nature portfolio

Peer Review File

Minimally invasive implantation of scalable high-density cortical microelectrode arrays for multimodal neural decoding and stimulation

Corresponding Author: Dr Benjamin Rapoport

Version 0:

Decision Letter:

Dear Dr Rapoport,

Thank you again for submitting to *Nature Biomedical Engineering* your manuscript, "Multimodal Neural Decoding Using a Scalable and Minimally Invasive Brain–Computer Interface Platform", and apologies for the time taken in making a decision. The manuscript has been seen by 3 experts, whose reports you will find at the end of this message.

You will see that the reviewers appreciate the work. However, they express concerns about the degree of support for the claims, and provide useful suggestions for improvement. We hope that with substantial further work you can address the criticisms and convince the reviewers of the merits of the study. In particular, we would expect that a revised version of the manuscript provides:

* Extended assessment and quantification of the resolution of the microECoG, as per the various comments of Reviewers #1 and #2.

* Thorough discussion about the speech decoding capabilities of the device, avoiding overstatements and clarifying the limitations of the work, as highlighted by all Reviewers.

* Rigorous methodological and statistical reporting, as well as clear description of the array, as per the many points of Reviewer #1 and #2.

In line with the suggestions from some of the reviewers, we are also encouraging the inclusion of a draft and schematic of the array, as well as representative images or pictures of the implanted device to help the reader visualise the presented technology.

When you are ready to resubmit your manuscript, please upload the revised files, a point-by-point rebuttal to the comments from all reviewers, the reporting summary, and a cover letter that explains the main improvements included in the revision and responds to any points highlighted in this decision.

Please follow the following recommendations:

* Clearly highlight any amendments to the text and figures to help the reviewers and editors find and understand the changes (yet keep in mind that excessive marking can hinder readability).

* If you and your co-authors disagree with a criticism, provide the arguments to the reviewer (optionally, indicate the relevant points in the cover letter).

* If a criticism or suggestion is not addressed, please indicate so in the rebuttal to the reviewer comments and explain the reason(s).

* Consider including responses to any criticisms raised by more than one reviewer at the beginning of the rebuttal, in a section addressed to all reviewers.

* The rebuttal should include the reviewer comments in point-by-point format (please note that we provide all reviewers will the reports as they appear at the end of this message).

* Provide the rebuttal to the reviewer comments and the cover letter as separate files.

We hope that you will be able to resubmit the manuscript within 20 weeks from the receipt of this message. If this is the case, you will be protected against potential scooping. Otherwise, we will be happy to consider a revised manuscript as long as the significance of the work is not compromised by work published elsewhere or accepted for publication at *Nature Biomedical Engineering*.

We hope that you will find the referee reports helpful when revising the work. Please do not hesitate to contact me should you have any questions.

Best wishes,

Valeria

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Dr Valeria Caprettini
Associate Editor, *Nature Biomedical Engineering*

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Reviewer #1 (Report for the authors (Required)):

