

Magnetic Resonance Identification Tags for Ultra-flexible Electrodes

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Additional Declarations:

Yes there is potential Competing Interest. The authors Tansel Baran Yasar, Peter Gombkoto, Eminhan Ozil, Wolfger von der Behrens, and Mehmet Fatih Yanik have filed a patent application (EP24176952) for the corresponding technologies "Ultra-flexible tentacle electrodes (UFTes)" and "Magnetic resonance identification tags" that are mentioned and described in the manuscript.

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Magnetic resonance identification tags for ultra-flexible electrodes

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Abstract

Ultra-flexible electrodes, due to their superior biocompatibility, are likely to lead the future of neuroprosthetics. However, identifying the locations of high-density ultra-flexible electrodes in the brain for accurately assigning neural signals to specific structures remains a major challenge. To address this, we developed magnetic resonance identification (MRID) -tags. Each ultra-flexible electrode bundle carries an MRID-tag with unique barcode patterns visible in MRI (MRI-barcode) for identification of the bundle and the anatomical positions of individual electrodes. We generate the MRI-barcode by patterning superparamagnetic iron-oxide nanoparticles into electrode fibers (10 μ m²) with dot-matrix nanoparticle coating technique. We chronically tested MRID-tagged ultra-flexible electrodes *in vivo* in the dorsal hippocampus of freely-moving rats, where distinct electrophysiological landmarks validated our electrode localization results. We were able to localize individual electrodes with a mean accuracy of 83 μ m. MRID-tagged ultra-flexible electrodes demonstrated months-long recording stability with mean single-unit signal-to-noise ratios as high as 20.

Introduction

High-density distributed single-neuron level electrophysiology is an important tool for understanding brain functions and disorders in basic research, and for improving the quality of diagnosis and therapeutics in clinic¹⁻⁶. Various electrophysiological probes have been developed with different mechanical/material properties, geometries, and electronics to achieve high-density distributed electrophysiology^{3,7,8}.

While each technology has its own strengths and limitations, flexible probes are increasingly favored for their minimal footprint ($< \sim 1000 \mu\text{m}^2$) and improved biocompatibility⁸⁻¹⁰. Stiff probes (e.g., silicon probes) often cause significant glial scarring¹¹, and recording drifts due to brain micromotions⁷. This reduces the signal-to-noise ratio (SNR) of recordings and the total number of recorded single neurons over time. In contrast, flexible probes ensure a stable recording capability over long implantation durations⁹.

Previously, we developed the ultra-flexible tentacle electrodes (UFTEs) along these lines to achieve arbitrary depth penetration capability, minimal electrode footprint, high-density, distributed, exceptionally high SNR, months-long brain activity recordings facilitated by a novel implantation technique⁹.

Identifying the exact locations of implanted electrodes in the brain is important to accurately interpret the recorded data and to stimulate only desired brain structures. Error-prone surgical procedures, patient-to-patient morphological variance and vasculatures through the implantation trajectory introduce error and variance to each electrode implantation. In human microwire recordings (guided through clinical depth electrodes), microwires randomly spread into the tissue as they are inserted, where precise location of each electrode channel remains unknown, leading to major uncertainties in the interpretation of precise brain structure and functional associations^{12,13}. The variance and error increase with high-density distributed implantations. To overcome this, in clinical and non-human primates (NHP) studies, noninvasive imaging techniques such as computed tomography (CT) and MRI are essential for *in vivo* electrode localization¹⁴⁻¹⁶. However, the micron-scale footprints of ultra-flexible electrodes make it impossible to identify their locations in the brain after implantation, even post-mortem. Yet, a reliable *in vivo* localization technique for ultra-flexible electrodes is essential to translate them to clinical practices and NHP studies.

Here, we developed magnetic resonance identification (MRID) tags to identify UFTE bundles and localize electrode channels in MRI. MRID-tags are made of T2/T2* contrast agents i.e. superparamagnetic iron(II, III)-oxide nanoparticles (IONPs)¹⁷⁻²⁰ (Fig. 1A). We coat IONPs into individual ultra-flexible electrode fibers in unique barcode-like patterns as dot-matrices (Fig. 1A). Each dot in the matrix is an assembly of thousands of IONPs, as shown in Fig. 1A. We achieve precise assemblies using a dot-matrix nanoparticle coating technique adapted from the topography-controlled capillary and convective assembly (CCA)²¹⁻²³ techniques.

We implanted MRID-tagged 64-channel UFTEs in rat brains (Fig. 1B). Each implanted UFTE bundle carries a unique MRID-tag (i.e. with a unique MRI-barcode) for identification (Fig. 1C) and reconstruction of implantation trajectory in MRI space. Positions of electrodes are determined based on their relative distances in each MRI-barcode and subsequently

registered to the Waxholm Space (WHS) atlas for anatomical labeling with laminar precision (Fig. 1C)²⁴

We validated the accuracy of MRID-based electrode localization by LFP and single-unit neuronal recordings along the longitudinal axis of electrodes, using the well-defined electrophysiological landmarks in the dorsal hippocampus (dHPC)^{25,26}. Different lamina of CA1²⁷ and dentate gyrus (DG)²⁸ exhibit distinct oscillations—theta rhythms and sharp-wave ripples (SWRs)—providing cellular-resolution information about the locations of electrode sites^{6,25,26,29–31}.

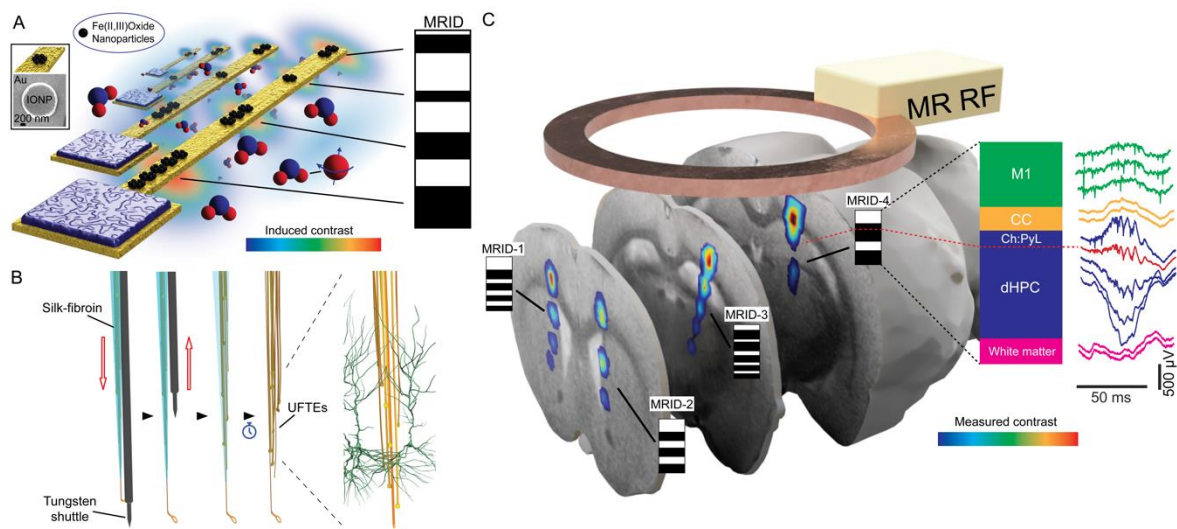


Figure 1. MRID-tags allow high-resolution identification of ultra-flexible electrodes in the brain. **A.** Iron-oxide nanoparticles (IONPs) are wafer-level patterned on ultra-flexible electrode wires as a dot-matrix. The SEM image shows a sample dot where IONP is clustered circularly. IONP patterns on electrode wires induce unique barcode-like patterns locally in structural MRI images by reducing the T2/T2* relaxation time of neighboring water protons. **B.** Ultra-flexible tentacle electrode (UFTE) bundles are coated with silk fibroin and hooked to a tungsten shuttle⁹. The tungsten shuttle pushes the compacted UFTE bundle into arbitrary depths in the tissue and gets retracted, leaving the UFTE bundle in the tissue. Silk-fibroin dissolves over time, leading UFTE fibers to integrate into tissue⁹. **C.** MRID-tagged multiple UFTEs implanted for distributed recordings. Each UFTE bundle has an MRID-tag with a unique pattern for identification. MRID-tags, furthermore, carry information about the precise positions of the individual electrode channels within the brain.

Results

Dot-matrix nanoparticle coating for MRID-tag fabrication

We wafer-scale microfabricate UFTEs with MRID-tags⁹ as illustrated in Fig. 2A (Methods). Following the deposition of the bottom polyimide, titanium (Ti) and gold (Au) layers, MRID-tags are fabricated by patterning IONP layers on the Au structures. The top polyimide layer

encapsulates the IONP and Ti/Au structures. We etch the polyimide to construct the mechanically independent fibers and expose the active recording areas. Finally, PEDOT:PSS is coated onto active recording sites to lower the electrical electrode-tissue impedance.

We coat IONPs (25 nm in diameter) modularly in physically independent micrometer scale ($\sim 2\ \mu\text{m}$) circular assemblies (i.e. dots) on Au wires of individual electrode fibers (Fig. 2A&B, Methods). We construct barcodes from millimeters-wide coatings of clusters of micron-scale dot-matrices. We coat a thin positive photoresist layer on the sample to define recessed dot-matrix topography (Fig. 2A, B, Methods). The dots are well aligned and positioned on the Au wire tracks, as shown in Fig. 2A, with lithography. After developing the dot-matrix pattern on the photoresist, we expose the Au layer beneath, as shown in Fig. 2A.

We inject a fixed amount of IONP colloidal suspension in dH_2O , which covers all the UFTE fibers to be coated, in between the sample and the horizontal confinement slide (Fig. 2B). The sample is moved linearly at a constant speed in the direction of the leading edge of the colloid meniscus, creating a dragging movement of the meniscus over the recessed dot-matrix topography on the sample (Fig. 2B). The meniscus pins at the upper-edge while the nanoparticles are accumulated in the trap due to laminar flows^{21,22} (Fig. 2B). The trailing edge of the trap prevents nanoparticles from escaping (Fig. 2B). When the pinning breaks, the meniscus fully detaches from the corresponding trap, leaving a fixed volume of colloidal suspension in the trap. As the water evaporates, a micro-scale drop-casting-like assembly happens. Our results show that IONPs in each dot form a crater shape (Suppl Fig. 1B). This suggests that a drop-casting-like assembly is occurring in circular traps with the trap diameters we used in this work.

