report simple reference structure fabrication and validate the precise localization of subdural micro- and standard electrodes in magnetic resonance imaging (MRI) in phantom experiments. Approach. Electrode contacts with diameters of 0.3 mm and 4 mm are localized in 1.5 T MRI using reference structures made of silicone and iron oxide nanoparticle doping. The precision of the localization procedure was assessed for several standard MRI sequences and implant orientations in phantom experiments and compared to common clinical localization procedures. Main results. A localization precision of 0.41 ± 0.20 mm could be achieved for both electrode diameters compared to 1.46 ± 0.69 mm that was achieved for 4 mm standard electrode contacts localized using a common clinical standard method. The new reference structures are intrinsically bio-compatible, and they can be detected with currently available feature detection software so that a clinical implementation of this technology should be feasible. Significance. Neuropathologies are increasingly diagnosed and treated with subdural electrodes, where the exact localization of the electrode contacts with respect to the patient’s cortical anatomy is a prerequisite for the procedure. Post-implantation electrode localization using MRI may be advantageous compared to the common alternative of CT-MRI image co-registration, as it avoids systematic localization errors associated with the co-registration itself, as well as brain shift and implant movement. Additionally, MRI provides superior soft tissue contrast for the identification of brain lesions without exposing the patient to ionizing radiation. Recent studies show that smaller electrodes and high-density electrode grids are ideal for clinical and research purposes, but the localization of these devices in MRI has not been demonstrated.

1. Introduction

Implanted subdural electrodes are increasingly used for diagnosis and treatment of patients with neuropathic pain and neuro-degenerative diseases. For example, electrodes are implanted in the pre-surgical diagnosis of refractive epilepsy (Hermes et al. 2010, Kuß et al. 2011, Yang et al. 2012, Gupta et al. 2014). Electroencephalogram (EEG) measurements with implanted electrodes achieve much higher spatial and temporal resolution of cortical activity than magnetic resonance imaging (MRI) and surface electroencephalographs, and this higher resolution can be used to delineate for example eloquent areas (Nakai et al. 2017). The improved localization of epileptic foci justifies the invasive nature of EEG measurements making epilepsy surgery a smaller, safer, and more
effective intervention (Skoch et al. 2017). Commonly used subdural electrodes, here termed ‘standard electrodes’, have electrode diameters of several mm and an inter-electrode spacing of 1 cm. Aside from epilepsy, ECoGs can also be used intraoperatively during tumor surgery (Berger et al. 1989, Mikuni et al. 2006, Falah et al. 2015), or with long-term placement in chronic pain relief (Fontaine et al. 2009, Mo et al. 2019). Research applications of subdural electrodes comprise the implementation of neuroprosthetics (Ordonez et al. 2012) and brain computer interfaces, where higher density of electrodes (smaller diameters) resulted in better decoding performance ( Muller et al. 2016).

To map cortical functions more precisely, mini-electrode (contact diameter ≤ 1 mm) grids with higher spatial coverage and resolution were proposed (Gupta et al. 2014), which provided more information from the cortical surface than standard grids (Chang 2015). Micro-electrode contacts with diameters of several 100 μm enabled the detection of high frequency oscillations in small nerve cell ensembles (Zijlmans et al. 2017), and ultra-high-frequency recordings up to 800 Hz have been reported using a hybrid ECoG array with standard and mini electrode contacts in patients (Jiang et al. 2018) and up to 2500 Hz in large animal models (Giertmuhelen et al. 2014).

For both, clinical and research applications it is a prerequisite to accurately localize the electrode contacts (Hermes et al. 2010, Dykstra et al. 2012, Yang et al. 2012, Branco et al. 2018b). The value of knowing the position of the electrode contacts, however, is highest when it can be related to the individual cortical anatomy (Gupta et al. 2014).