This work presents a novel approach for brain-computer interfaces (BCIs) based on high-density micro-ECOG arrays. The novelty and the impact of the work lie in its ability to achieve minimally-invasive surgical implantation while simultaneously offering high spatial and temporal resolution for bi-directional interfacing with the brain. The work has great potential to effectively address the inherent trade-off between invasiveness and resolution in neural interface. By providing a novel approach in large animal models and human that could offer an optimal compromise between invasiveness and resolution, this work holds significant promise for many clinically relevant applications. The work includes studies both in a large animal model (pig) and human intraoperative recording, providing direct clinical translation indication of the technology. In general, the concept and the data amount are impressive, the data quality could improve, and the presentation is severely lacking. Specifically, the merit of the manuscript lies on two claims: minimally invasiveness and high resolution. While I fully appreciate the minimally invasive implantation reported in the work, I still have questions and concerns centered on the high resolution of this micro-ecog array. The authors have made considerable efforts on demonstrating the resolution, but there are still ambiguity and inconsistency that require additional analysis and discussion. Additionally, the presentation of the manuscript is sub-bar, lacks clarify, violates some of the common standards for journal publications, and needs significant improvements. My detailed comments are the following:
1. The correlation between channels shows inconsistency likely depending on the time scale used in the analysis and the details of how correlation was computed. Short-duration snapshots, such as Fig. 1 e, 1f, and most of the panels in figure 3, show severe oversampling and high similarity among nearby several channels. This is contradicting with SFig. 4, which shows a sharp decrease of correlation coefficient even when spacing by one contact. How was the correlation coefficient computed? There was no method session. Specifically, were the signal high pass filtered to remove DC variation? Is the amplitude normalized to remove the variation of SNR on each contact? There is no errorbar or STD range in SFig. 4. Please add errors as STD and clarify how many contacts were used to compute these correlation coefficients.
Additionally, to clarify the inconsistency, I suggest adding a plot showing correlation coefficient at a few representative distance as function of time of the recording. Please provide details of how many contacts were used and the STD of the measurements.
2. Supplemental figure 4 is very important to quantify the resolution of the micro-ECOG array but it is quite unclear. “(a) Correlation map of the Pearson correlation coefficient r2 computed for signals recorded during spontaneous cortical activity, with correlations across the entire array in each sub-plot referenced to one of 25 electrodes (white stars) distributed evenly over the array, as represented by the array of subplots.” I don’t understand this sentence or what the plots try to present. There is an array of black pixels in all the panels. What are they?
All the correlation analysis is as a function of electrode number. It surprises me that no matter how big the contact size is (20 , 50, 100 um), the decay of correlation as a function of number of electrodes go down almost the same. Why? Is the separation between contacts the same no matter what is the contact size? Can the authors replot these curves as a function of distance?
3. related to the issue above, there is no clear description throughout the manuscript about the specific pitch and dimension of the array. The only description is “The first comprises 529 electrodes of multiple sizes ranging in diameter from 20 to 200 μm, while the second version comprises 1024 channels of three different diameters (977 at 50 μm and 42 at 380 μm, with an additional 5 reference electrodes at 500 μm).” Please add a table showing the pitch of the contacts and the dimension of the array for every device in the study that provides some measurements. please also comment on the optimal electrode size and why.
4. Fig. 2 cosmetic issue: the letter labeling in panel d and e are very confusing. Please move all panel label out of the figure if authors would like to stick with single letter labeling. g, h: please add an arrow pointing to the implants. Why is h so blurry? I cannot find the device.
Other issue: k, l: “Histologic analysis demonstrated microscopic preservation of the cortical surface architecture and no systematic differences between implanted and non-implanted control regions (k and l, respectively, hematoxylin and eosin).”

where is the implantation region? and where is the non-implanted control regions? with no device how did the authors identified the implantation region?
5. Fig. 3. The panel number are not ordered properly. e. g. b comes before a. they need to be ordered according to the journal's requirement.
6. Fig. 4 is critical to demonstrate resolution. it needs some clarification. First, how many animals were used in the experiment of rostrum stimulation? The errorbar appears to be defined from one animal's data using 25 different deep learning models. Can you define the errorbar as STD or SE using animal as independent sample? This is the most critical piece of data for resolution and need more than one animal to be convincing.
What is the chance level? What is Ctrl?
The decrease of decoding accuracy from complete to sparse array is very small. can the authors provide more sparse arrays (e.g. ¼ of the density, 1/8 of the density) and quantify how the decoding accuracy decrease with the sparsity? This will be very useful to evaluate resolution and guide future technological development.
Panel l and m is not clear. Please provide x y scale bar and colorbar.
Why is the motor decoding relatively low accuracy? These are big movements. What is the chance level?
7. human study should be its own section.
I was super excited to see the manuscript included human studies but was somewhat disappointed by the result. The decoding was limited to only the speech onset, instead of being able to decode specific words. The patients were apparently given repeated words as shown in the S. Video. Is it that the recording could not decode these words? If not, the results can not be named as "speech decoding", because there was no speech to be decoded. It can be the arrays were recording an arousal state change. Please articulate why individual words could not be decoded. What limitation did this study reveal about the technology?