When traps are large enough, we hypothesize that the meniscus makes an intermediate contact with the Au surface below (Fig. 2C). We observed results suggesting this was the dominant mechanism when we used elongated (e.g. strips) traps in the matrix instead of dots (Suppl Fig. 1C). We observe that the porous Au surface is more hydrophobic with increased contact angles varying between $40\text{-}60^\circ$ (Fig. 2C). Possibly, a capillary dominant assembly occurs at that contact angle so that the porous structure acts as a capillary trap. Finally, the trailing upper-edge of the photoresist breaks the meniscus, leaving a fixed volume of colloidal suspension in the trap, resulting in a local drop-casting-like assembly.

Before the IONP coating, we chemically roughen the exposed gold surface at the dots to create a rough and porous gold surface (Methods). After the etching, pores with sizes within $<100\ \text{nm}$ range are formed (Fig. 2C inset). The porous surface increases the effective surface area for weaker Au- Fe_3O_4 bonds compared to $\text{Fe}_3\text{O}_4\text{-Fe}_3\text{O}_4$ bonds (Fig. 2C). Therefore, the IONP assemblies adhere stronger to the Au surface thanks to the increased effective surface area. Strong adhesion is critical for later when the sacrificial photoresist layer is lifted off chemically so that IONP assemblies remain on the Au surfaces.

After the coating, we chemically (i.e. wet lift-off) remove the photoresist layer and excess IONPs. According to our observations, a low-vapor pressure (i.e. less-volatile) organic solvent is necessary to re-disperse excess nanoparticles following the dissolution of the photoresist to prevent excess nanoparticles from adhering to undesired locations on the surface. We apply gentle mechanical agitations to help the re-dispersion of excess IONPs in the organic solvent

during lift-off. We achieve a clean lift-off with this method, which only leaves the desired IONP dots on the surface, as observed in the SEM images in Fig. 2D.

We coated IONPs successfully on smooth Au, roughened Au and polyimide surfaces (Fig. 2D). By increasing the surface area between IONP and Au surfaces, we ensure a stronger adhesion of IONP assembly to Au surface. We were also able to coat IONPs in different diameter circular traps (1.25, 1.7, 2 μm after the development) reliably, as shown in Fig. 2E.

Coated circular IONP assemblies well-align to the existing Au wires on the sample (Fig. 2F, top panel). In Fig. 2F (center and bottom panels), the microscopy images show millimeter-scale barcode patterns formed by the circular IONP assemblies where the inset images show the actual design layouts for each barcode pattern.

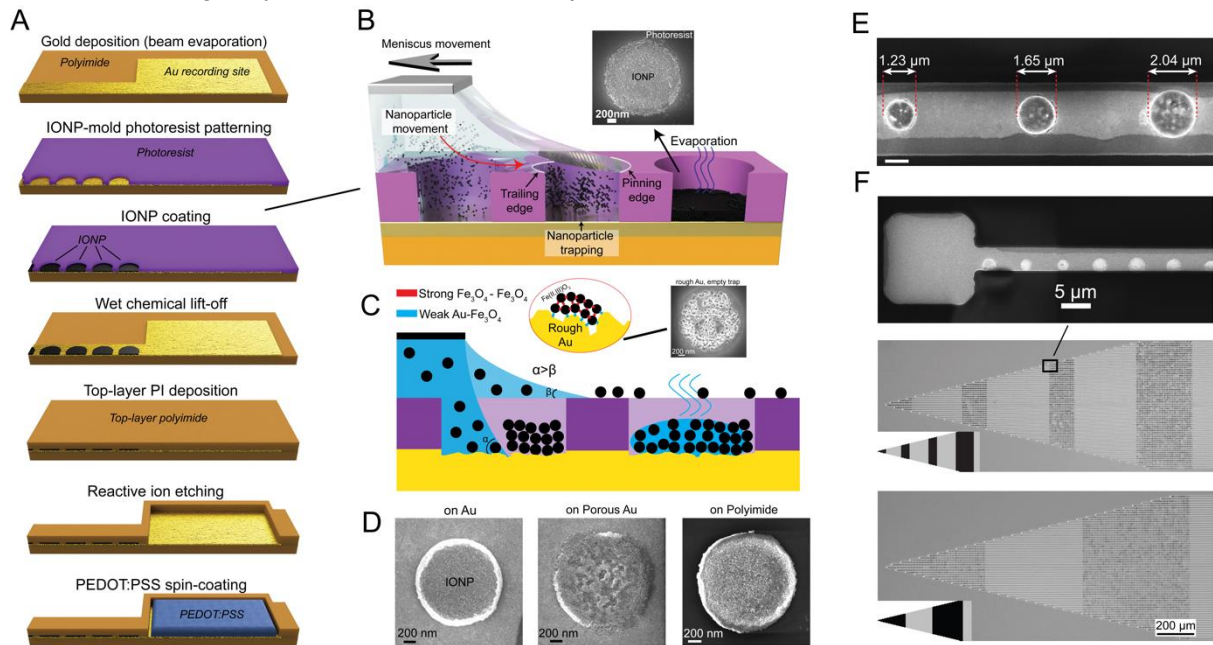


Figure 2. Microfabrication and characterization of ultra-flexible electrodes with MRID-tags. **A.** Microfabrication steps from top to bottom; gold deposition, photoresist patterning to form recessed dot-matrix template for IONP coating, IONP coating, photoresist and excess IONP lift-off, polyimide deposition, polyimide etching for mechanically independent fibers and exposed Au surface at active recording site, PEDOT:PSS coating onto active recording sites. **B.** Dot-matrix CCA explained. IONP colloidal suspension in between the confinement-slide and substrate forms a meniscus. The meniscus drags over the dot-matrix. Nanoparticles migrate into the molds due to laminar flow. SEM shows IONP assembly in a mold. **C.** Intermediate hybrid meniscus explained. Roughened porous Au surface is hydrophobic and makes a larger contact angle ($\sigma \sim 40\text{-}60^\circ$, $\beta \sim 20^\circ$) with the meniscus. Porous surface acts as vertical confinement yielding capillary assembly. Porous surface also increases the surface area between Au surface and Fe_3O_4 (i.e. IONPs). Excess water evaporates from remaining dispersion, constructing a multi-layer IONP assembly in disk shape. **D.** SEM images show the IONP coating tested on different surfaces, left to right: e-beam evaporated Au, roughened porous Au, and spin-coated hydrophobic polyimide surfaces, respectively. **E.** SEM image shows the different sizes of circular assemblies tested. 1.25, 1.65, and 2.00 μm circular IONP assemblies (1, 1.25, and 1.50 μm dots on photomask, slight lateral enlargement is observed due to development). **F.** IONP coating alignment and patterning results. SEM image of a circular IONP assembly shown aligned on Au wire (top panel). The center and bottom panels

show millimeter-scale patterns on UFTE bundles. A pattern with 4 bars (center) and a pattern with 2 bars (bottom) are shown from optical microscope images where the insets (bottom-left for each microscopy image) show the actual design layouts.

MRI characterization and Channel Mapping

Fig. 3A illustrates the MRID-tag concept. IONPs are wafer-scale coated on Au wires in dot-matrices to form barcode patterns in 2-dimensional (2D) layouts. When we remove UFTEs from the wafer, individual fibers collapse into a linear bundle⁹. Bundle formation reduces the lateral gap between IONPs in individual fibers. Since lateral and vertical separation ($< \sim 5 \mu\text{m}$) between individual IONP circular assemblies are almost two orders of magnitude smaller than MRI voxel sizes, we can assume dot-matrix coated IONPs as single solid-body assemblies of IONPs (i.e. *IONP islands*) in MRI space. The center of mass (CoM) of each IONP island can be precisely calculated from the 2D design layout. The thickness of the UFTE bundle scales with the number of fibers: In this experiment with 64-channels UFTE bundles, the bundle thickness (area $< 1000 \mu\text{m}^2$) is smaller than a single voxel in MRI. The longitudinal lengths of IONP islands are an order of magnitude larger than bundle thicknesses. Under these assumptions, we can model the UFTE bundles as a 1-dimensional (1D) fiber expressed by CoMs.

We imaged the T2*-weighted contrast by MRID-tags (*Methods*) at increasing TEs. IONP islands induce spatially continuous contrasts around them with the contrast intensity as a function of the density of dots and distance from the island (Fig. 3A). Induced continuous contrasts follow 2D Gaussian functions where the peak contrast intensity is centered at CoM of a given IONP island. We find the best-fit 2D Gaussian curves explaining the contrast of each IONP island to estimate the CoM positions (i.e., centers of 2D Gaussian fits) in MRI (Fig. 3A). We reconstructed the barcodes starting from the deepest (i.e. ventral) IONP island, where bars are centered at estimated CoMs with a width of 2σ of corresponding best-fit Gaussian (Fig. 3A, *Methods*).

Sample *in vivo* results from an implanted bundle with quad-pattern barcode MRID-tag is given in Fig. 3B. Multiple images with increasing TE show the spatial and temporal dynamics of induced contrast (Fig. 3B). To characterize the induced patterns, we detected the contrastive pixels with pixel intensity lower than -2 z-score of the intensity distribution of baseline (Fig. 3B) which is the anatomical area where the pixel is located. IONP islands with lower IONP density become detectable at increasing TEs (Fig. 3B, IONP island 1).

We quantified the contrast level of each pixel around MRID-tags with a sliding window and created heatmap-like contrast maps around MRID-tags (*Methods*, Equation 2, Fig. 3B). The heatmap contrast map reveals the induced 2D Gaussian-shaped contrasts, which we can use to find the best-fit (Fig. 3B).

We reconstruct the implantation trajectory with best-fit Gaussian centers (i.e. estimated CoMs) in 3D MRI space (Fig. 3B). We compared the distances between estimated CoMs on reconstructed trajectory to the actual distances between calculated CoMs on the design layout ($n=5$ bundles, *in vivo* data). We found a median $28.70 \mu\text{m}$ ($n=16$, number of IONP islands) difference between the calculated and estimated inter-CoMs distances. (Fig. 3C).

222

223 We position the actual trajectory that is defined by calculated CoMs in 3D MRI space near the
224 reconstructed trajectory (Fig. 3D, Methods). We use a point-set registration to find the best-fit
225 of actual trajectory on the reconstructed trajectory (Methods) which minimizes the total sum of
226 distances between each calculated and estimated CoM pair (Fig. 3D) while keeping the
227 dimensions of the actual trajectory based on the predefined constraints (Methods). The
228 registration converges to a global minimum when more than 3 IONP islands are present in an
229 MRID-tag.

230

231 For individual electrode localization, we position each electrode channel on the best-fit
232 trajectory in 3D MRI space by their relative known distances (from design layouts) to each
233 calculated CoMs (Fig. 3B, D). We then warp the pixel coordinates of each electrode to the
234 WHS to anatomically label each electrode channel (Fig. 3D, Suppl. Fig. 3).