To document the placement of the electrodes, digital photos are taken during surgical implantation (Hermes et al. 2010). Alternatively, cross-sectional imaging methods such as MRI (Schulze-Bonhage et al. 2002, Yang et al. 2012) or computed tomography (CT) are used for localization (Braithwaite et al. 2016, Zhao et al. 2018, 2019), in which the CT image is often co-registered to the high resolution MRI to overcome the limited CT soft tissue contrast (Hermes et al. 2010, Dykstra et al. 2012, Princich et al. 2013, Taimouri et al. 2014, Blenkmann et al. 2015, Groppe et al. 2017, Hamilton et al. 2017, Laplante et al. 2017, Hinds et al. 2018, Trotta et al. 2018, Branco et al. 2018a). Many recently developed software pipelines pursue the full automation of electrode contact localization, including three-dimensional coordinate registration with respect to the patient’s individual anatomy and ‘normalized’ brain atlas for comparison with the population. These data are subsequently also available for surgical navigation systems (Gupta et al. 2014).

During electrode implantation a piece of the skull is temporarily removed (craniotomy) which can result in unwanted displacement of brain tissue. To minimize this brain shift, electrodes are placed on the brain surface and slipped sideways underneath the skull which makes photographic documentation impossible (Gupta et al. 2014). Prior to the craniotomy, the electrode contact positions are usually mapped to three-dimensional anatomical images from high resolution MRI data sets. This mapping is often done manually using anatomical landmarks such as gyri, sulci and blood vessels for reference (Dalal et al. 2008, Dykstra et al. 2012, Taimouri et al. 2014), and is thus dependent on excellent visibility of the landmarks through the implant. Additional problems for photographic documentation may be intra-operative bleeding and high electrode densities (Gupta et al. 2014, Chang 2015). Yet, photographic localization is still widely considered as the gold standard and serves as ground truth for novel localization approaches (Dalal et al. 2008, Tao et al. 2009, Hermes et al. 2010, Dykstra et al. 2012, Yang et al. 2012, Groppe et al. 2017).

For the localization of mini-electrodes, high resolution CT provides three-dimensional data with good visibility of the metal electrode contacts (Branco et al. 2018a), but the mapping to the anatomy is hampered by tissue deformation, brain shift, and cavities from prior tissue resection. These distortions are not present in the pre-operative MRI data, and, thus, cross-modality image co-registration leads to systematic errors (Yang et al. 2012, Gupta et al. 2014). Also, in this approach the patient is exposed to high doses of ionizing radiation.

Using MRI directly for electrode localization may help to overcome these limitations, and offers updated anatomical data with a high sensitivity for the detection of complications that may have occurred during surgical intervention (Yang et al. 2012). As the onset and progression of neurodegeneration is often monitored with MRI (Cury et al. 2019), it is more sensitive in the detection of post-operative complications, and MR images can be easily co-registered to pre-implantation MRI. In addition, MRI provides neuro-functional examination methods to detect epilepsy foci that can be important for fundamental epilepsy therapy research (Carmichael et al. 2010, Min et al. 2012, Hawsawi et al. 2017).

The trend towards miniaturized electrode contacts makes it more challenging to distinguish between electrode contacts and surrounding tissue. So far, only mini-electrodes could be localized (Hamilton et al. 2017, Branco et al. 2018a); however, this was not possible with MRI. This work proposes a new method for MRI-based localization of standard and micro-sized subdural electrode contacts. Electrode implants were equipped with structures that are visible in MRI, and which are located at a fixed distance to the electrode contacts. Preliminary work served as a proof of concept in an ex-vivo sheep brain setting, where electrode localization was achieved despite the more extreme brain curvature (Erhardt et al. 2017). Here, the fabrication of three different
types of reference structures is described, and their localization precision with MRI is compared to conventional clinical localization procedures.

2. Methods

2.1. Sample fabrication

Subdural electrodes usually consist of a polymer substate with linear or planar arrays of metal electrode contacts. In this work, six different electrode prototypes were fabricated with three types of reference structures: (1) ‘NanoLoc’: superparamagnetic iron oxide (SPIO) nanoparticle (NP) doped silicone; (2) ‘RefLoc’: elevated silicone structures on the passive implant side; and (3) ‘EdgeLoc’: notches at the edges of the silicone slab (figure 1). Each reference structure was equipped either with 4.0 mm clinical standard electrodes or 0.3 mm microelectrodes in a 3 × 3 matrix. For comparison, two commercial electrodes were also studied: ‘AdTech strip’ subdural electrode with four 4.0 mm stainless steel contacts, 2.3 mm opening and 15 mm inter-electrode spacing (TS04R-SS15X-000), and an ‘AdTech grid’ subdural electrode array with 3 × 6 stainless steel contacts with a diameter of 4.0 mm, 2.3 mm opening and 10 mm inter-electrode spacing (EG18S; both from Ad-Tech Medical Instrument Corporation, Racine, WI, USA).

