**NEUROTECHNOLOGY**

Human brain mapping with multithousand-channel PtNRGrids resolves spatiotemporal dynamics

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Electrophysiological devices are critical for mapping eloquent and diseased brain regions and for therapeutic neuromodulation in clinical settings and are extensively used for research in brain-machine interfaces. However, the existing clinical and experimental devices are often limited in either spatial resolution or cortical coverage. Here, we developed scalable manufacturing processes with a dense electrical connection scheme to achieve reconfigurable thin-film, multithousand-channel neurophysiological recording grids using platinum nanorods (PtNRGrids). With PtNRGrids, we have achieved a multithousand-channel array of small (30 μm) contacts with low impedance, providing high spatial and temporal resolution over a large cortical area. We demonstrated that PtNRGrids can resolve submillimeter functional organization of the barrel cortex in anesthetized rats that captured the tissue structure. In the clinical setting, PtNRGrids resolved fine, complex temporal dynamics from the cortical surface in an awake human patient performing grasping tasks. In addition, the PtNRGrids identified the spatial spread and dynamics of epileptic discharges in a patient undergoing epilepsy surgery at 1-mm spatial resolution, including activity induced by direct electrical stimulation. Collectively, these findings demonstrated the power of the PtNRGrids to transform clinical mapping and research with brain-machine interfaces.

**INTRODUCTION**

Functional mapping with direct electrical stimulation paired with neurophysiological recording is the gold standard for mapping the human brain and delineating the margins between functional and pathological tissue (1–4). Neurophysiological recording with nonpenetrating surface electrocorticography (ECoG) grids has been used for more than six decades to attain reliable clinical information and improve patient outcomes during surgical interventions (3, 4). ECoG grids can have cortical coverage of up to 8 cm by 8 cm and interelectrode pitch as small as 4 mm (2, 5–10). Higher-resolution grids such as the penetrating Utah arrays have less coverage (4 mm by 4 mm) and better pitch (0.4 mm) than ECoG grids but require invasive surgery to be implanted in deep brain areas (1, 11–14). These are the de facto standard for research on chronic neural prostheses for motor control and decoding language, as well as for providing sensory feedback in paraplegic individuals via closed-loop devices (5–10, 12, 15–23). Although great progress has been made using these devices, the next steps in neuromprostheses and neural decoding require higher spatial resolution (24–26) and expanded coverage of the cortex.

We used advanced thin-film microfabrication techniques and a biocompatible platinum nanorod (PtNR) (27) microelectrode material to develop large–surface area ECoG grids with both high resolution and broad spatial coverage. Our PtNRGrids are built on thin, conformal parylene C substrates, and the distribution of contacts is reconfigurable for different pitches and area coverage. We used compact one-touch connectors to enable a simple and reliable interface with thousands of channels that is amenable to the constraints of the operating room. Here, we demonstrated the use of these PtNRGrids to isolate submillimeter functional boundaries (FBs) of individual cortical columns in controlled animal experiments and neural mapping from both awake and anesthetized patients undergoing tumor or epileptogenic tissue resection.

**RESULTS**

Fabrication of multithousand-channel PtNRGrids and connectorization

PtNRGrids were composed of contacts embedded in flexible sheets of 6.6-μm-thick parylene C, especially designed for recording neural activity on the cortical surface (Fig. 1). The layout, shape, and size of the PtNRGrids were generated with customizable designs by leveraging established microelectromechanical systems fabrication techniques on large 18 cm–by–18 cm glass wafers and a newly developed, biocompatible PtNR (27) microelectrode material. This process produced multiple 17-cm-long and up to 8 cm–by–8 cm large–area coverage electrodes ranging from 1024 to 2048 electrode contacts or channels with high uniformity and yield (Fig. 1). The 30-μm-wide PtNR contacts were recessed by ~2 μm below the surface of parylene C to prevent shear forces on PtNRs during implant (Fig. 1B) (27). Between the PtNR contacts and the bond pads, we routed gold traces that were 500 nm thick, 4 μm wide, 6 μm apart, more than 10 cm long, and fully encapsulated between two layers of parylene C to prevent shear forces on PtNRs during implant (Fig. 1B) (27). Between the PtNR contacts and the bond pads, we routed gold traces that were 500 nm thick, 4 μm wide, 6 μm apart, more than 10 cm long, and fully encapsulated between two layers of parylene C to prevent shear forces on PtNRs during implant (Fig. 1B) (27).
parylene C (3.5 µm at the bottom and 3.1 µm at the top; Figs. S1 and S2). We patterned perforation holes in the parylene C throughout the thin grid to perfuse saline and cerebrospinal fluid away from the electrode contacts. Therefore, an intimate interface between the PtNRGrids and the surface of the brain was maintained, and electrochemical shunting between nearby recording contacts was avoided (Fig. S3). In addition, the large perfusion holes with diameters of 0.5 mm (Fig. 1C) and 0.9 mm (Fig. 1D) distributed across the grid provided access for probes of a handheld clinical stimulator to directly stimulate any point of the cortex through the grid. We varied the pitch/coverage of the 30-µm PtNR contacts from 150 µm/5 mm by 5 mm for rodent brain mapping (Fig. 1B) to 200 µm/3 mm by 13 mm (Fig. 1E), 1 mm/32 mm by 32 mm (Fig. 1C), and 1.8 mm/80 mm by 80 mm (Fig. 1D) for human brain mapping. The detailed fabrication process of the PtNRGrids can be found in the Supplementary Materials. The fabrication process of the multithousand-channel PtNRGrids is also compatible with poly(2,3-dihydrothieno-1,4-dioxin)-poly(styrenesulfonate) (PEDOT:PSS) (Fig. S4).