235

236 We compared the measured contrast intensities to the coated IONPs densities (n=4 bundles).
237 We define a region of interest (ROI) that is big enough and centered to cover the entire IONP
238 island to measure and quantify the mean contrast intensities (Methods). We set the IONP
239 density as the number of IONP dots that are in the given ROI divided by the number of pixels
240 of the ROI ($\# \text{ of IONP dots} \times \text{pixel}^{-1}$). We observe a perfectly linear correlation between our
241 IONP density to the induced contrast intensities (Fig. 3E).

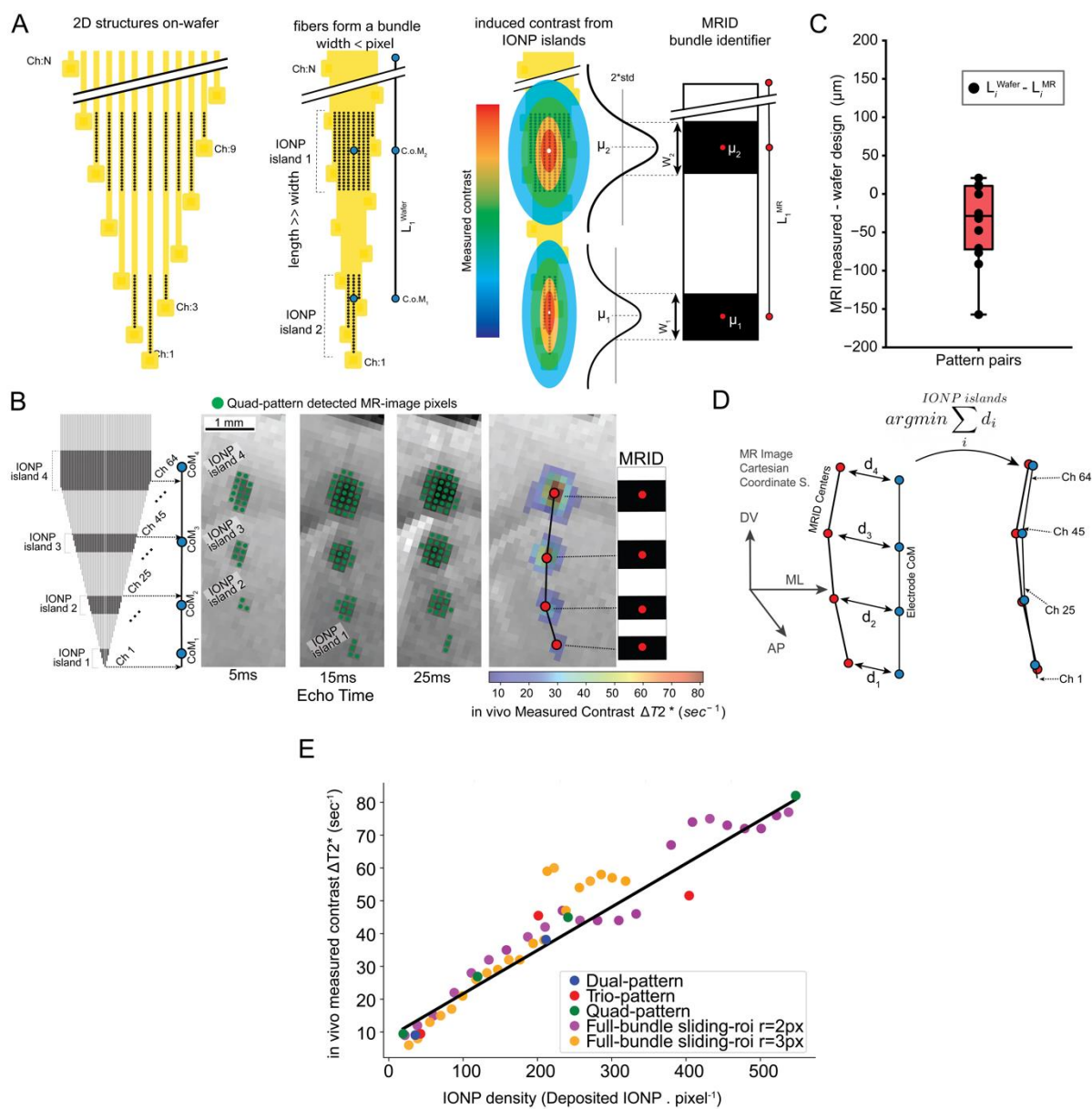


Figure 3. Localization of MRID-tagged electrode channels within the brain by MRI. A. Left-to-right: IONPs (**black**) coated on Ti/Au (**yellow**) wires on 2D fabrication layout. Bundle formation of independent fibers. Centers-of-masses (CoMs) (**blue dots**) of the IONP islands are calculated from the 2D layout. 1D-track defined by the CoMs is shown. IONP islands induce MRI contrasts which are centered at the CoMs. Gaussian curves are fitted onto measured contrasts. Curve centers (**red dots**) reconstruct the trajectory of the bundle in MRI space. MRID-barcode is reconstructed with the centers and 2σ of the fitted curves in the longitudinal axis. **B.** 2D layout for Ti/Au tracks (**light gray**) and circular IONP islands (**black**) of the sample MRID-tag on the left-most panel. CoMs (**blue dots**) were calculated and constructed a 1D track. Channels are mapped onto the 1D track. *In vivo* results at echo timepoints (5, 15, and 25ms) show the induced contrasts from IONP islands. Pixels with intensities < -2 **z-score** of the baseline ($n > 100$ pixels for baseline, depending on the size of the baseline anatomical region) are detected as contrastive pixels. MRI contrast by MRID-tags is shown as a heatmap, 2D Gaussian curves are fitted on each island (curve centers: **red dots**). MRID-barcode is reconstructed. **C.** Accuracy of reconstructed bundles. Each dot represents the length difference (μm) between consecutive CoMs ($L_i^{\text{Wafer}} - L_i^{\text{MRI}}$). **D.** Channel mapping explained. Reconstructed trajectory (**red dots**) is in 3D MRI space. Actual trajectory is transferred into the MRI space to an arbitrary initial position. The best fit of the calculated trajectory on the measured trajectory is found. Channels are linearly interpolated along the best-fit trajectory with their relative distances to calculated CoMs. **E.** *in vivo* measured MRI contrast levels as a function of IONP coating density showing the linear correlation with best-fit line (**black**).

Validation of localization with electrophysiology and histology

We validated the accuracy of MRID-based electrode localization with electrophysiological landmarks in the dHPC, a region characterized by well-defined oscillatory signatures and neuronal firing patterns during sharp-wave ripples (Fig. 1A,C)^{6,25,26}. After we localize the electrodes by MRID-tags (Suppl. Fig. 3), we identify the electrode channels in CA1 pyramidal layer (PyL) via WHS diffusion-weighted images by finding the pixel intensity minimum along the 1D registered trajectory in dCA1 (Fig. 4B). The hippocampal fissure (HF) served as the second landmark, defined by the border between CA1 and DG^{6,25,32} based on WHS anatomical labels. Following the MRI-based identification of electrode channels located at the dCA1 PyL and HF, we used hippocampus-specific electrophysiological landmarks to identify corresponding contact sites. The highest ripple power was detected at 184.14 Hz in CA1 PyL ($n = 463$ SWRs; Fig. 4C, first column, red arrow), designating this site as the dCA1 PyL reference point (0 μm in Fig. 4C, second panel). We compute phase differences of theta cycles relative to the PyL as reference ($n=2303$, peak at PyL: 0° , Methods). A progressive phase shift is observed from 0° in the CA1 PyL toward dorsal channels (Fig. 4C). This shift is accompanied by an initial increase in theta amplitude, peaking near superficial CA1 before declining significantly beyond the HF. The maximum theta power channel is identified (Fig. 4C, **black "X"**), and theta power changes across channels are used to functionally locate the HF. A significant drop in theta power (z-test, $p < 0.0015$; CI [0.0570, 0.1689]; $z = 3.1786$) and a saturated phase shift mark the putative HF position (Fig. 4C, **blue circle**). The average phase difference between the CA1 PyL and the HF was 150.92° ($n = 3$ bundles), with individual bundle values as follows: Bundle 1: $167.77^\circ \pm 14.40^\circ$ ($n = 2306$ cycles), Bundle 2: $146.81^\circ \pm$

19.93° (n = 2303 cycles), Bundle 3: 138.20° ± 25.57° (n = 397 cycles). To assess the accuracy of MRI localization, we measured the distances between MRI-detected and electrophysiologically-detected PyL and HF as the error (mean = 100 μm, SD = 86.6 μm for dHPC PyL; mean = 66.66 μm, SD = 57.73 μm for HF, n=3 bundles, Fig. 4D).

The first column of Fig. 4E illustrates representative spike waveforms ($V_{\text{peak-to-peak}} > 200 \mu\text{V}$) aligned with their respective assigned structural labels (M1, CA1, DG) based on contact site locations. The PyL in CA1 and DG regions are distinguishable based on neuronal density, with a short gap before neurons reappear in the DG. The first neuron, located in the CA1 PyL based on electrophysiological analysis (i.e., maximum ripple power amplitude in CA1), is at the 0 μm position. The Fig. 4E second column presents the mean amplitudes of spike waveforms recorded as high as 800 μV. Fig. 4F displays the correlation matrix derived from binned (2 ms) spike data, which was subsequently analyzed using hierarchical clustering (Suppl. Fig. 4.1, Methods). This analysis aimed to distinguish stronger intra-areal correlations from weak inter-areal correlations and to identify putative structural borders. Hierarchical clustering of neuronal activity correlations revealed three distinct functional clusters (Methods). We assessed the homogeneity of MRI-based anatomical labels (M1, CA1, and DG) within each functional cluster. The clustered neurons matched the M1 label in 10 out of 13 cases. According to the MRI atlas, two unmatched neurons were located in the CC - an anatomically improbable location for single neuron recording- and one was assigned to a CA1-labeled site. In CA1, 12 out of 13 CA1 neurons were correctly matched. These discrepancies occurred at the anatomical borders and remained within the error margin that is consistent with the single-voxel resolution of MRI. 28 out of 28 DG neurons were correctly matched. The overall **classification accuracy (correct/total)** was **92.59%**.