The prototypes were fabricated by laser cutting of silicone rubber and metal foil as described in (Schuettler et al 2005). A ceramic plate was placed on a Laurell WS-650-23B spin coater and spun at 100 min⁻¹ for 15 s while 4 ml of n-heptane diluted silicone rubber (MED1000 medical grade, NuSil Technology LLC, Carpinteria, USA) with a ratio of 1:1 were applied. The spin coater was then accelerated to 2000 min⁻¹ at which it spun for another 90 s, which resulted in a silicone rubber thickness of approximately 30 µm. The silicone rubber was then covered with a 25 µm-thick MP35N metal foil (MP35N®-LTI, Hamilton Precision Metals, Lancaster, US) for the 4.0 mm electrode contacts and a 25 µm Pt/Ir 90/10 foil (Goodfellow GmbH, Hamburg, Germany) for the 0.3 mm electrode contacts. Circular electrode contacts were shaped into the metal foil by a passively mode-locked Nd:YVO4 picosecond laser emitting at a wavelength of 1064 nm, which was frequency-tripled to 355 nm (Rapid 10, Coherent, Santa Clara, USA). Metal tracks were omitted for simplicity. An intermediate cleaning step with a microbrush dipped into isopropanol removed the remaining metal residue. Moreover, the 30 µm silicone layer that covered the electrode contact on the active implant side (targeted tissue side) was not removed to avoid MRI image distortions due to air bubbles acquired during mounting the samples to the phantom. The remaining silicone thickness varied with the reference structure concept implemented on the individual sample. According to (Vomero et al 2020), subdural electrodes should be attached directly to the brain surface as this leads to a better signal recording; thus, the kind of reference structure should be chosen according to the curvature the electrode system is applied to. While the thickness of the EdgeLoc samples was comparable to that of commercial implants, the NanoLoc structures can be shaped freely in all dimensions or deployed in a single spot, which means that the implant thickness can be 50 µm or less. Thus, the implant can be made highly flexible without altering the outside silicone slab shape nor its handling. The following reference structure specific manufacturing process steps have already been used during the electrode fabrication procedure, or, in case of the NanoLoc structures, can be integrated with minimal additional effort.

2.1.1. NanoLoc

For the fabrication of the NanoLoc prototypes, custom made SPIO NPs were prepared by a thermal decomposition of iron oleate precursor that allowed for an in-situ surface functionalized of prepared NPs with oleic acid (supplementary appendix 1, which can be found in the supplementary materials (stacks.iop.org/JNE/17/046044/mmedia)), as previously described (Park et al 2004, Gessner et al 2019). In short, iron oleate was prepared by refluxing 20 mmol of iron(III)chloride hexahydrate (Merck, 99%) and 60 mmol sodium oleate (TCI, > 97%) in a mixture of 70 ml cyclohexane, 40 ml ethanol and 30 ml water at 70 °C for four hours. The received precursor in the organic phase was separated and washed with water, followed by the removal of the solvent under reduced pressure. Magnetic NPs were obtained upon dissolving 5 mmol of the as-received precursor in 98.2 mmol octadecene (Alfa Aesar, 90%) and 5 mmol of oleic acid (Alfa Aesar, 90%) and heating the mixture to 315 °C for 30 min. NPs were precipitated via ethanol and received via centrifugation. Due to the presence of oleate groups on the NP surface, they were easily dispersible in hydrophobic solvents and were stored in n-heptane until their further use. Subsequently, the functionalized NPs were dispersed in n-heptane while being exposed to ultrasound to facilitate the dispersion of the particles. The brown fluid of NPs in n-heptane was then mixed with MED1000 in a 1:1 volume ratio using the same method of preparation as for the silicone rubber. This generated a homogenous dispersion of NPs in the silicone rubber substance with a similar viscosity. The electrode contacts were covered with an extra 140 µm layer of silicone on the inactive side by spin coating (rotation speed of 500 min⁻¹). Then, cross-shaped cavities (cf figure 1) were laser-cut into the silicone slab which were filled with SPIO NP doped silicone rubber via a syringe with a 0.2 mm diameter dispenser needle. The SPIO NP concentration in the silicone was 3 mg ml⁻¹ (or 0.2 wt.%) iron. This NP concentration was chosen as optimal agreement between unambiguity and excessive concealment based on preliminary concentration tests of 8
different concentrations between 0 and 9 mg ml$^{-1}$ (or 0–0.6 wt.% iron (Erhardt et al 2018a)).