A major bottleneck for scaling microelectrode arrays toward hundreds or thousands of channels was the connectorization of electrodes to acquisition circuits. Inspired by solutions used in the microelectronics industry, which can reliably route high-bandwidth connections to thousands of channels (28, 29), we used an off-the-shelf land grid array (LGA), LGA1155 CPU socket, that was originally designed for the Intel’s Sandy Bridge computer processors. Manufacturing the grids on large-area substrates ensures sufficient space to bond the PtNRGrids to custom LGA-printed circuit boards (PCBs) that mate with the LGA1155 socket without compromising the large area coverage of PtNRGrids or their long thin-film metal leads (Fig. 1D). An additional extender board was used to further increase the separation between the surgical field and a custom acquisition board (fig. S5) and for improved intraoperative handling procedures. The acquisition board connects to a 1024-channel electrophysiology control system, provided by Intan Technologies LLC (fig. S6). The entire PtNRGrid and connector (Fig. 1C) were compatible with the conventional processes (30) used to sterilize surgical equipment, maintaining contact yields up to 99.4% with a narrow 1-kHz impedance distribution centered at 11 kilohm with an SD of 2 kilohm (Fig. 1, E and F), achieved with manual bonding of the electrodes to the PCB (fig. S3). The 1-kHz impedance magnitude, averaged over seven different PtNRGrids used in successful human recording experiments, was 10 ± 2 kilohm. The scalable process allowed us to obtain up to 95.2% contact yield with impedances ≤ 100 kilohm even when the total channel count increased to 2048 (Fig. 1F). The simple, one-touch connector methodology enabled our neurosurgical and research team to swiftly and reliably connect thousands of channels to the acquisition board across the boundary between the sterile and non-sterile zones. As a result, sterilization was limited to the disposable
grid and its connector, eliminating the need to sterilize the acquisition electronics. The setup allowed us to record simultaneously from 1024 channels with a sampling rate of 20,000 samples/s, thereby capturing full-bandwidth neurophysiological activity.

The measured parasitic capacitance between neighboring channels on the PtNRGrids showed 10 million times higher impedance at 1 kHz than the electrochemical impedance, resulting in −60 dB cross-talk as estimated by our measurements and simulations (see figs. S7 to S12). The PtNRGrids also exhibited mechanical stability exceeding the American National Standards Institute/Association for the Advancement of Medical Instrumentation ANSI/AAMI C186:2019 recommendations (fig. S13).

**PtNRGrids isolate functional cortical columns from the surface of the brain**

To test the broadband and high-resolution recording capabilities of the PtNRGrids, we mapped the primary somatosensory cortex of anesthetized rats. The rat cortex has well-defined organization of the somatosensory cortical structures, especially around the barrel cortex, where a series of sensory cortical columns map one to one with the whiskers. (31, 32) A square-shaped 1024-channel PtNRGrid with 150-μm pitch (Fig. 1B) was implanted to record from the entire right primary somatosensory barrel cortex (Fig. 2). To evoke sensory activity, air puffs were delivered through a microcapillary tube to individually stimulate the contralateral-side whiskers (Fig. 2A and fig. S14). We consistently observed large-amplitude raw evoked responses (N = 50) for whisker (E4) stimulation (Fig. 2B). The raw waveforms exhibit localized, high-amplitude responses as large as 500 μV with peak responses observed ~30 ms after the onset of the air puff (Fig. 2C). These responses propagated as traveling waves across the cortical surface (fig. S15). The cortical wave propagation was calculated by taking the spatial phase gradients of the beta band (13 to 30 Hz) following the methods described in the works of Rubino et al. (33) and Muller et al. (34). Vector fields express the propagating directions of beta waves, and blue and red colors in the background show amplitudes of beta and high-gamma activities (HGAs), respectively (fig. S15). We observed well-differentiated regions for the sources of the beta waves and their destinations, as well as submillimeter-scale spiraling waves.

The spatial localization of individual stimuli is best represented in the gamma band (30 to 190 Hz), as expected, and observed in the root mean square (RMS) power of the measured responses when bandpass filtered (Fig. 2D). The HGA (70 to 190 Hz) is known to be highly correlated to the location and timing of cortical activation with a strong link to spiking activities (35), so we used HGA to map the FBs of the rat barrel cortex (Fig. 2E). We observed clearly distinguishable submillimeter sensory boundaries that classified the responses to different whisker rows and columns, revealing spatially organized barrels with high spatial resolution. The locations of...
sensory-responsive areas were also identified by evoking cortical responses with air-puff stimulation of the neck, trunk, and tail and by electrical stimulation of the forepaw and hindpaw (Fig. 2E). The detailed signal processing procedures for HGA mapping (figs. S16 to S19) and the results across different rats (n = 4) could be found in the Supplementary Materials (fig. S20). After completion of functional mapping, the implanted area was marked, and histochemical analyses were used to examine the anatomy under the implant.

The anatomical and FBs were in agreement, as outlined using the vesicular glutamate transporter 2 (VGLUT2), a well-established marker of thalamocortical afferents that compose the homunculus, including the barrels (Fig. 2F) (36). The localized HGA responses to whisker stimuli agree remarkably well with the VGLUT2-labeled positions of the barrels and the homunculus-labeled positions of the forelimb, hindlimb, neck, trunk, and tail (Fig. 2G). Thus, this single-grid–based mapping provides a reliable, real-time high-resolution functional mapping of the rat brain, which contrasts with the traditional serial probing while recording evoked responses (37, 38).