PCA-k-means clustering of neuronal firing patterns during SWRs revealed significant increases in firing rates in neurons recorded from CA1 and DG contact sites (MRI-labeled), whereas M1 (MRI-labeled) neurons showed no significant changes (Fig. 4G, Suppl. Fig. 4.2; Methods). M1 neurons: No significant modulation during SWRs (z-scored firing rate: SWR = 0.1244 ± 0.1229 , Spontaneous = 1.0067 ± 0.3569 ; $t(20) = 2.5446$, $p = 0.0193$, two-sample t-test $\alpha = 0.01$). DG neurons: Increased firing during SWRs (z-scored firing rate: SWR = 1.0067 ± 0.3569 , Spontaneous = -0.1162 ± 0.0196 ; $t(20) = 10.4181$, $p = 1.58 \times 10^{-9}$). CA1 neurons: Strong activation during SWRs (z-scored firing rate: SWR = 1.3084 ± 0.6125 , Spontaneous = -0.1539 ± 0.0147 ; $t(20) = 7.9164$, $p = 1.3 \times 10^{-7}$). Neurons recorded from CA1 and DG sites are functionally engaged during SWRs. In contrast, M1 neurons did not exhibit SWR-related activity. These findings confirm the accuracy of MRI-based localization.

After five months of chronic experimentation, we performed electrolytic brain lesions to image the trajectory of electrodes in immunohistological images (Suppl. Fig. 5).

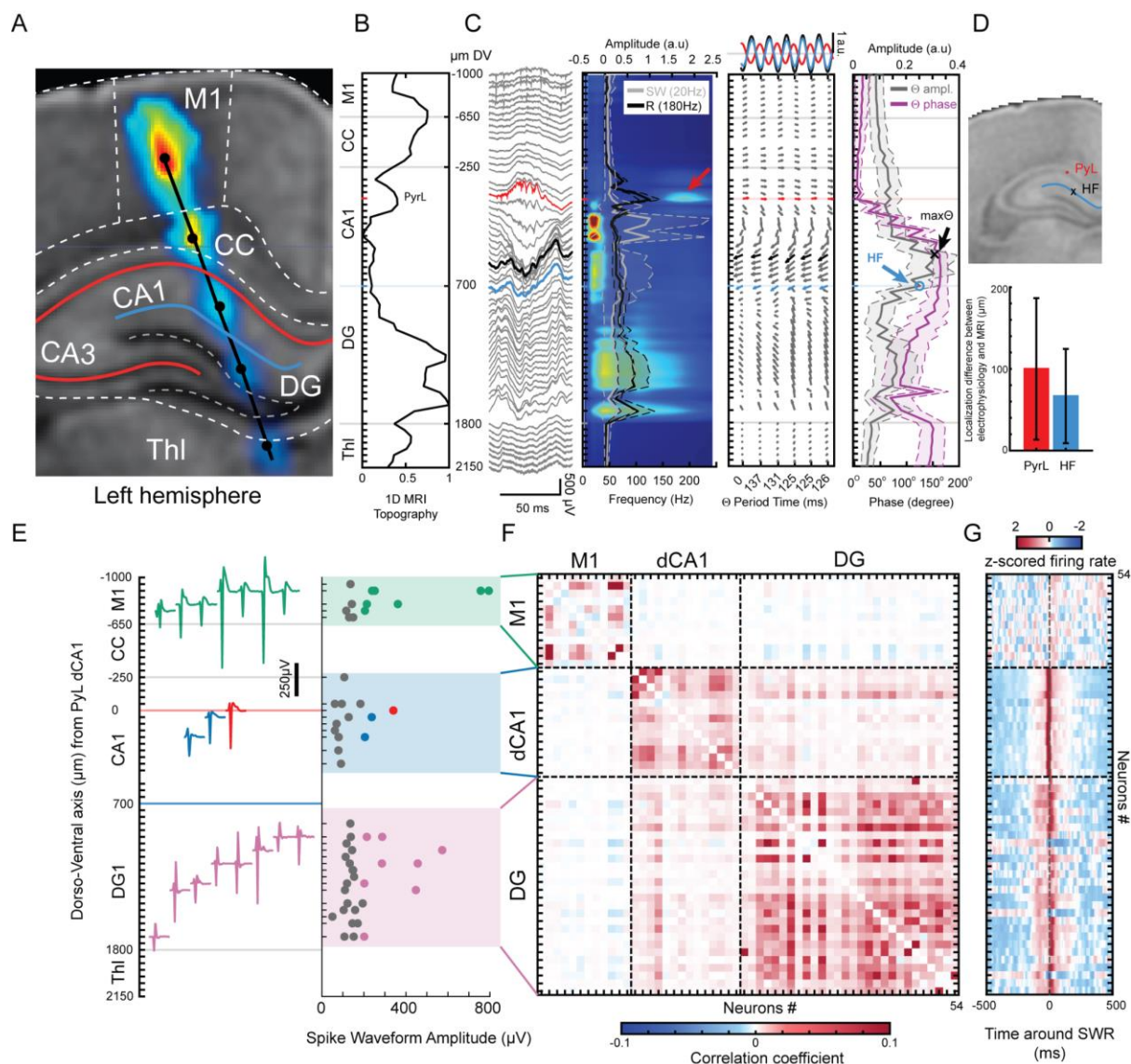


Figure 4. The accuracy of MRID-based electrode localization validated by electrophysiological landmarks. **A.** Electrode locations (black lines) were mapped onto the Waxholm Space rat brain atlas (coronal view). The pyramidal layer (PyL) of dorsal CA1-CA2-CA3 is highlighted in red, while the granular layer of the dentate gyrus (DG) is marked by a gray dashed line. The white dashed line outlines the hippocampus (HP), corpus callosum (CC), motor cortex (M1), and brain boundaries. **B.** Electrode alignment visualized using MRI-based topography. **C.** The first column shows raw sharp-wave ripple (SWR) activity along the electrode axis, with contact sites spaced at 50 μm. The red tick marks the first PyL site from dCA1. The second column presents the average SWR frequency decomposition (n=463), showing ripple power along the DV axis at 184.14 Hz (black line ± SD, dashed) and sharp-wave frequency at 20 Hz (gray line ± SD, dashed). The red arrow marks the ripple power peak. The third column shows theta-filtered (4–10 Hz) LFP traces from three channels: PyL (red), maximum theta power (black), and the nearest HF channel (blue), with phase distributions aligned to the theta peaks from PyL. The fourth column displays theta power (gray) ± SD (dashed) and phase shifts (purple) relative to PyL. The black arrow indicates maximum theta, while the blue arrow marks HF. **D.** The upper panel shows MRI-localized PyL (red) and HF (blue) with the CA1-DG border (light blue). The lower panel compares MRI- and

electrophysiologically-localized PyL and HF distances across three MRID bundles. **E.** Waveforms ($>200\ \mu\text{V}$) are color-coded: M1 (green), dCA1 (blue and red [$0\mu\text{m}$] in PyL), and DG (purple). A 2-ms binned cross-correlation matrix with delineated structural borders (dashed lines). **G.** z-scored neuronal firing rates along the dorsoventral axis during SWRs.

Chronic *in vivo* stability of MRID-tagged electrodes

We carried out freely-moving electrophysiology recordings once a week ($n=3$ bundles, $n=2$ animals) over 5 months. MRID-tagged UFTEs exhibit a robust and stable chronic recording performance. We measured the electrode-tissue impedances at 1 kHz before each recording session every week *in vivo*. Mean impedance magnitudes of $635.66\ \text{k}\Omega \pm 91.80\ \text{k}\Omega$ ($\pm$ s.e.m, working channels $n=120$) and $234.80\ \text{k}\Omega \pm 15.41\ \text{k}\Omega$ ($\pm$ s.e.m, working channels $n=46$) on days 13 and 10, respectively from two animals, post-implantation. Mean impedance magnitudes of $147.97\ \text{k}\Omega \pm 17.57\ \text{k}\Omega$ ($\pm$ s.e.m, working channels $n=125$) and $194.28\ \text{k}\Omega \pm 25.34\ \text{k}\Omega$ ($\pm$ s.e.m, working channels $n=52$) on days 153 and 161, respectively from two animals, post-implantation. The electrical electrode-tissue impedances drop and stabilize to a global mean of $161.20\ \text{k}\Omega$ over weeks. Mean $\pm$ s.e.m impedances from one animal are plotted chronically in Fig. 5A.

We detected the chronically recorded and trackable single units (Methods). Spikes were detected and sorted into clusters as described in our previous work^{9,33}. Each cluster was identified as single- or multi-unit in a semi-automatic manner (Methods). The clusters were separated from noise and neighboring clusters with expert judgment during the manual sorting. 90% and 78% of the single-units were tracked for 16 and 22 weeks, respectively. Some selected single-unit mean waveforms (single-unit ID: 13, 23, 25, 31, and 42) were plotted over weeks in Fig. 5A.

Chronic single-unit SNR levels were calculated using single-units from concatenated spike-sorted data. SNR of a session was defined by the mean ratio of the peak-to-trough amplitudes of all single-units within that session to the session V_{rms} . Electrodes exhibited a high-SNR stable recording over weeks. In Animal#1, we observed that SNR levels increased from 16.49 ± 1.47 (s.e.m) to 20.38 ± 2.08 (s.e.m) over a 23 weeks long recording period, as shown in Fig. 5A. The increase in SNR is reversely correlated with the mean impedance values such that as the impedances decrease, the SNR levels increase.

We investigated the induced MRI contrast from MRID-tags chronically ($n=5$ bundles, $n=18$ IONP islands, $n=3$ rats). In one animal (Animal #1), the MRID-tag spanned the entire UFTE bundle along the implantation trajectory which induced a single-body contrast. In MRI sessions of that animal, we aligned three imaging-slices ($136 \times 136\ \mu\text{m}$ pixel dimensions, $800\ \mu\text{m}$ thickness) in axial (i.e. horizontal) orientation that slices the trajectory horizontally.

The other MRID-tags ($n=5$, animals #2 and #3) were imaged with a single slice in coronal or sagittal orientation ($136 \times 136\ \mu\text{m}$ pixel dimensions, $800\ \mu\text{m}$ thickness). We measured the induced contrast by each IONP island in MRID-tags and extracted induced contrast heatmaps. If an IONP island was imaged in multiple orientations, we chose the orientation that gives the maximum contrast. We sorted the measured contrast intensities within each IONP island in descending order. Then, we calculated the mean contrast intensity from the five most

387 contrastive pixels in each IONP island in each session. Over five months long implantation
388 duration, mean induced contrast intensities by MRID-tags showed 104.37%, 75.91%, and
389 99.56% (for Animal #1, #2, and #3, respectively. Animal #2 implantation was for 3.5 months
390 long) changes compared to 1 week after the implantation as shown in Fig. 5B. The contrast
391 intensities from IONP islands, which are close to the insertion point, are most prone to intensity
392 drops. MRID-tags remained detectable robustly over long durations of chronic implantation.