8. Fig.6. many panels were not discussed in the text. The "near" electrode were not properly defined – is it just that single random red ring in g that were a random number of electrode away from the stimulation electrodes? why that seemingly random distance away from the stimulation electrode? The discussion section seems to indicate this is "precision neuromodulation". I don't get what is precise here. temporally it takes more than 2s for the stimulation effect to go away; spatially its affects a relatively large area. Please articulate either in the result section or discussion
9. some of the discussion will be changed in response to my comments so I will not comment much on the current version of the discussion.

Reviewer #2 (Report for the authors (Required)):

This manuscript by Hettick and many co-workers at Precision Neuroscience describes the company's flexible micro-ECoG interface. While the device appears to be a nice addition to the already large space of recording devices under development and does seem to be fairly robust (with high potential for translational use), it does not seem particularly novel, given the many different micro-ECoG solutions that have been described previously. There is great emphasis on the meaningless buzz-phrase "minimally invasive" (which appears in the article 15 times), which one assumes is meant to establish a marketing position as somehow superior to competitors. Most of the mentions do not add substantively to the manuscript and should be deleted, although keeping the phrase in the title is probably okay. Similarly, there is emphasis on the speed of implantation, again presumably to contrast against competitor devices which may require more surgical time for implantation. These claims should be de-emphasized, and the "Results: Minimal Invasiveness and Speed" section could be completely removed. If the authors are focusing on implant technique, the manuscript may be more appropriate for a surgical specialty journal and should include a full-length video of the entire implant to bolster their claims of speed.

The authors appear to be attempting to portray intracortical recording electrodes as an inferior alternative due to safety concerns with statements like the following: "Microelectrode arrays that penetrate the brain have facilitated high-spatial-resolution recordings for brain–computer interfaces, but at the cost of invasiveness and tissue damage that scale with the number of implanted electrodes" (none of the citations listed for this statement addresses scaling of tissue damage with number of implanted electrodes); "Such systems are also difficult to remove or replace without causing damage to surrounding brain tissue, and signals from penetrating electrodes are less stable over time than those from surface electrodes" (no citations for this claim) and "Clinically useful neural interfaces must balance the need for improved function, achieved through increasing channel counts and spatial resolution, against the invasiveness of the surgical procedure and damage to brain tissue associated with penetrating intracortical electrode arrays" (again the meaningless "invasiveness" term, and no citations for this statement). It is certainly true that there are trade-offs in terms of performance vs. longevity / stability, but there is no evidence currently that chronic ECoG is any safer than chronic intracortical recording. Given that this is a commercial device being presented by the company that makes it, readers should be wary about straw man arguments meant to possibly bolster marketing claims.

The authors claim to "demonstrate accurate neural decoding of somatosensory, visual and volitional walking activity," although the decoding is rather rudimentary (essentially merely differentiating between different sensory stimulation localities with ~75% accuracy and differentiating between head and limb movement with 68% accuracy). In their "speech decoding" example, they merely decode voice onset; this is far below the capability reported by, e.g., the Chang group using a much sparser array to do accurate, large-vocabulary speech decoding. Although there certainly is finer-scale resolution obtainable with these arrays, it's unclear what actual benefit they will have for BCI, given these modest results.

The surgical technique is clever and does appear to have been successful, although it is impossible to fully assess since there is no mention of the number of pigs used for the study, and what the variations in implant technique might have been.

Under “Results: Safety and Reliability” the authors state that “Histologic evaluation of cortical sections immediately beneath implantation sites following acute (≤8 h) and chronic (>30 day) implants revealed no evidence of acute or chronic tissue injury.” How many animals were in the chronic cohort? What did recordings look like at 30 days? They claim this system is easy to explant – what did the 30-day explant procedure look like? Did it require a full craniotomy, or could the arrays simply be pulled free from the epidural space? Much more data are needed to assess these claims.

In the caption of figure 2, the authors state that “Safety was also assessed using standard, semi-quantitative histology techniques following 30-day chronic array implantation.” However, these techniques are not described in the methods section, other than routine H&E staining, which is not a particularly sensitive indicator of local damage. Again, how many animals were sacrificed, and what was the variation? What assurances are there that the data were not “cherry picked” to illustrate this device and implant technique in the most favorable light?