**PtNRGrids resolve the curvilinear nature of the human M1-S1 FB**

Precise intraoperative localization of the central sulcus, the boundary between primary somatomotor (M1) and somatosensory (S1) cortices, is a necessary approach in several neurosurgical procedures, particularly in the resection of tumors. This anatomical boundary is identified by a functional phase reversal of somatosensory evoked potentials (SSEPs) at the boundary between M1 and S1 (39, 40), an a priori assumed anatomico-functional relationship. Most commonly, these SSEPs, recorded in response to electrical stimulation pulses to the peripheral nerves, are evoked 20 ms after stimulus and demonstrate opposite polarity in their potentials across this boundary. The presence of pathological tissue can induce a shift in the functional organization and location far from its presumed anatomical localization (41, 42) and make traditional sulcal markers harder to discern with low spatial resolution of clinical ECoG grids.

We recorded SSEPs from awake subjects (n = 4) undergoing tumor resection, each with a 1024-channel PtNRGrid with 1-mm spacing (Fig. 1C) placed across the central sulcus near the hand region of the somatomotor sensory cortex while peripheral nerves were stimulated (Fig. 3, A and D, and figs. S21 and S22). The implantation site of the PtNRGrid was marked and identified on a reconstructed model of the patient’s brain along with lesion location based on functional magnetic resonance imaging (fMRI) and structural MRI (Fig. 3A). We observed a small stimulus artifact from peripheral nerve stimulation that was followed by high-amplitude SSEPs at 10 to 40 ms (Fig. 3B). These waveforms revealed characteristic positive and negative peaks (43) that reversed phase at the FB denoting the M1-S1 FB (Fig. 3B). The spatially mapped SSEP waveforms captured by the entire PtNRGrid (fig. S23) again clearly demonstrate phase reversal boundary on the cortical surface. Similar SSEP waveforms were recorded with a conventional, dual-column, 2 × 8, 16-channel clinical ECoG grid with 10-mm spacing and 2.3-mm-diameter recording contacts (Fig. 3C and figs. S24 and S25). The maximum interpeak amplitude of SSEPs measured by the PtNRGrid was 214 μV (Fig. 3B), whereas SSEPs measured by the clinical ECoG grid (Fig. 3C) on the same patient only showed 5-μV interpeak amplitude.

The PtNRGrids revealed the precise curvilinear nature of the M1-S1 FB with millimeter-scale resolution at a sampling frequency of 20 kHz. The subject’s lesion (Fig. 3A) contributed to the broadening and distorting of the SEP waveforms on both the PtNRGrids (Fig. 3B) and on the clinical ECoG (Fig. 3C), in agreement with the findings of prior clinical studies (39). In addition, the SSEPs recorded with the PtNRGrid were minimally affected by the presence of underlying surface blood vessels (44). The waveform shapes and amplitudes (“CS” denoting the anatomical central sulcus in Fig. 3B and fig. S26) of the channels on top of the blood vessel did not show any noticeable difference compared to those of the adjacent channels. Although the SSEPs were minimally affected by the blood vessel (fig. S26), it is reported that higher-frequency signals (30 to 70 Hz) could be attenuated by 30 to 40% by the presence of the blood vessel (44).

To construct the two-dimensional maps for the curvilinear FB, we used the conventional potential-based phase reversal technique (Fig. 3E) and a correlation technique that we devised to identify the FB in diseased tissue (Fig. 3F). We calculated the Pearson correlation coefficients of the waveforms between 5 and 50 ms after stimulus for all the working channels with respect to the channel in the middle of the grid. Channels with correlation coefficients above or below 0.5 were separated by a dotted line to depict the M1-S1 FB (Fig. 3F), which agrees well with that deduced directly from potentials maps (Fig. 3E). We observed a highly detailed spatial map depicting considerable offset, based on SSEPs (Fig. 3) and HGA (Fig. 4), between the M1-S1 FB and the anatomical central sulcus using the PtNRGrid (FB versus CS in Fig. 3D), consistent with functional reorganization with brain lesions (41, 42). However, it is important to note that these SSEPs are projections of event-related potentials from deeper layers that are often oblique to the plane of the cortical surface. Extension of this FB below the surface must be validated with depth recordings (45). Nevertheless, the M1-S1 FB revealed by the PtNRGrid was concordant with the gold standard clinical mapping using conventional bipolar stimulation and with higher resolution than conventional clinical ECoG grid passive gamma mapping using CortiQ system.

We also recorded SSEPs from the human brain using a 2048-channel PtNRGrid with 1.8-mm pitch (Fig. 1D and figs. S27 to S29). The waveforms (30 to 3000 Hz, N = 22) exhibit clear P20-N20 peak responses of ~20 ms after the median nerve stimulation (Fig. 3G). The severe anatomical distortion and the limited time of recording precluded assessing a FB in this return surgery (fig. S30). Nevertheless, the results of Fig. 3G illustrate that the scalable PtNRGrids enable multithousand-channel recordings from the human brain. PEDOT:PSS electrodes (1024 channels) with 1-mm pitch and 100-μm electrode contact diameter also recorded SSEPs from the human brain with an interpeak amplitude up to 57 μV (fig. S31).