393
394 We checked the immunohistology to analyze any adverse immune reaction to the MRID-
395 tagged UFTEs. After 3.5 months long implantation of MRID-tagged UFTEs (n=4 bundles, in
396 Animal#2), the brain was dissected, prepared and immunostained to image the neuronal
397 (Nissl), microglia (IBA-1) and activated astrocytes (GFAP) densities (Methods). From the
398 borders of UFTE cross-sections, equidistance circular contours (40 μ m thick) were defined
399 (Fig. 5C). We statistically compared (n=13 brain slices, Welch's t-test) the mean normalized
400 fluorescence intensity (FI) around UFTEs (<320 μ m distance) to the control condition (>700
401 μ m) at each defined circular contour. Neuronal density intensity remained within 10% change
402 at the surrounding of UFTEs where at the direct vicinity of UFTEs the neuronal density was
403 increased by a mean percentage of $2.63\% \pm 11.1\%$ s.e.m (Welch's t-test, non-significant for
404 all regions). We measured a slight increase in activated astrocyte intensity within the 40 μ m
405 and 80 μ m of UFTEs with a mean percentage of $24.97\% \pm 19.76\%$ (s.e.m) (Welch's t-test, p-
406 value=0.0076) and with a mean percentage of $13.84\% \pm 4.70\%$ (s.e.m) (Welch's t-test, p-
407 value=0.00016). Activated microglia density also remained within 10% change at the
408 surrounding of UFTEs, where at the direct vicinity of UFTEs, there was a mean intensity
409 increase by $5.89\% \pm 13.13\%$ s.e.m (Welch's t-test, non-significant for all regions).

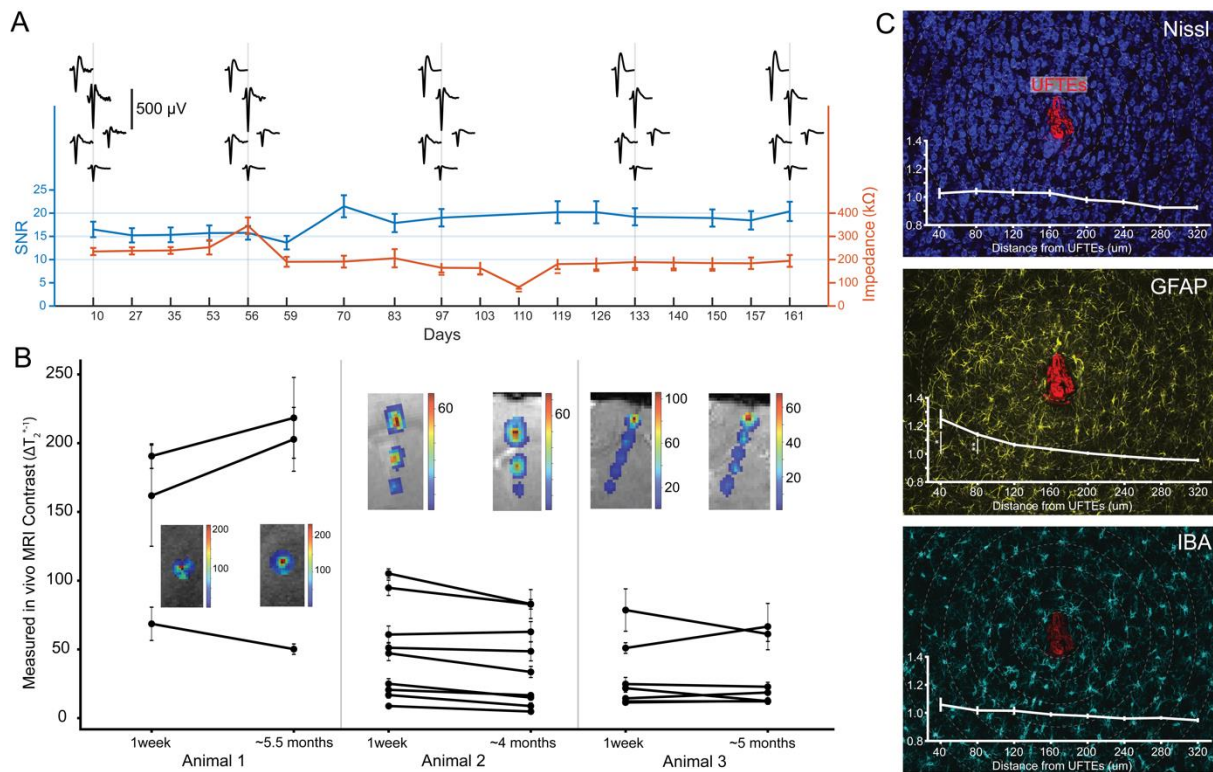


Figure 5. Chronic months-long electrophysiological and MRI-contrast stability of MRID-tagged ultra-flexible electrodes *in vivo*. **A.** Chronic impedances from working electrode channels $<5\text{M}\Omega$ magnitude@1kHz (day 10: 46, day 161: 52 channels) are plotted, error-bars denote the standard error of the mean (s.e.m). SNR values from single-units recorded each week ($n=68, 61, 53$ on sessions 1, 13, and 19) are plotted, error-bars denote the s.e.m. 5 sample single-units are plotted chronically on weeks 1, 5, 10, 15, and 19. **B.** Chronic *in vivo* induced MRI contrasts ($n=3$ animals, $n=18$ IONP islands) over five months. Mean and s.t.d contrast intensities (5 most contrastive pixels) from each IONP island is plotted at week-1 and at week-23 (Animal#1), week-14 (Animal#2), and week-22 (Animal#3) after the implantation. A sample measured contrast image is given for each week and animals. Two-sample dependent t-test is applied to the mean contrast intensities ($n=18$, t -statistic = 0.465, p -value = 0.647, $df = 18$). The mean changes in contrast intensities are 104.37%, 75.91% and 99.56% for Animal#1, 2, and 3 respectively. **C.** Fluorescence immunohistology (Animal #2) with *nissl*, *GFAP*, and *IBA-1* staining for neurons, astrocytes and microglia, respectively. UFTes are visible in red color. From the border of UFTes 8 circular areas were defined with 40 μ m separation. The circular dashed contours on the images denote every 50 μ m from the center of the UFTes. The FI intensity changes are normalized with the mean of a large area >700 μ m away from the border of the UFTes and compared to the control condition ($n=13$ brain slices, $n=4$ bundles, Welch's two-sample t-test, * and ** denote p -values < 0.05 and < 0.001).

Discussion

Ultra-flexible electrodes are typically invisible in MRI, posing major challenges for accurate implantation, validation, and data interpretation in basic research and clinical applications. We developed MRID-tags for precision localization and identification of ultra-flexible electrodes.

We wafer-scale fabricate ultra-flexible electrodes with MRID-tags by coating IONPs using a dot-matrix convective and capillary coating technique. Modular dot-matrix assembly of IONPs prevents possible uneven surface stress on individual ultra-flexible electrode fibers and preserves their ultra-flexibility, which is crucial for forming straight linear bundles of fibers for implantation. The dot-matrix nanoparticle coating is a single-step technique without the need for specific surface treatments and intermediate stamps to transfer the nanoparticles onto the samples. We successfully coat nanoparticles on hydrophilic and hydrophobic surfaces while preserving the material properties and surface morphology. Using this technique, we can fabricate MRID-tags into any wafer-scale-production ultra-flexible neural electrodes. Our technique is only limited by the available surface area on the existing structures which determines the amount of coated nanoparticles. Some applications may require significantly larger quantities of coated nanoparticles. To overcome this, for example, an intermediate thin layer of polyimide can be used, where the effective surface area for coating doubles.

We successfully imaged and detected MRID-tags chronically implanted in rat brains. We detect the induced contrast by MRID-tags spatially and temporally by taking multiple TE images of an imaging-slice. This allowed us to accurately identify the *centers of masses* of each induced pattern (i.e. IONP islands) in MRI-barcode. We showed that the detected CoMs align well with the calculated CoMs allowing accurate reconstruction of implantation trajectories. We implemented a point-set registration algorithm to accurately determine the positions of individual electrode channels in 3D MRI space and to label them anatomically with reference WHS atlas.

The peripheral implant apparatus including cranial screws and electronics in the vicinity of the brain can cause shadow artifacts in images. These large shadows might overlap with the contrast induced by the MRID-tags. To reduce such image artifacts, we used PEEK and non-magnetic metals for implant apparatus. MRID-tags were detectable everywhere in the brain except in the immediate vicinity of titanium cranial screws during such chronic implantation.

We observe a linear correlation between the measured MRI contrast and the density of coated IONPs. This linear correlation is the direct outcome of the precision of our fabrication technique. With this capability, we can engineer specific contrast levels depending on the applications when the conditions are well known e.g. scanner type and implantation configuration etc.

We used the electrophysiological landmarks in dorsal hippocampus to validate our MRID-tagged electrode localization pipeline. We detected the dCA1 PyL and its border with the DG, known as the HF as electrophysiological landmarks where we observe normalized amplitudes and phase shifts in SWRs and theta oscillations consistent with the previous findings^{6,25,26}. Using these electrophysiological landmarks as ground truth, we showed that MRID-based localization of contact sites closely aligned with well-defined neural structures.

Single-unit cross-correlations revealed functional groups where intra-area units exhibit high correlations in M1, CA1 and DG. SWR-associated neuronal activity showed clear modulation in CA1 and DG, while remaining unchanged in M1, which draws a distinct functional border between dHPC and cortex. We showed that the majority of anatomical labels from our MRI analysis matched the functional groups revealed by the single-unit firing rates.

MRID-tagged UFTes exhibited stable impedances, high SNRs, reliable unit tracking, and consistent SNR over months. Impedances gradually decreased before stabilizing, likely due to silk-fibroin dissolution and post-implantation tissue recovery. A high proportion of single units remained trackable for extended durations, with SNR improving over time, inversely correlating with impedance reduction. MRI contrast induced by MRID-tags remained stable over months, with only minor reduced contrast intensity observed in superficial (i.e. dorsal) IONP islands, likely due to tissue healing. We observed no major immune response in the brain, consistent with our previous findings⁹. Only a mild increase in activated astrocyte density was observed near the implant sites. Neuronal and activated microglia densities remained unchanged.

The capability to reliably localize the finest and least invasive ultra-flexible neural implants promises refined targeting and tracking of electrophysiological signals in clinical applications such as deep-brain stimulation and intracranial epilepsy probes. This capability can also allow precisely targeted interventions in movement disorders, cognitive augmentation, and neurorehabilitation in high-density brain-machine interfaces. The use of MRID-tagged ultra-flexible electrodes can allow safe long-term neural interfaces in NHP research and human clinical applications.

Methods

Microfabrication of the ultra-flexible electrodes and MRID-tags

We fabricated the UFTes following the same layer-by-layer lithography based recipe from our previous work⁹. We coated a bare silicon wafer on its polished side with 1 μm thick PI2610 polyimide (PI) and cured it in the programmable oven (*CLO-2AH-S, Koyo ThermoSystems*). On the base polyimide layer, we deposited and patterned 10 nm titanium (Ti) and 150 nm gold (Au) to construct the electrode recording sites, wires, and soldering pads.