2.1.2. RefLoc
In the RefLoc prototypes the electrode contacts were covered with a 140 µm-thick layer of silicone before a superficial layer of MP35N metal was applied. The reference structure shapes were cut into the metal with the picosecond-laser, and the metal in the structure was removed. An additional 500 µm-thick layer of silicone was applied by spin coating, and the samples were left to cure overnight. The 500 µm silicone layer was then cut with the laser using the same shapes as for the previously cut metal, just with an offset of 20 µm to the outside of the structure, so that the laser beam would hit the metal instead of cutting through the entire implant. The excess silicone was then removed with the metal mask.

2.1.3. EdgeLoc
For the EdgeLoc sample fabrication, a 700 µm-thick layer of silicone was deposited on the passive side of the electrode contacts and left to cure overnight. Three reference structures were cut with the picosecond-laser into each edge at the level of the electrode contacts (cf Figure 1), so that the position of the electrodes could be determined from the intersection of the connection lines between the opposite edges. To have exact dimensions of the prototype samples, the thickness of the reference structures was measured five times with digital calipers, and the values were averaged (table 1).

2.2. Experimental setup
As a geometrical reference, a sample holder was constructed of 1 cm thick polymethylmethacrylate (PMMA) board into which 2 × 2 mm$^2$ squared cross-section pillars were milled (figure 2). These PMMA pillars were filled to the top with 1% agarose (Sigma-Aldrich) to provide MRI signal and to prevent aggregations of air bubbles. On the top double-sided adhesive tape was used to mount the electrode samples. The bottom of the pillars was attached to a phantom container using LEGO (Billund, Denmark) bricks. The four liter polyethylene container was filled with tap water to provide an adequate electrical load for

![Figure 1](https://example.com)
Table 1. (Erhardt 2020): Sample dimensions of the implants with reference structures.

|                      | NanoLoc | RefLoc | EdgeLoc |
|----------------------|---------|--------|---------|
| Electrode diameter in mm | 0.3     | 4.0    | 3.0     |
| Electrode material    | Pt/Ir   | MP35N  | Pt/Ir   |
| Total sample thickness in mm | 0.29    | 0.81   | 0.72    |
| Reference structure thickness in mm | 0.29    | 0.51   | 0.75    |
| Reference structure design width in mm | 0.50    | 1+3    | 3.00    |

Figure 2. (Erhardt 2020): (a) Schematic of the phantom with samples (NanoLoc left, RefLoc right) mounted on PMMA pillars. (b) Photo of PMMA pillars with two samples.

2.4. Evaluation of the displacement error by image processing

For reference, a photograph of each electrode sample was taken on the PMMA pillars prior to MR imaging. A digital camera (CANON DSLR type EOS 550D) was used with a macro lens (focal length: 60 mm) that was placed vertically above the sample at a distance of 38 cm. MR images were acquired parallel to the implant plane in three slices showing a cross-section of the PMMA pillars, the implant plane, and artifacts above the implant.

For comparison with the low-resolution MRI data, each reference photograph was scaled down to the MRI matrix size (128 × 256 pixel) such that the PMMA pillars matched in both images. The same scaling and rotation was then applied to the other MRI image data at the implant and the artifact slice, to co-register the reference photographs and MRI images. The displacement error $D$ between the electrode positions on the photograph and the locations in the MRI data was prepared according to the process.
illustrated in figure 3. Note that the electrode contacts in the MRI data were manually localized using the reference structures for guidance by placing markers after drawing connecting lines between the reference structures as indicated in figures 3(e), (f). For the commercial control implants the electrode center was manually selected in the center-of-mass of the MR artifact as is commonly done in clinical practice. Finally, $D$ was determined as the distance between the center-of-mass coordinates of the markers placed on the electrodes in both the photograph and the MR image (cf figure 3(h)), using a Python script (data and code is available upon direct request). The pixel length of this image processing procedure corresponded to 160 $\mu$m and thus exhibited a maximum error of half a pixel—80 $\mu$m.