**PtNRGrids reveal large-scale spatiotemporal dynamics of motor and sensory activity in humans**

Motivated by the rise of interest in using ECoG grids for brain-machine interfaces (5, 8–10, 21–23), we investigated whether the high spatial and temporal resolution of the PtNRGrid could be used to map sensory- and motor-evoked activities. Following the phase reversal mapping of the functional M1-S1 boundary and with the same PtNRGrid placement on the same participant, we either stimulated individual fingers with vibrotactile stimulators or asked the patient...
We next demonstrated the high spatiotemporal capabilities of the PtNRGrids during a hand grasping task (Fig. 4, D to L). As with the vibrotactile stimulation, we observed highly localized HGA on the PtNRGrid during the motion (Fig. 4G), near completion of motion (Fig. 4H), and for 100 ms after completion of motion (Fig. 4I) (see also movie S1). Furthermore, coordination between the S1 and M1 cortices during the grasping task could be seen at high resolution via the PtNRGrid. In a snapshot of the dynamics through time along a single line of electrodes cut across a corner of the grid (highlighted by the yellow rectangle in Fig. 4I), we illustrate the spatial dynamics for the selected 16 channels across the M1-S1 boundary for the HG (Fig. 4E) and beta (Fig. 4F) bands. These band-specific (spectrotemporal) dynamics showed remarkable correlation with the hand movement captured by time-locked flex sensors on the subject's hand (Fig. 4D). Distinctive HGA in the M1 cortex was observed during motor initiation, was seen in both M1 and S1 cortices during the hand closure onset, and, lastly, lingered only within the S1 cortex when the motion was complete. High-amplitude beta wave in the M1 cortex was observed before the motion, during the planning stage, attenuated during execution of the motion, and increased once again after the motion was completed (Fig. 4, D to F). Similar behavior was observed under trials of repeated hand grabbing motion (see fig. S33). These observations of alternating amplitude in HGA and beta activity before, during, and after the motion agree with prior observations (46–48).

Last, we showed that with the large channel count of the PtNRGrid, we could construct maps of brain wave propagation at high spatial resolution within a physiologically relevant cortical coverage (Fig. 4, J to L, and fig. S34). During the hand grasping task, we calculated the spatial gradient of the phase of the beta waves (13 to 30 Hz) (33, 34) recorded by our PtNRGrids to infer propagation direction (Fig. 4, J to L, and movies S2 and S3). We further overlaid streamlines originating from selected regions in the S1 and M1 cortices on top of the vector fields for a visual aid of the long-range propagation directions. We found clear propagation dynamics across the M1-S1 FB, which correlated with the hand grabbing motion. In the preparation stage of the motion, we observed noticeable long-range beta waves propagating from the S1 cortex to M1 cortex (Fig. 4I). During the motion, the beta waves were suppressed to perform specific hand movements (Fig. 4A and fig. S32). After individual fingertip stimulation, we observed a clear enhancement in HGA as large as 3σ from baseline (Fig. 4B), the largest of which was localized only in the primary somatosensory cortex (Fig. 4B). Vibrotactile stimulation of each fingertip evoked spatially distinctive HGA patterns, with some channels tuning to all fingertips with varying magnitudes. After superimposing HGA on an optical image of the implanted PtNRGrid, we could observe the fine spatial distribution of the neural correlates of vibrotactile stimulation and compare this with the M1-S1 boundary and the cortical anatomy using phase reversal (Fig. 4C).

Fig. 3. Mapping the curvilinear nature of the functional sensory/motor regions in the human brain with millimeter resolution. (A) Reconstructed model of the patient's brain and the electrode implantation locations. Electrodes were implanted near the hand region, and the peripheral nerve was electrically stimulated. Somatosensory evoked potential (SSEP) waveforms along a line across the central sulcus (CS) and M1-S1 functional boundary (FB) recorded with a 32 × 32 PtNRGrid with 1-mm spacing and a 2 × 8 clinical grid with 10-mm spacing. (D) Implantation picture of the electrodes near the hand region. (E) A 1024-channel potential mapping of the stimulation-evoked waves 28 ms after the stimulation [as opposed to 20 ms due to distortion from brain lesion as shown in (B) and (C)]. (F) Correlation coefficient mapping with respect to the waveforms measured with respect to the channel in the center of the grid. (G) Human brain SSEPs from a 2048-channel PtNRGrid. Channels are sorted according to the peak potential amplitude and polarity at 20 ms after the stimulation, and channels with high contact impedance were excluded from the plot. PrG: precentral gyrus, PoG: postcentral gyrus.
and exhibited lack of coherence in the vector fields (Fig. 4K). After the motion was complete, the propagating direction reversed, as represented by the streamlines (Fig. 4L and atop a reconstructed brain model in movie S4). Similar propagating wave dynamics were reproduced in multiple hand grabbing motions (fig. S35). Higher wave propagation speed was observed between the electrodes placed across the central sulcus, which is an artifact, considering that the adjacent electrodes placed across the sulcus are separated by up to a few centimeters on an unfolded cortical surface (fig. S36). Because slightly different frequency windows of 9 to 18 Hz (34) and 10 to 45 Hz (33) were selected in prior works for the propagating beta wave analysis, we repeated the propagating beta wave analysis at three different frequency windows: 13 to 30, 9 to 18, and 10 to 45 Hz (figs. S37 and S38). All three beta wave frequency windows showed that the beta wave amplitude (fig. S37) and propagating wave directions (fig. S38) before, during, and after the hand movement were consistent with each other. By detecting the propagation dynamics of beta waves with high spatial resolution at physiologically relevant coverage using our PtNRGrids, we have enhanced functional mapping by revealing large-scale brain activity across frequency bands.