For the dot-matrix nanoparticle coating mold; we lithographically patterned a thin photoresist layer (AZ1505, *Microchemicasls GmbH*) on the sample. After the development, recessed dot-matrix patterns exposing Au surfaces was achieved. Development profiles are checked under optical microscope (Nikon Eclipse L200D).

The sample is dipped into 1:99 diluted gold etchant and agitated for 15 seconds to roughen the exposed Au surfaces in dot-matrix patterns. The sample is rinsed and dried.

The sample is placed on the wafer-chuck attached to the linear motorized stage of the custom nanoparticle coating setup (Suppl. Fig. 1A). Electrode wires, which are to be coated with nanoparticles, are parallel to the movement of the linear stage. A glass microscope slide is placed above the sample with 500 μm separation. A micromanipulator and a horizontal microscope is used for precise positioning of the glass slide. Using a micropipette, 2 μl colloidal suspension of 0.25 mg/ml (25 nm average particle size) iron(II,III)-oxide nanoparticles (*Sigma Aldrich 900042*) is injected in between the sample and glass slide where the electrode wires are. The meniscus that is formed by colloidal suspension is imaged with horizontal microscope to measure the contact angle. The sample is moved in the direction, where the meniscus contact line is, at the constant velocity of 5 $\mu\text{m}/\text{sec}$ until the meniscus is no longer on the dot-

matrix. Remaining colloidal suspension is removed with a micropipette. The operation is repeated for each electrode bundle.

AZ100 Remover (*1-aminopropan-2-ol and dipropylene glycol methyl ether*, *Microchemicals GmbH*) in 5 inch wide beaker is heated up to 80C in water bath on a hotplate in a controlled manner. The sample is placed in the 80C AZ100 Remover for 10 minutes. A gentle mechanical agitation is applied to the sample using a Pasteur pipette every 5 minutes. The process is repeated with a clean 80C AZ100 Remover bath for another 10 minutes. The sample is rinsed in consecutive isopropanol and running dH₂O baths afterwards and dried with N₂ gun. Following the removal of photoresist and excess IONP, the coating results are validated in optical (Nikon Eclipse L200D) and scanning electron microscopy (Zeiss Gemini ULTRA 55). Top insulating PI layer is deposited on the sample as described in first paragraph.

We coated another 1 μm thick polyimide layer on the sample and cured it. We etched the polyimide in between individual electrode fibers and at the outer borders⁹ to construct mechanically independent electrode fibers. We etched the top layer polyimide on active recording sites to expose the Au surface underneath. We checked the quality of etching under optical microscope (Nikon Eclipse L200D). We coated the sample with 2.5 μm thick sacrificial parylene-C layer with chemical vapor deposition (PDS 2010 Labcoater 2; Speciality Coating Systems Inc.)⁹.

We roughened Au surface on the recording sites with chemical etchant. We spin-coated ~450 nm thick PEDOT:PSS (*Clevios PH 1000, Heraeus Epurio*), *ethylene glycol (Sigma Aldrich)*, *dodecyl benzene sulfonic acid (Sigma Aldrich)*, and *(3-Glycidyloxypropyl) trimethoxysilane (Sigma Aldrich)* on electrode recording sites to lower the electrode-tissue impedance⁹.

Assembly of the UFTEs

We soldered 70-pin mezzanine (AXF5A7012A, AXF6A7012A Panasonic) female and male type connectors on the custom design flexible and rigid PCBs, respectively. Two 36-pin (A79024, Omnetics) female omnetics connectors are soldered from both sides at the other end of the rigid PCB (Suppl. Fig. 2B). We soldered the 64-channel UFTEs to the flexible-PCB after peeling them off the silicon wafer (Suppl. Fig. 2B). We applied a medical grade epoxy (EP40MED, MasterBond Inc.) on the soldering area to mechanically secure soldering between electrodes and PCBs. Flexible PCB is plugged to rigid PCB with mezzanine connectors, and rigid-PCB is plugged to the 64-channel (RHD 64-Channel Recording Headstage, Intan Technologies) recording headstage. *In vitro* impedances at 1kHz were measured in saline (Ringer's solution, B.Braun) with two-electrode configuration where an Ag/AgCl wire was used as reference/counter electrode (Suppl. Fig. 2A). After soldering and quality check of UFTEs, we assembled them with tungsten insertion shuttles as described in⁹.

Modular titaniumHelmet and 3-D printed housing

The *titaniumHelmet* from the previous work⁹ is adapted in this work⁹. The *titaniumHelmet* spans a maximum of 23.95 mm in the anterior-posterior axis and 11.30mm laterally as stated

previously⁹. We replaced the base part (Suppl. Fig. 2B) with a PEEK made base to prevent the MRI image artefacts induced by base while keeping the outer shell as grade 5 Titanium (Ti-6Al-4V). The PEEK base two anterior screw holes (1mm diameter) and one posterior screw hole (1mm diameter). The PEEK base is permanently screwed onto the skull with 0.9mm cranial titanium screws (length 3mm, M-5100.03, Medartis) and cemented. Five lateral screw holes with threads (M1.2) on the base are used for assembling the outer shell of titaniumHelmet to the base.

We 3-D printed a custom design inner housing to hold the connectors during freely-moving recording (Suppl. Fig. 2E). The 3-D printed inner housing has 3 parts assembled inside the titaniumHelmet (Suppl. Fig. 2E). These pieces have precise slots to position the connector PCBs in. Flexible-PCBs folded twice during the assembly of the helmet, and rigid PCBs are positioned in their dedicated slots, where omnetics connectors facing up (dorsal) (Suppl. Fig. 2E). This inner housing tightly holds the PCBs ensuring a reliable plugging of omnetics connectors to the Intan headstages before the freely-moving recordings, and maintains the connection throughout the recording.

Surgical procedures

We used female Long Evans rats (n=3 rats, 24-80 weeks of age, ~300 g of weight at the time of the surgery, Janvier Labs and Charles River Laboratories). Female rats were chosen due to lower chance of cage-mate fighting, and to prevent single housing. The rats were housed in groups in standard IVC cages (Allentown) and had ad libitum access to food and water. The cages were kept at 23°C room temperature, 52% room and 58% cage humidity, and on an inverted light cycle (12h dark / 12h light).

We anaesthetized the rats with inhalation isoflurane (Attane, Piramal Pharma Ltd) mixed in oxygen. We monitored the respiration rate, heart rate and blood oxygenation levels of the rat throughout the entire duration when animal was under anesthesia (Model 1030, Small Animal Instruments Inc.). We adjusted the level of anesthetics and analgesics during the surgery based on the vital signs readout. Analgesic Meloxicam (Metacam, Boehringer Ingelheim) was subcutaneously injected at the torso. A mixture of Ringer's solution and glucose (Aequifusine, B. Braun) was injected subcutaneously in torso at fixed intervals during the surgery to maintain the water, electrolyte and sugar levels of the animal. *We trimmed and shaved the hair on the rat's head and cleaned the scalp with Betadine* (Mundipharma Deutschland GmbH). A mixture of Bupivacaine (Bupivacain Sintetica, Sintetica), Lidocain used for local anesthetic (maximally 7 mg/kg bodyweight is injected under the skin at the site of the surgery) and NaCl solution is subcutaneously injected at the scalp at multiple locations. We fixed the rat's head at the stereotaxic frame with earbars and incised the skin with a single cut in anterior-posterior axis. We cleared the connective tissue to expose the skull surface especially the Bregma and Lambda of the skull. We iteratively ensured the parallelity and levelness of the skull with the ground surface. We identified and drilled the craniotomy locations; three craniotomy holes were drilled for fixating the base with 0.9mm drill bit (Medartis), two lateral craniotomy holes that were used to ensure a strong cementing base were drilled with 1.2mm drill bit (Medartis), and two holes for the electrode implantation craniotomies were drilled with 0.9mm dental drill bits. We fixated the PEEK base with screws and dental cements. MRID-tagged 64-channel UFTE bundles (n=3) were through the dorsal hippocampus (dHPC) of rats (Animal 1: {AP: -3.24mm, ML: 2.2mm}, Animal 3: {Bundles coordinates left- and right- hemisphere; AP_{Left}: -

3.0mm ML_{Left}: 2.2mm AP_{Right}: -2.7mm, ML_{Right}: -2.45mm}) same way as described in⁹ The ribbon part of UFTEs were covered with dental cement on the skull. We positioned the lower end of the flexible PCBs on the skull and cemented it from its lateral anchor extensions (*Suppl. Fig. 2B*). Once we implanted all the MRID-tagged UFTEs and secured their PCBs with cement, we assembled the 3-D printed inner housing together with TitaniumHelmet. We cleaned the wound and sutured gaps in anterior and posterior parts of the scalp. We stopped the isoflurane flow and transferred the rat into a clean, warm cage with wet food pellets, bedding and nesting material. We closely observed the rat until it fully wakes up.

Imaging rat brain in vivo in MRI

We scanned and imaged the rat's brain and MRID-tags in MRI once a month after the implantation. Before the MRI scanning, we anaesthetized the rats with inhalation isoflurane (Attane, Piramal Pharma Ltd) mixed in oxygen. We disassembled the outer titanium shells and 3-D printed pieces only leaving the PEEK base and connector PCBs on the animal's head. We positioned the rat on the warm MRI cradle in head prone position fixated with earbars. We monitored the respiration rate, heart rate and blood oxygenation levels of the rat during when animal was under anesthesia (Model 1030, Small Animal Instruments Inc.). The 30mm diameter ring surface receive only coil (¹H planar receive-only 30mm surface coil, Bruker) is positioned on the animal's head. The flexible connector PCBs are guided through the inner loop of coil and pulled towards as posterior as possible further away from the imaging region of interest (*Supplementary*). The PCBs are gently fixed via a 3M tape at the posterior. We positioned the head of the rat at the isocenter of the MRI (7 Tesla PharmaScan 70/16, Bruker) bore. We matched the impedance of RF transmission coil per scanning session. We took a localizer scan and ran automatic adjustment settings, e.g. shimming. After localizing the subject, we took three TurboRARE spin-echo (SE) scans (TE:33ms, TR: 2500ms, RARE factor: 8, echo spacing: 11, excitation angle: 90, refocusing angle: 180) in axial, coronal, sagittal slicing orientations (slice thicknesses: 800 μ m, 450 μ m, 550 μ m respectively) covering the entire brain (field-of-views: 35mm x 35mm, 18.4mm x 12mm, 35mm x 35mm and image dimensions: 256 x 256, 180 x 120, 256 x 256, respectively). We mapped the B0 field homogeneity in the bore with B0MAP sequence (2 echo images TE₀: 1.64ms and TE₁: 5.45ms, flip angle: 30, TR: 20ms, image size: 64x64x64, FOV: 45mm x 45mm x 45mm). We took T2*Map multiple gradient echo (MGE) images (Echo images: 8, TE₀: 4.09ms, echo-spacing: 4ms, TR: 800ms, flip angle: 50, FOV: 35mm x 35mm, image size: 256 x 256) in coronal and sagittal slice orientation where slices (slice thickness: 800 μ m) are aligned to MRID-tags based on whole brain SE images. Using the same slice orientation and FOV from T2*Map MGE images, we took FLASH (TE: 6ms, TR: 200ms, flip angle: 30, image size: 512 x 512) and TurboRARE SE (TE:33ms, TR: 2500ms, RARE factor: 8, echo spacing: 11, excitation angle: 90, refocusing angle: 180) images.