### 2.4.1. Number of data points.

The AdTech strip with four electrode contacts was imaged four times with four sequences resulting in 16 data points per sequences and 64 for the average displacement error $D$ each in transverse and sagittal orientation (total $n = 128$). Additionally, $D$ of the AdTech strip values was broken down into x- and y-components $D_x$ and $D_y$, to evaluate the orientation-dependency of the susceptibility artifacts (cf figure 3(h)). For the AdTech grid (exhibiting 18 electrode contacts), imaged in four sequences and two orientations $n = 144$ data points were yielded. The same amount applies for the number of contacts localized by one type of reference structures, however, comprising of two different electrode diameters.

### 3. Results

The MR images of the reference structures in sagittal orientation of all imaging sequences (except the EPI sequence) are shown in figure 4, and a selection of EPI images is shown in figure 5. With the conventional clinical imaging sequences in figure 4 the reference structures could be visualized well, whereas the EPI sequence (figure 5) shows severe image distortions due to susceptibility mismatches. Despite that high sensitivity, the 0.3 mm electrodes could not be detected in EPI nor any of the other MR images. Compared to a single average, the GRE acquisition with 16 averages has a higher SNR which resulted in a better delineation that is particularly noticeable at the reference structures. In the SE images, most 4 mm electrodes show a hyperintense rim which has been described for SE-based pulse sequences. With STIR all reference structures are well delineated while the susceptibility artifacts of the electrodes and the SPIO NPs lead to weak image disturbances. Extreme image disturbances in the EPI sequence resulted from commercial implants and the SPIO NPs.

The susceptibility artefact shapes in different slice orientations are exemplarily illustrated in figure 6 with GRE images of the AdTech strip. A metal disc appears more asymmetric in the sagittal view when compared to the transverse orientation. Also, the shape of the NanoLoc structures appeared rounder in the transverse image than in the sagittal one and thus turned the x-shape almost into a square.

### 3.1. Electrode localization

In figure 7 the overall $D$ for the commercial implants and the samples with reference structure is shown for different orientations to the magnetic field and electrode contact diameters. The EdgeLoc system had the smallest overall $D$ of 0.41 ± 0.20 mm ($n = 144$) followed by the NanoLoc 0.56 ± 0.30 mm ($n = 144$) and RefLoc 0.60 ± 0.33 mm ($n = 135$) structures compared to the commercial AdTech strip 1.24 ± 0.59 mm ($n = 128$) and grid of 1.46 ± 0.69 mm ($n = 144$).

The largest $D$ values for all reference structures were found for the 4 mm electrode contacts in transverse orientation. All reference structure systems showed a higher $D$ in transverse orientation of more than 0.2 mm than in sagittal orientation, while this difference lies within the standard deviation. The orientation had minimal effect on $D$ of the commercial implants, the $D$ of the GRE images however differed by 0.4 mm between sagittal and transverse orientation for the AdTech strip (supplementary appendix 2, right).

The overall $D$ was 0.11 mm larger for the 4.0 mm electrode contacts compared to the 0.3 mm electrode contacts localized with reference structures. For the RefLoc system no results could be determined for the 0.3 mm electrodes in the GRE1 images in transverse orientation as the reference structures could not be differentiated from the noise in the image.

No significant differences were found in $D$ for the different sequence types. The electrode diameter had more than 0.1 mm higher $D$ for the 4 mm electrodes...
Figure 3. (Erhardt 2020): Image processing for the evaluation of the displacement error at the example of electrode localization with EdgeLoc reference structures in sagittal orientation imaged using GRE16. (a) Photograph of the implants on the PMMA pillars, the squares clearly visible. (b) Reference position of the electrode contacts indicated by circles and dots. (c) White grid aligned along the edges of the pillars. (d) MRI of the pillar cross section aligned to the white grid. (e) MRI of the implant plane with lines connecting the EdgeLoc structures. (f) Electrode contact markers placed according to connector lines. The markers for the AdTech strip on the top were placed in the center of mass of the imaging artifact. (g) Reference position and markers from MRI localization. (h) Markers on black background for calculation of $D$ using a python script.

when localized using RefLoc and NanoLoc. When comparing $D$ in localization using reference structures with respect to the separate analysis of $D$ in x and y direction for the AdTech strip electrode localization showed on average over all sequences a value of $D_x$ of 1.18 mm and $D_y$ of 0.25 mm (supplementary appendix 2, right). On average, standard deviations were larger for the commercial implants in sagittal orientation (cf. supplementary appendix 2).