**Fig. 4. Functional mapping with millimeter resolution: PtNRGrid records detailed sensory and motor spatiotemporal dynamics in humans.** (A) Schematics of the sensory and motor experiments. For sensory experiment, individual fingers were stimulated by vibrotactile stimulation in sequence with 1-s stimulation at 2-s intervals. For the motor experiment, the patient was asked to perform a grasping task. (B) Spatial mapping of HGA of individual fingers in response to vibrotactile stimulations. (C) Overlay plot of HGA sensory responses for individual fingers superimposed on top of a photo of the surface of the patient’s brain. (D) Motion of the hand recorded with the bending sensor. The amplitude of (E) HGA and (F) beta activity of channels selected along the yellow diagonal rectangle in (I) plotted over a 1-s time window during the motion. Spatial mapping of HGA over three different time points during the hand grabbing motion. (G) Initially localized HGA appears on the motor region, (H) then both the motor and sensory regions show HGA, and, (I) eventually, the HGA only appears on the sensory region. Propagating beta waves and waveforms across the CS in the (J) planning stage of the motion, (K) during the motion, and (L) after the completion of motion. The red and blue streamlines originate from the sensory and motor cortices, respectively. The background color represents the amplitude of the beta wave potential, and the arrowheads indicates the propagating direction of the beta waves. Right plots are raw waveforms for the yellow box in (I) around the timestamps of (J) to (L).

PtNRGrids record pathological wave dynamics

Last, we determined the utility of PtNRGrids for high-resolution intraoperative neuromonitoring to detect ictal onset zones and patterns of seizure spread. PtNRGrids (1-mm spacing, 32 × 32 contacts, and 0.5-mm-diameter perfusion holes; Fig. 1C) were placed over the cortex in a patient with intractable epilepsy related to a left anterior temporal lobe cavernoma who was elected for surgical resection (Fig. 5A). Using PtNRGrids allowed passive recordings of local field potential and active electrical stimulation through the perfusion holes (uniformly distributed at 0.5-mm diameter and 1-mm spaced; Fig. 5A) using a standard handheld clinical stimulator.
Fig. 5. Pathological mapping with millimeter resolution: PtNRGrids reveal detailed spatiotemporal dynamics of spontaneous and stimulated epileptiform discharges from a patient with epilepsy. (A) Left: Reconstructed model of electrode placement on the temporal lobe of the patient's brain and the schematics of charge-balanced biphasic direct current stimulation with the bipolar (Ojemann) probe. Middle: Magnified model near the electrode. Right: Photo showing the cortical tissues directly being stimulated through the electrode. Inset is a magnified image showing the 0.5-mm-diameter perfusion holes that are distributed at a 1-mm pitch on the electrode, allowing direct current stimulation at any point on the grid. Positions of the superior temporal sulcus (STS), superior temporal gyrus (STG), and middle temporal gyrus (MTG) are marked on the photo. Anatomical orientation arrows indicate anterior (A), posterior (P), and inferior (I). (B to F) Spontaneous epileptiform discharges. (B) Spatial mapping of the 10- to 59-Hz spontaneous brain wave amplitude. The location of STS is marked with dotted lines. (C) Streamlines plot at 0.9 s depicting the spontaneous propagating wave together with the vectors indicating the direction of propagating waves. Automatically detected epileptiform discharges for all channels in (D) 4-s and (F) 20-s time windows. (E) Raw waveforms selected from arrow-marked channels of (D). The channels are sorted according to the distance from the right lower (RL) corner of the electrode; the channel in the midline is closest to the lower right corner. (G) Time course and recordings of the stimulation pulse artifacts for time locking with evoked response. The stimulation sequence number and duration of stimulation time are indicated below the waveforms. (H) Number of channels showing epileptiform activity over time. (I) Spatial mapping of epileptiform discharge rate after each stimulation trial. Stimulation locations on or near the electrode are indicated by pair of blue dots for the 14 stimulation trials. (J to M) Stimulation-evoked epileptiform discharges, similar to (B) to (F). (J) Spatial mapping of the 10- to 59-Hz stimulation-evoked brain wave amplitude. (K) Streamlines plot at 2.7 s depicting the stimulation-evoked propagating wave together with the vectors indicating the direction of propagating waves. (L) Automatically detected epileptiform discharges for all channels in a 4-s time window. The channels are sorted according to the distance from the stimulation point. (M) Raw waveforms selected from arrow-marked channels of (L). Propagating waves for (C) spontaneous epileptiform discharge and (K) stimulation-evoked epileptiform discharge. The red streamlines for (C) originate from the right lower corner, whereas those for (K) originate near the stimulation location. The blue circles in (K) are the bipolar stimulator contact points on the cortex.
than the less-frequent spontaneous epileptiform discharges. These charges occurred every 0.3 s and continued for a longer duration events according to distance from the stimulation center (Fig. 5L), movie S7). By sorting the automatically detected epileptiform activity persisted across the entire recording. Regardless of time (Fig. 5, D and F). After sorting the channels according to the distance from the lower right corner, we found a 20-s window with repetitive epileptiform events occurring about every 4 s across the entire grid (Fig. 5F), which is magnified to show a single event of a recurring epileptiform waveform within a 4-s time window (Fig. 5, D and E). These repeated epileptiform waves consistently originated from the lower right corner of the grid, spread across the entire grid within 1 s, and subsequently disappeared 1 s later. Automatically detected epileptiform events (Fig. 5E) exhibit clear temporal shifts between the spontaneous epileptiform waveforms from channel to channel (overlayed on a reconstructed brain model of the participant in movie S6). Collectively, these maps and videos provide further evidence of utility for the PtNRGrids for high-resolution mapping of such pathologic activity.