Brain registration SAMRI

We registered the MRI images from each imaging session to the reference WHS atlas using the Small Animal Magnetic Resonance Imaging toolbox (SAMRI)^{34,35}. We first converted all the images to NIFTI format from Bruker format. We biascorrected³⁶ the coronal whole brain SE images before the registration (*Suppl. Fig. 3*). After biascorrection, we registered the

coronal whole brain SE images to WHS T2* images in rigid, affine and elastic registrations consecutively^{35,37} (Suppl. Fig. 3). After the registration, we checked the quality of the registration by looking at the outer borders, corpus callosum and olfactory bulb on the warped coronal whole brain SE images overlapped with WHS anatomical segmentation. We applied the resulting transformation³⁷ to the other images within the session to have all images in WHS reference space.

MRID Analysis

On unregistered raw T2*Map MGE images, we manually segmented the MRID-tags and surrounding anatomy using ITK-SNAP³⁸ at the echo image where the patterns are the largest. We assigned a separate label for each IONP island (Suppl. Fig. 3). We excluded the areas, where strong magnetic field inhomogeneities (e.g. due to air gaps) are present, from the segmentation. Furthermore, we segmented the same images entirely based on anatomy ignoring the MRID patterns such that each pixel in an MRID pattern has an assigned anatomical label. After manual segmentation, we have two segmentation images for MRID-pattern segmentation and anatomical segmentation.

The induced contrast is linearly correlated with concentration of IONPs in a medium defined by the relaxivity equation (Equation 1)³⁹. T_i denotes the observed relaxation time constant, T_i^0 denotes the relaxation time constant of the medium without any contrast in the medium ($[CM]=0$), and r_i denotes the relaxivity constant of the contrast (where $i: 1, 2, 2^*$). IONPs in MRID-tags are encapsulated in polyimide layers, therefore we cannot measure the local concentration directly, but instead we have an observed-concentration. The observed concentration is correlated with the number of dots (i.e., in the corresponding dot-matrix) in a given IONP island.

$$\frac{1}{T_i} = \frac{1}{T_i^0} + r_i \cdot [CM] \quad (1)$$

To obtain an area's $T2^*$ relaxation time, we fitted a relaxation curve (Equation 2) on the mean pixel intensities of that area over increasing TEs. Relaxation time is defined as the time point when pixel intensity drops to 37%⁴⁰. Based on the anatomical segmentation, each pixel is assigned to an anatomical structure. We first fit the exponential decay curve (Equation 2) to the mean pixel intensities from corresponding anatomical region ($n>100$ number of pixels) to find the S_0 (the signal intensity at TE: 0ms), $T2^*$ (the relaxation time in seconds), and A (the offset). We centered a 3x3 pixels window at the given pixel on segmented MRID patterns, collecting pixel intensity values ($n=9$, pixel intensities) at each echo image. We, then, fitted the exponential decay curve to the mean pixel intensities from the 3x3 window to find the $T2^*$ relaxation time of the given pixel. We fixed the S_0 and A to the values from anatomical region in the curve fitting. We made this assumption since IONPs are encapsulated into a tiny footprint.

We calculated the relaxation time $T_{2^*}^{j,k}$ at pixel $[j,k]$ based on the relaxation curve. Moreover, we calculated the relaxation time $T_{2^*}^0$ of the baseline brain area where the pixel is located. Here, the measured contrast level $c_{2^*}^{j,k}$ at pixel $[j,k]$ can be calculated with Equation 3. We created the heatmap contrast intensity images using $c_{2^*}^{j,k}$ values. We transferred these images into 3D MRI space using the affine transformation from raw images.

$$S = S_0 e^{\frac{-t}{T_2^*}} + A \quad (2)$$

$$c_i^{j,k} = \frac{1}{T_i^{j,k}} - \frac{1}{T_i^0} \quad i: \{1, 2, 2^*\} \quad (3)$$

We fitted a 2-dimensional gaussian curve on each MRID pattern on contrast intensity images in both coronal and sagittal slice orientations. We extracted the 3-dimensional (in medio-lateral, dorso-ventral, and antero-posterior axes) pixel indices of fitted gaussian centers. We picked the pixel index in dorso-ventral axis from the slice orientation (coronal or sagittal) at which the contrast intensity is higher.

The loss function, to be minimized, of point-set registration is the summation of all Euclidean distances in between calculated-estimated CoM pairs (Equation 3, $k: \{1, \dots, M\}$, M is the number of IONP islands). UFTE implantation trajectories are not necessarily straight lines which sometimes follow slight arc- or S-shapes. We assume that the relative distances between CoM pairs and electrode channels remain constant during implantation. Under these assumptions, we can formulate the bundle trajectory in the spherical coordinate system. We can define each calculated CoM as a node connected to other nodes with a fixed distance r_k but variable inclination and azimuth angles (θ_k and φ_k). The first CoM₁ is only defined in the Cartesian coordinate system where it is initially positioned to the arbitrary $p_{1initial} = (x_{1initial}, y_{1initial}, z_{1initial})$. The relation between each consecutive calculated CoM pair in the Cartesian coordinate system is given in Equation 4. Then, our point-set registration task simply becomes a search on p_1 , θ_k and φ_k to minimize the loss function L (Equation 5) (shown in Fig. 3C).

$$L = \sum_k d_k \quad (3)$$

$$CoM_{k+1} = CoM_k + (r_k \sin\theta_k \cos\varphi_k, r_k \sin\theta_k \sin\varphi_k, r_k \cos\theta_k) \quad (4)$$

$$\text{where } CoM_1 = p_1 = (x_1, y_1, z_1)$$

$$\arg_{p_1, \theta_k, \varphi_k} \min \sum_k d_k \quad (5)$$

To find the set of $[p_1, \theta_k, \varphi_k]$ minimizing the loss function, we implemented the Nelder-Mead downhill simplex heuristic search method⁴¹. The first point initially positioned, $p_{1initial}$ near the first measured CoM with a randomly sampled slight shift to allow the search algorithm to converge fast.

To compare the IONP density to the induced contrast intensity, we centered a circular window ($r = \text{IONP island length} / 2$) at the gaussian centers. We calculated the relaxation times and contrast intensities from the circular window using Equations 1-3. We calculated the IONP density as the number of dots in the given IONP island divided by the number pixels in the circular window ($\# \text{ of IONP dots} \times \text{pixel}^{-1}$). For the fully coated bundle, we fitted a line along the trajectory of the bundle. Along this line, we slid regions of interest at different sizes and calculated the contrast intensity for each ROI. For each ROI, we calculated the number of dots in that region using the design layout.

We generated a fixed length vertical (4500 pixels, 1 pixel == 1 μ m) empty rectangle template for MRID barcode reconstruction. At the bottom, we colored a horizontal black bar in the empty rectangle template with height of 2 x sigma of the most ventral MRID pattern gaussian fit in dorso-ventral axis. From the center of the black bar, we moved up with the distance between the most and second ventral gaussian centers. We colored another horizontal black bar centered around that point with the height of 2xsigma of the second most ventral MRID pattern. We repeated this process for all the MRID patterns filling up the barcode template towards up.

In vivo recordings from rats

The rats were already familiar with the testing environment. We used one of three environments: (i) a 50×50×50 cm Plexiglas cage covered with copper mesh on its sides and bottom (with an open top) and a floor lined with bedding that was changed after each recording session, (ii) a square arena measuring 1.5×1.5 m covered with green PVC, or (iii) an 80 cm-diameter circular open-field desk, also covered with green PVC.

Recordings began within six days after surgery, at least twice a month. In all environments, a glass Petri dish containing a single drop of concentrated milk (Kondensmilch, Coop Switzerland) was a positive reward after connecting the recording system to the rat.

For data acquisition, we used an Intan Technologies 2×64-channel head stage (part# C315) with RHX Data Acquisition Software (<https://www.intantech.com>) to record broadband data at a 20,000 Hz/channel sampling rate and 16-bit resolution. A high-pass filter with a 0.1 Hz cutoff frequency was applied at the hardware level to eliminate the DC component of the signal.

Spike sorting for selected recording sessions was performed using JRCLUST 4.0.0.³³ First, the pipeline filtered the raw data with a 4th-order bandpass filter, with cutoff frequencies set at 300 and 5000 Hz. Next, common average referencing was applied by computing the median across all intact channels and subtracting this median from each channel's filtered trace, minimizing artifacts from instrumentation or strong muscle movements. Spikes were then detected in the filtered and software-referenced traces as described by Quian-Quiroga et al. (qqFactor = 5, only negative peaks detected). Events detected within a 60 mm spatial and 0.25 ms temporal vicinity ("evtDetectRad," "evtMergeRad," and "refracInt") were merged into a single spiking event to prevent duplicate detections across multiple recording contacts.

To reduce the dimensionality of the detected spike waveforms, JRCLUST applied principal component analysis (PCA) with three features per recording contact ("nPCsPerSite"). Spikes were then clustered automatically using the Density Peak clustering algorithm⁴², with logarithmic rho and delta cutoffs set at -2.5 and 0.6, respectively ("log10RhoCut" and "log10DeltaCut"). Manual curation was performed following automatic clustering to eliminate noise clusters and finalize spike cluster identities.