4. Discussion

In this work a method for the localization of standard and micro-sized subdural electrodes in MRI images
Figure 4. (Erhardt 2020): MR images of commercial implants and reference structure samples oriented in the sagittal plane while acquired with various sequences.
is proposed. Implants are equipped with reference structures at a fixed distance to the electrode contacts that can be detected in MRI, and the precision of the localization is determined.

The reference structures could be visualized and detected with all sequences except for EPI and GRE1 for RefLoc—0.3 mm—GRE1 in the transverse orientation setting. This result shows that a minimum SNR is required to detect the structures, and even with a short acquisition time of only 23 s (GRE1) this SNR can be achieved (cf Table 2). Increasing the number of averages increases SNR: with 16 averages...
(GRE16) the detection of the RefLoc structures was also possible in transverse orientation (cf figure 4). In a clinical context this 16fold longer acquisition time might not always be acceptable, and the number of averages would have to be carefully selected as a compromise between acquisition time and SNR. Electrode and marker detection with EPI are always challenging due to the strong susceptibility differences of the metal electrodes and the superparamagnetic NanoLoc structures that lead to severe image artifacts which make EPI inappropriate for localization of the electrodes. For fMRI studies with EPI sequences EdgeLoc and RefLoc 0.3 mm electrodes should be preferred as they showed the smallest image distortions. The results of the imaging experiments with conventional gradient and spin echo sequences show that different MR sequences can be used for electrode localization and structural soft tissue imaging in the vicinity of the implants. To localize the electrodes precisely, a single acquisition protocol is sufficient, and artifacts in other imaging sequences might be tolerable.

The $\Delta \chi_v$ between metal and surrounding tissue causes local B-field variation and thereby changes the Larmor frequency near the electrodes. The associated encoding displacement occurs in direction of the frequency encoding gradient (Schenck 1996) explaining the more than factor 4 larger $D_x$ than $D_y$. The asymmetric imaging artifact that cause eccentric display of the electrode contact (cf figure 6) results in inaccurate marker placement of manually localizing subjects. Both effects can be reduced by increasing the readout bandwidth as seen in the STIR images of the NanoLoc structures where the artifacts hardly exceed the reference structures (figure 4). The requirement of stronger gradient amplitudes may be restricted by hardware, potentially occurring peripheral nerve stimulation in the patient and shorter read out time that is associated with a decrease in SNR.

A higher displacement error $D$ is observed in transverse orientation for all experiments except for the SE images of the AdTech grid, where the imaging artifact showed signal hyperintensities. These strong signals may not have been considered an artifact during manual marker detection—this shows that for localization additional reference structures combined with a user-independent automatic detection might be advantageous over manual detection of the electrode artifacts.

Electrode contact localization can be improved by matching the magnetic susceptibility of the reference structures with that of the surrounding tissue ($\Delta \chi_v$ of silicone to water is 0.927 ppm (Wapler et al 2014)) as is the case with RefLoc and EdgeLoc. With NanoLoc, the superparamagnetic NPs cause a strong susceptibility artifact, but the concentration of NPs could be varied to adjust the artifact size such that the reference structures can be identified unambiguously and precisely without being concealed by the surrounding tissues. However, both reference structures enabled the localization of micro and standard electrode contacts in a 1.5 T system in clinically acceptable acquisition times with a higher precision than reported to date.

Due to partial volume effects, the detection of the reference structures in the localizer images is strongly affected by the voxel size. EdgeLoc samples have been imaged with thicker slabs and a parallel orientation of the edges of the reference structure, whereas RefLoc and NanoLoc structures have a more diagonal orientation of the edges—this could explain the higher precision of the EdgeLoc localization (0.41 ± 0.20 mm) over RefLoc (0.60 ± 0.33 mm) and NanoLoc (0.56 ± 0.30 mm) (Mulder et al 2019).