Active mapping was performed in the same patient (Fig. 5, G to M). Using the same epileptiform discharge detection algorithm as Fig. 5D, we counted the number of channels on the PtNRGrid that detected epileptiform discharges and plotted the number of events as a function of time (Fig. 5H). Spontaneous and repetitive epileptiform activity persisted across the entire recording. Regardless of the stimulation location, we observed that stimulation pulses with short duration (<1 s) did not increase the underlying spontaneous epileptiform discharge activity (Fig. 5I). However, longer stimulation trials of 1.4 to 1.9 s such as trials 4, 5, and 6 significantly increased the number of epileptiform discharge events ($P < 0.001$) for the recording channels within 16 mm from the stimulation point ($N = 471, 199, and 304$ for trials 4, 5, and 6, respectively), particularly events with characteristics similar to interictal discharges. The duration of the pulse determines the total delivered charge density that is correlated with evoked responses (54, 55). The spatially resolved heatmaps of the stimulation-evoked activity can be clearly observed where it can be noted that the longer trials (4 and 6) were characterized by significantly enhanced after-discharges detected around the stimulation positions ($P < 0.001$) (Fig. 5I).

In stimulation-evoked epileptiform discharges, we found a clear enhancement of the amplitude of detected epileptiform activity within the 10- to 59-Hz frequency window, which persisted for more than 5 s after the bipolar stimulation ceased (Fig. 5; see also movie S7). By sorting the automatically detected epileptiform events according to distance from the stimulation center (Fig. 5L), we observed that the first epileptiform events were initiated near the stimulated region. After stimulation, bursts of epileptiform discharges occurred every 0.3 s and continued for a longer duration than the less-frequent spontaneous epileptiform discharges. These phenomena are clearly exhibited in the raw waveform recordings from selected channels (Fig. 5, L and M) and can be viewed atop a reconstructed brain model of the participant (movie S8).

Last, we investigated the origin and spatiotemporal dynamics of both the spontaneous and stimulation-induced epileptiform activity using vector fields and streamlines. Immediately before epileptiform events, the vector fields are mostly incoherent (figs. S40 and S41) but become coherent near the larger-amplitude epileptiform events. The characteristics of the spontaneous epileptiform activity can be inferred from the red streamlines that originate from the right lower corner near the location of the lesion in this patient (Fig. 5C). In contrast, the streamlines for stimulation-evoked epileptiform activity originate and spread away from the position of the stimulator (Fig. 5K), demonstrating high-resolution spatial and temporal mapping of the sites of origin. Representative coherent streamlines and vector field arrows were selected to better illustrate the long-range propagating dynamics of epileptiform events (Fig. 5, C and K). The entire streamlines and vector field of epileptogenic activities at different time points are shown in fig. S40 for the spontaneous and in fig. S41 for the stimulation-evoked activities. The epileptogenic tissue tested by this experiment was removed as a planned left temporal lobectomy, which included lesional (cavernoma) tissue and all the epileptic neocortical tissue discerned by prior stereoelectroencephalography seizure mapping and was deemed resectable as well by the PtNRGrid. The patient remained seizure free to the date of this manuscript synthesis, which is about 6 months after surgery.

**DISCUSSION**

Our studies demonstrate the range of utility of PtNRGrids for high spatial and temporal recording of neural activity for research and clinical intraoperative use. The PtNRGrids were built on thin, transparent, and conformal substrates and were reconfigured in pitch and total cortical coverage with 1024 and 2048 low-impedance contacts over an area as large as 8 cm by 8 cm, scalable for rodent or human work. The fabrication was performed on a large-area, 180 mm–by–180 mm glass substrate with thin-film processes substantially advancing the manufacture of neural probes beyond the conventional 100-mm and 150-mm silicon (Si) substrates. The larger-area manufacturing afforded the capability to connect to thousands of channels and the formation of long metal strips to isolate the sterile surgical medium from the acquisition electronics for patient safety. In addition, the fabrication process afforded large-area coverage of the PtNRGrids on the brain (up to 8 cm by 8 cm achieved in this work) and safety and sterility in the operating room for intraoperative monitoring purposes. Successful transition to the large-area glass substrates opens the possibility of integrating the display panel–manufacturing technology with neurotechnology and promises excellent scalability, considering the size of the glass panel used in display industry (up to a few square meters) and the high-resolution lithography capability (1.2 μm for both metal line and space) of flat panel displays (56). The large-area glass substrates also offer potential advances in manufacturing biomedical devices for use in humans that can leverage electronic (thin-film transistors) and optoelectronic (light-emitting diodes and imagers) advances achieved by the display industry for utility in human biomedical devices. A commonly voiced concern over increasing the channel count of microelectrode arrays is the potential for electrical cross-talk to
introduce artifacts into the neurophysiological recordings. This
electrical cross-talk is primarily a result of parasitic capacitance
between neighboring leads and thus will scale directly with increas-
ing trace length and inversely with their trace pitch. Thus, traces
should be kept short to reduce these parasitic paths. The termination
impedance of neighboring channels to tissue (the electrochemical
interfacial impedance) also needs to be accounted for, especially
for conventional high-impedance electrochemical interfaces, which
can affect cross-talk through parasitic capacitance paths. However,
this is not a concern for the low-impedance PtNR contacts, which
maintain 1-kHz impedances that are at least 10 million times lower
than the impedance of the parasitic capacitances.