Local Field Potential Data Processing

To extract and analyze local field potentials (LFPs), we applied a low-pass filtering and down-sampling procedure to the raw electrophysiological data recorded at 20 kHz. The raw data were stored in binary .dat files in a 16-bit integer format, containing signals from all recording

channels. The data were processed using a custom MATLAB script with several steps. First, the recording file was memory-mapped for efficient access, and a binary output file (.lfp) was created to store the processed signals. To isolate the LFP component, we applied a 600th-order finite impulse response (FIR) low-pass filter with a 245 Hz passband frequency and a 250 Hz stopband frequency at a 20 kHz sampling rate. The filter was designed using MATLAB's designfilt function and applied bidirectionally using filtfilt to minimize phase distortion. Each recorded channel was extracted and converted to microvolts using a scaling factor of 0.195 $\mu\text{V/bit}$, and the low-pass filter was applied sequentially to each channel. After filtering, the data were downsampled by a factor of 10, reducing the sampling rate from 20 kHz to 2 kHz, which was appropriate for LFP analysis while maintaining computational efficiency. Finally, the filtered and down-sampled signals were stored in a .lfp binary file in the same 16-bit integer format for further analysis.

Sharp-Wave Ripple Detection, Alignment, and Frequency Decomposition of Local Field Potentials

LFP signals were recorded from eight selected channels spanning CA1 strata: stratum radiatum (SWR-negative deflection), pyramidal layer (ripple detection), and stratum oriens (SWR-positive deflection). Signals were downsampled to 2 kHz for local field potential (LFP) analysis.

SWRs were detected using a convolutional neural network (CNN)-based SWR detection method⁴³. For manual curation, a MATLAB-based graphical interface was developed, enabling interactive browsing of multichannel LFP traces, bandpass-filtered signals, ripple power, and wavelet-transformed data across hippocampal layers. SWRs could be manually inspected and annotated by specifying event onset and offset points. To standardize SWR alignment, we converted detected SWR intervals to a central alignment time point. This involved a two-step procedure: (1) Identifying the peak of SWR bandpass power (averaged across all channels). (2) Aligning a fixed-length window of mean bandpass LFP around the power peak using cross-correlation maximization, with a shift limit of 5 ms (10 frames at 2 kHz) to maintain phase consistency at 200 Hz. Aligned SWR events were used for frequency decomposition via wavelet transformation to identify the site of maximum ripple power across all LFP channels along the dorso-ventral axis. The CA1 pyramidal layer (PyL) was identified as the peak ripple site (184.14 Hz), serving as the reference point (0 μm) for subsequent analyses. The LFP signal was then bandpass-filtered (4–10 Hz), and theta cycles were identified using Hilbert transformation. Theta peaks (0° phase) in PyL served as the reference for computing phase differences along the dorso-ventral axis.

Identification of the Hippocampal Fissure via Theta Power Amplitude Analysis Along the Dorso-Ventral Axis

To identify significant changes in theta amplitude along the electrode axis, we implemented a computational approach in MATLAB comprising the following steps (1) The normalized amplitude of the signal was calculated across all channels, and the mean and standard deviation were computed. The maximum power was identified by locating the peak value in the averaged normalized amplitude of the theta oscillation on all channels. (2) A decline threshold was calculated to identify the point of a significant decline in amplitude after the maximum theta power peak. This threshold was defined as the mean difference between

consecutive amplitude values minus three times the standard deviation of these differences. (3) Starting from the index of the peak of the theta power, the algorithm iterated through subsequent amplitude values to detect the first point where the difference between consecutive amplitudes fell below the calculated decline threshold. This point was defined as the onset of a significant decline. (4) A one-sample z-test was performed at the identified decline point to statistically validate the significance of the decline. The test compared the absolute difference between consecutive amplitude values at this point against the distribution of all amplitude differences. The following parameters were extracted: z-value, *p*-value, Confidence intervals. (5) The algorithm reported the index of the decline onset, the corresponding distance along the electrode axis, and the amplitude value.

Spike Train Analysis for Functional Identification of Structural Borders

Hierarchical Clustering Analysis

Hierarchical clustering was performed on a symmetric correlation matrix to identify meaningful groupings among variables and visualize relationships in a dendrogram. The steps in the analysis are detailed below: (1) The spike trains of *n* neurons were binned into discrete time intervals to generate a binned activity matrix, *A*, where $A_{i,t}$ represents the spike count of neuron *i* in time bin *t* (bin size 10ms). (2) To account for differences in spike patterns across neurons, the activity matrix was normalized by z-scoring the binned spike counts across time. (3) A pairwise correlation matrix (*C*) was computed from the z-scored spike count matrix to quantify the similarity of activity patterns between neurons. To remove self-similarity, the diagonal elements of the correlation matrix were set to zero. (4) The correlation matrix was transformed into a distance matrix using $1-C$. The upper (or lower) triangle of the distance matrix was then extracted and converted into a condensed distance vector using the squareform function. This vector was used as input for hierarchical clustering via the linkage function. The optimal threshold for cluster separation was determined using the elbow method. The distances between successive merges were extracted from the third column of the linkage matrix, and the first-order differences ($\Delta d_i = d_{i+1} - d_i$) were calculated. This index is determined as:

$$elbowIndex = \arg \max_i \Delta d_i$$

Additionally, anatomical labels were assigned based on MRI-localized channels, corresponding to the neurons recorded from contact sites, thereby providing spatial context for identifying the putative anatomical labels of the clusters.

PCA-K-Means Clustering of Z-Scored Firing Rates During SWR

PCA was performed on the neuronal population activity matrix to reduce its dimensionality while preserving the majority of the variance. This technique transforms the original high-dimensional dataset into a lower-dimensional space by identifying principal components—linear combinations of the original variables—that capture the maximum variance.

To retain the most meaningful structure of the data while minimizing information loss, we selected the minimum number of principal components (PCs) required to explain 95% of the

total variance. This approach balances the need for reducing dimensionality with maintaining the integrity of the dataset. Following PCA, k-means clustering was applied on the selected principal components to categorize neuronal activity patterns during SWR. The Calinski-Harabasz criterion was used to determine the optimal number of clusters, ensuring that within-cluster variance was minimized while between-cluster variance was maximized. The final output consisted of cluster labels assigned to neurons based on their firing activity.

This combined approach of PCA-based feature extraction and k-means clustering enables an efficient and interpretable classification of neuronal population activity, facilitating a better understanding of how different neurons respond varying around the SWR events. A 50 ms window centered on SWR events was compared to a 50 ms baseline window of spontaneous activity (250ms earlier than SWR event) using a two-sample t-test (ttest2) with a significance level (α) set to 0.01.

Electrolytical Lesioning

We electrolytically lesioned the brain from selected and working channels (impedance magnitude at 1kHz $<5\text{M}\Omega$). We applied $\pm 7\text{ }\mu\text{A}$ direct current (DC) for 5 seconds (for each polarity). After applying DC from each selected channels, we waited for 45 minutes for lesion formation in the tissue.

Immunostaining

Rat brain sections were prepared for histological analysis according to an established protocol. After thoroughly washing the brains with PBS, they were horizontally sectioned into 100 μm thick slices using a vibratome (Leica VT1200S) at a speed of 50 $\mu\text{m}/\text{sec}$. The sections were stored overnight in PBS at 4°C before proceeding with immunostaining.

The sections were first incubated in a permeabilization solution containing 0.3% Triton X-100 in PBS for 30 minutes at room temperature with gentle shaking. Blocking was then performed using a buffer containing 1% Bovine Serum Albumin (BSA) and 0.3% Triton X-100 in PBS for 2 hours at room temperature. Primary antibodies, Rabbit anti-IBA1 (019-19741, FUJIFILM Wako) for microglia and Chicken anti-GFAP (PA1-10004, Thermo Fisher) for astrocytes, were diluted to a concentration of 1:1000 in the blocking buffer and applied to the sections. The sections were incubated for 3 days at room temperature.

After the primary antibody incubation, the sections were washed once with 0.3% Triton X-100 in PBS, followed by three 10-minute washes with PBS alone. For secondary antibodies, either Donkey anti-Rabbit Alexa Fluor 488 (A48283, Thermo Fisher) or Goat anti-Rabbit Alexa Fluor 555 plus Fab2 (A48283, Thermo Fisher) was used to detect Rabbit anti-IBA1, while Goat anti-Chicken Alexa Fluor 647 (A32933, Thermo Fisher) or Goat anti-Chicken Alexa Fluor 647 (A32931, Thermo Fisher) was used to detect Chicken anti-GFAP. The secondary antibodies were diluted to a concentration of 1:500 in the blocking buffer and applied to the sections, which were then incubated for 2 days at room temperature. Following this incubation, the sections were washed once with 0.3% Triton X-100 in PBS, followed by three 10-minute washes with PBS alone.

The sections were then counterstained with either Neurotrace 530/615 Red Fluorescent Nissl Stain (N21482, Thermo Fisher) or Neurotrace 640/660 Fluorescent Nissl Stain (N21483, Thermo Fisher) at a concentration of 1:200 overnight. Subsequently, the sections were washed once with 0.3% Triton X-100 in PBS, followed by three washes with PBS alone for 10 minutes each, counterstained with DAPI at a concentration of 1:1000 for 30 minutes, and then washed once more with 0.3% Triton X-100 in PBS and three times with PBS alone for 15 minutes each. Finally, the sections were mounted on glass slides using iohexol as the mounting medium, ensuring they were completely dry and sealed with nail polish.

Imaging of Histological Brain Slices and Statistical Analysis

Imaging of the prepared brain sections was performed using an Olympus IXplore Spin spinning disk confocal microscope. Serial 100 μm -thick brain slices were initially scanned with the Olympus UPLXAPO 4x/0.16 air objective to obtain single-plane overview images of the entire brain slice. This initial scan allowed for the precise localization of electrodes within the brain. High-resolution z-stacks of the identified electrode implantation sites were then acquired using either the Olympus UPLXAPO 20x/0.80 air objective or the Olympus UPLSAPO 30x/1.05 silicon objective. These high-resolution scans were used to quantify microglia, astrocytes, and neurons in the vicinity of the electrodes within the brain tissue.

The confocal setup utilized a Prime BSI Scientific sCMOS camera to capture 16-bit images at a resolution of 2048 x 2048 pixels. Fluorescence excitation was achieved with laser lines at 405 nm, 488 nm, 561 nm, and 640 nm, and exposure times varied from 200 to 300 ms depending on the channel. Laser intensities were adjusted between 5% and 20%, corresponding to 0.5 to 5 mW, to optimize imaging conditions. Z-stacks were acquired with a z-step size of 5 to 10 μm .

From the borders of UFTE cross-sections, equidistance circular contours (40 μm separation, until 320 μm) were defined (Figure 5C). We calculated the mean fluorescence intensity (FI) in all three imaging channels for the areas defined by eight consecutive contours ($n=13$ brain slices). The mean FIs were normalized to the mean of a large reference area (>700 μm away from the UFTEs). To define the control condition, we handpicked a region further away from (700 μm) the UFTEs and defined identical contours. The mean FI from control condition were also normalized. We masked the big vessels in the images. Welch's two-sample t-test is applied at each circular area defined by the contour between ROI (i.e. around the UFTEs) and control.

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