When comparing the results for two electrode diameters, the microelectrodes showed a 0.11 mm smaller localization even though the same reference structures were used. The difference is more pronounced for electrodes with Refloc and NanoLoc, as the stronger susceptibility artifacts of the larger electrode diameters lead to a more pronounced local image distortion.

As expected, a smaller localization error was found for electrodes with reference structures, even if these structures were detected manually which always introduces additional errors. To overcome these limitations, a user-independent automatic electrode localization using, for example, phase-only cross-correlation algorithms (De Oliveira et al 2008) could be applied which provides sub-pixel precision in the localization without the need for user interaction.

The material for the geometrical reference, PMMA, was chosen for its small $D$ to water of ~0.023 ppm (Wapler et al 2014). The resulting displacement in the MRI image calculated for 1.5 T and the lowest bandwidth of 130 Hz per pixel used equals 11.3 $\mu$m and was thus neglected. The periodic nature and known dimensions of the grid enabled easy detection for an overlay of a virtual periodic grid (figure 3(c)) that matched both, the pillars in the reference photo and the MRI data and thus fulfilled its purpose as a reference geometry. No relevant barrel or pincushion shaped distortion in its photograph was found. The maximum error of 80 $\mu$m inherent to the Python script calculation was neglected.

### 4.1. Reference structures

The use of reference structures has the potential to minimize localization errors: for standard electrode diameters the error could already be reduced to about 30%, and microelectrodes that were not visible in the MRI images could be localized indirectly.

While CT-based localization methods have been subject to considerable attention recently, this study avoids any ionizing radiation by using an MRI-based
localization. Despite the use of diagnostic use of MRI in clinical practice, only a few studies report on subdural electrode localization with MRI, probably due to the associated risk of thermal injury for patients (Carmichael et al 2008, Johannes B. Erhardt et al, 2018, Erhardt et al 2019). A retrospective study in 1999 in 108 patients claimed electrode localization with MRI to be safe (Davis et al 1999). The first systematic experimental study addressing thermal safety of cortical grids in MRI was published in 2008, providing safety recommendations for MRI at 1.5 T and 3 T (Carmichael et al 2008, Vulliemoz et al 2011). In 2012 Yang and coworkers reported no adverse outcomes in over one thousand patients with subdural electrodes as a result of MRI (Yang et al 2012). Up to the time being, to our knowledge no adverse events related to MRI have been reported.

So far, the use of reference structures for electrode contact localization in MRI has not been reported. Yang and coworkers achieved a spatial accuracy of 0.96 ± 0.81 mm across 271 electrodes by manually selecting 2–3 electrode positions prior to determining the remaining electrode positions of an entire grid with a software pipeline. Their precision compares well to the D found here for the AdTech grid of 1.46 ± 0.69 mm (n = 144 electrode contacts), especially when considering that the localization was performed manually by an untrained user. Also, our values were averaged over two orientations and four different sequence parameter settings recorded with a 1.5 T system, whereas Yang et al reported T1 weighted imaging in either 1.5 T or 3 T depending on availability. Note that the electrodes in this study were placed on a two-dimensional space. Regarding the field strength of the MRI system used, it was demonstrated that detection of reference structures is feasible at 1.5 T. While this behavior cannot be simply transferred to 3 T, higher field strengths are expected to further improve detection of reference structures and thus localization precision while manual localization without reference structures may be subject to higher displacement errors due to larger electrode induced imaging artefacts. The distance between reference structures and electrode contacts could easily be adapted.

Yang and coworkers reported a higher precision of their method compared to post-implantation CT methods that relied on co-registration with pre-implantation MRI images (Yang et al 2012). Even higher precision might be achieved by combining the use of reference structures and their detection with automatic algorithms for initial gross localization, and continuing for the remaining with the proposed software pipeline. Since reference structures showed even higher precision for the localization of 0.3 mm electrode contacts compared to standard sizes, the localization of high-density grids and ultra-high-density electrode arrays appears feasible with MRI.

5. Conclusion

Reference structures enable the precise localization of micro- and clinical standard electrode contacts in MRI. The superior soft tissue contrast of MRI might improve sensitivity for surgical complications after implantation, and it avoids systematic errors from cross-modality image co-registration which are present in CT-based localization methods. Further experiments are necessary to prove the accurate localization of (ultra) high-density grids.

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