We show high-fidelity broadband recordings from rodents,
where the high spatial resolution of the PtNRGrids enabled identi-
fication of individual cortical columns from the surface of the brain.
The PtNRGrids were easily translated to the intraoperative setting,
allowing the first human recordings with 1024-channel PtNRGrids
from 13 subjects and 2048-channel PtNRGrids from 1 subject. The
PtNRGrids mapped sensory and pathological epileptiform activity
from the surface of the brain and detected relevant somatosensory
dynamics in high spatial resolution over a physiologically relevant
cortical coverage. Previous investigations of propagation character-
istics of beta waves in the human brain were carried out with a rela-
tively small area coverage of 4 mm by 4 mm using Utah arrays
(33, 57) or with ECoG grids with sparse 1-cm spatial resolution (34).

The PtNRGrids revealed the precise curvilinear nature of the
M1-S1 FB with millimeter-scale resolution at a sampling frequency
of 20 kHz, superior to the low-resolution boundaries identified with
conventional ECoG grids (43) or the temporally limited fMRI (58).
The SSEPs measured with PtNRGrids had interpeak amplitudes up
to 214 µV, compared to the 5-µV interpeak amplitudes measured
on the same patient with the clinical grid. Note that interpeak
amplitudes have been observed to fall within a range of 5 to 120 µV
in a 230-patient study of clinical ECoG grid recordings (39). The
lower amplitudes on the clinical grid can be attributed to both a
spatial averaging on their ~6000× larger surface area than the PtNR
contacts and a lower conformity to the brain surface resulting from
the 1-mm-thick substrate used in clinical grids (compared to the
6.6-µm-thick parylene C substrate used in our PtNRGrids). It is also
possible that the clinical ECoG grid that has sparsely distributed
contacts (1 cm) missed the cortical region with the highest SSEP
amplitude because it is a usual practice to adjust the location and
angle of the clinical ECoG grid to obtain maximum peak amplitude
(39). We demonstrated high-resolution recordings from the surface
of the human brain with 1024- and 2048-channel PtNRGrids, which
enable high-resolution intraoperative recordings in neurosurgical
operations, estimated to be as many as 13.8 million annually (59).
However, the system in its current form does not enable chronic
recordings, which have different design considerations that are
beyond the scope of this work. To achieve chronic recordings, either
denser custom-made connectors that are slim enough to be exter-
nalized through the scalp, as done in epilepsy monitoring, or direct
integration of integrated circuits and wireless transceivers to the
implant becomes necessary (25, 60). The engineering challenges for
each part of the implant increase, and their safety and the durability
of efficacy become critical.

We demonstrated a recording density up to 4444 cm −2 (contact
pitch, 150 µm) using a single metallization layer of 10-µm-pitch
metal leads and 30-µm-diameter PtNR contacts. To increase the
recording density, the width of the metal leads would need to
decrease to enable tighter pitch, and thickness would need to in-
crease to maintain low metal lead impedance. There are practical
lithographic limitations for patterning narrow and thick metal leads
necessitating the use of multilayer metallization, which relaxes the
constrains on the metal lead width. By making dual- and triple-layer
electrodes, the electrode density can increase up to 17,776 cm −2
(contact pitch, 75 µm) and 71,104 cm −2 (contact pitch, 37.5 µm),
respectively. Higher recording densities beyond 71,104 cm −2 would
require a smaller PtNR contact diameter. A trade-off between the
recording density and the impedance magnitude of the individual
contacts will need to be considered.

The development of a real-time display of PtNRGrid recordings
in a meaningful and potentially medically informative way holds
the potential to improve surgical procedures. Although the higher-
resolution mapping can carry important implications for neurosur-
gical procedures, it is important to note that the surgical precision
in current clinical practice does not meet millimeter-scale resolu-
tion. However, surgical resection boundaries obtained with current
clinical electrodes are grossly determined with their 1-cm contact
spacing. We anticipate that the PtNRGrids that determine surgical
boundaries with millimeter-scale resolution might inform better
resection practices by delineating the curvilinear nature of the func-
tional and pathological boundaries that is not possible otherwise.
With the development of higher-precision resection methods such as
laser ablation or robot-assisted surgery, millimeter-scale spatial
resolution recording might be useful for performing millimeter-scale
resection of the brain tissue.

Last, the PtNRGrids were used for passive mapping in this work.
Although the PtNRGrid has perfusion holes that enabled bipolar
stimulation with external devices, direct current stimulation through
the grid is desired. In addition, microstimulation of smaller tissue
volume may be preferred, particularly for individual functional cor-
tical columns that were isolated using the PtNRGrids. Extension of
this work should enable stimulation through the PtNRGrids, which
were shown in our earlier work, to hold one of the highest charge
injection capacities for safe stimulation (27).

PtNRGrids hold promise for superior mapping during neuro-
surgical intervention through high spatial resolution and coverage
while maintaining excellent broadband temporal resolution com-
pared to the clinical electrodes. PtNRGrid technology has the
capacity to scale to more than 2048 channels, to pave the way for
better neurosurgical mapping strategies, and to enable possibilities
for therapies, brain-computer interfaces, and better patient outcomes
as the technology is advanced for chronic applications.

MATERIALS AND METHODS

Study design

Objectives of the study were to (i) demonstrate that 1024- and
2048-channel PtNRGrids have higher spatial resolution that better
delineated FBs in the human brain than the standard clinical elec-
trodes, (ii) test the signal amplitudes of PtNRGrids compared to the
standard clinical electrodes, (iii) isolate the neural correlates and
dynamic activity during motor and sensory tasks with high spatial
resolution with the PtNRGrids, and (iv) investigate the microscale
dynamics of spontaneous and stimulation-evoked epileptic dis-
charges with the PtNRGrids. All animal experiments were approved
by the University of California San Diego (UCSD) Institutional
Animal Care and Use Committee under protocol 016020. We successfully gathered surface ECoG recordings of all intended stimulus-evoked responses and gathered postmortem histological stains from two rats. These data were not blinded, and we did not include a randomization of subject selection in this study.

Twenty human subjects were recruited to participate in this study under two Institutional Review Board (IRB) approvals (UCSD IRB #181556 and Oregon Health and Science University IRB #190999). Subjects were considered for recruitment if the details of their surgery coincided with a particular experimental paradigm, for example, motor mapping experiments required patients with an exposure of the motor and sensorimotor cortex and required clinical motor mapping to be part of their normal clinical care. We selected the types of PtNRGrids and tasks depending on the location and size of the craniotomy determined by the clinical team. Participants were informed of the research and given time to understand the benefits and risks of participation before being asked for consent. Data from each participant were deidentified before analysis, and each experimental paradigm included controls for acquiring a baseline recording before or throughout the given recording period. Trial numbers within a given subject recording were determined on the basis of a maximum recording time of 15 min in the operating room setting along with the number of variables being swept. The data collected from subjects with severe brain tumor; low responsiveness due to age, anesthesia, or surgical procedures; or task-unrelated cortical exposure were excluded from the study. We did not include a randomization of subject selection in this study because patient data were considered separate datasets. Experimental conditions and a summary of all subjects are presented in table S1.

**Statistical analysis**

All statistical comparisons were performed using nonparametric measures, so we did not test for normality. Spontaneous epileptiform discharge rates for each recording channel detected using automatic algorithms (53) were estimated from the 6-min baseline recording data. After-discharge rates induced by stimulation for all recording channels were estimated from the 6-min baseline recording data. After-discharge rates induced by stimulation for all recording channels were the recording channels within a given subject recording were determined on the basis of the maximum recording time of 15 min in the operating room setting along with the number of variables being swept. The data collected from subjects with severe brain tumor; low responsiveness due to age, anesthesia, or surgical procedures; or task-unrelated cortical exposure were excluded from the study. We did not include a randomization of subject selection in this study because patient data were considered separate datasets. Experimental conditions and a summary of all subjects are presented in table S1.

**REFERENCES AND NOTES**


**SUPPLEMENTARY MATERIALS**

www.science.org/doi/10.1126/scitranslmed.abj1441

Supplementary Materials and Methods Fig. S1 to S41, Tables S1 and S2, Movies S1 to S8, References (61–64)

View/request a protocol for this paper from Bio-protocol.


the manuscript, and all authors discussed the results and contributed to the manuscript writing. **Competing interests:** The authors declare the following competing interests: Y.T., A.M.R., and S.A.D. have equity in Precision Neurotek Inc. that is cofounded by the team to commercialize PtNRGrids for intraoperative mapping. S.A.D. and H.O. have competing interests not related to this work including equity in FeelTheTouch LLC. S.A.D. was a paid consultant to MaXentric Technologies. D.R.C., K.J.T., and D.A.S. have equity in Surgical Simulations LLC. A.M.R. has an equity and is a cofounder of CerebroAI. A.M.R. received consulting fees from Abbott Inc. and Biotronik Inc. The other authors declare that they have no competing interests. **Data and materials availability:** All data obtained in this study are either presented in the paper and the Supplementary Materials or deposited in open database. Animal brain recording data could be accessed at OpenNeuro (https://openneuro.org/), and the human brain recording data could be found in Data Archive BRAIN Initiative (DABI) (https://dabi.loni.usc.edu/). Custom MATLAB code (version R2021a) in combination with open source automatic IID detection (www.ieeg.org) and propagating wave (https://mullerlab.github.io/) codes were used for the analyses and are available in GitHub (https://ytchoe.github.io/). The authors thank Dr. Woojin Choi for suggesting using the photoresist AZ5214 instead of NR9 3000 which significantly reduced the photolithography exposure time.

Submitted 23 April 2021
Accepted 15 December 2021
Published 19 January 2022
10.1126/scitranslmed.abj1441
Human brain mapping with multithousand-channel PtNRGrids resolves spatiotemporal dynamics


Sci. Transl. Med., 14 (628), eabj1441. • DOI: 10.1126/scitranslmed.abj1441

Cortex in high resolution
Recording brain cortical activity with high spatial and temporal resolution is critical for understanding brain circuitry in physiological and pathological conditions. In this study, Tchoe et al. developed a reconfigurable and scalable thin-film, multithousand-channel neurophysiological recording grids using platinum nanorods, called PtNRGrids, that could record thousands of channels with submillimeter resolution in the rat barrel cortex. In human subjects, PtNRGrids were able to provide high-resolution recordings of large and curvilinear brain areas and to resolve spatiotemporal dynamics of motor and sensory activities. The results suggest that PtNRGrids could be used in the preclinical and clinical setting for high spatial and temporal recording of neural activity.

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