Under “Results: System overview,” it would be helpful to have a photograph of the complete system as implanted in the awake, behaving animal. This would allow for a better comparison with BCI systems currently used in human clinical trials.

In the Discussion section, the authors state that “our early experience in human patients substantiates the clinical utility and usability of the system.” However, they don’t demonstrate the full end-to-end microslit technique in this setting, which presumably forms the basis of the “clinical utility and usability” claim. Micro-ECoG recordings are hardly novel and nearly any of these devices would be expected to provide similar “utility and usability.”

In summary, this manuscript describes a nice design which is incremental in nature and will likely at some point form the basis of a BCI system, given the resources the company has invested in development. However, the authors provide little convincing evidence that safety, decoding accuracy, or ease of use are better than devices currently being widely used to advance the state of the art in BCI.

Reviewer #3 (Report for the authors (Required)):

The work by Hettick and colleagues describes a novel high-channel count, high-density, electrocorticography platform. They illustrate its practical aspects in terms of minimally-invasive footprint to insert it onto the cortical convexity of an animal model. They additionally demonstrate its use during intraoperative recordings with human patients undergoing neurosurgery for other reasons.
In the animal model, they illustrate in-vivo signal viability during awake behavior, sensory physiology, decoding of behavioral state, and high-fidelity & spatially complex microstimulation.
In the human patients, they show signal viability and usability for (offline) speech decoding.
The primary content is supported by a rich set of supplemental material.
I believe that this is extremely important technological advancement that will be useful to the entire neuromodulation community, and may have real impact in human therapies. Provided that a few minor concerns are addressed, I believe that Nature Biomedical Engineering would be the perfect place for it, and I recommend publication.

General (major) comments:

1) It would be helpful to know what the relative in-vivo filtering and signal to noise properties of the recording ecosystem are. These are very important to ascertain what the resolvable behaviorally-associated signals are. These might be characterized along the lines shown in the manuscript and supplement to Miller, et al, "Power-Law Scaling in the Brain Surface Electric Potential", PLoS Comp Biol, 2009. Particularly along the lines of Figs. 1B, 4, and supp Figs 13-17.

2) I am not certain that the work really constitutes a full BCI platform. A) There is a novel ECoG array, with a novel, minimally-invasive, delivery mechanism for this array. These are impressive. B) The amplifier setup appears to be a customized intan-based system, but this is not described in sufficient detail in text or figures for me to understand what is important about this. C) The analyses appear to appropriate to address and interpret the recorded data. However, it is not clear what new contribution this is, what is decoded online (i.e. what is actually BCI), and how it is uniquely suited to the array or the amplifier. Items A, B, and C combined constitute a platform. However, the manuscript is primarily concerned with the array and its novel implantation. Therefore, I would propose that either the concept of this being a platform be expanded, or the title and text should be centered around the array, but not a new BCI platform. To be clear, I do believe that the array component (A) is sufficiently important and novel to merit publication in this journal on its own.

3) Both human and animal data should be made available. As a neurosurgeon, I would like to be able to ensure - myself - that the quality of the data is sufficient to resolve for the applications I would use the system for before I would feel comfortable moving to implant it into a patient.

Focused (minor, optional) comments:
- Figures 1,2, 3, 5, 6b-f, - If acceptable, I think it would be helpful if a small amount of text were embedded in the figure so that it is clear what the purpose of each panel is (rather than having to learn this going back and forth to the caption).
- Figure 1 - There are several 'pale gray lines' throughout the figure that should be removed.
- Figure 3 general - panels b, e, f, g, and i do not have a scale. This should be remedied.
- Figure 3f - do the flat traces correspond to no response at all? Or are they artifactually flat? If they are non-physiologic, I would omit the traces.

Kai Miller

Version 1:

Decision Letter:

Dear Dr Rapoport,

Thank you for your revised manuscript, "Multimodal Neural Decoding Using Scalable Microelectrode Array Technology for Minimally Invasive Brain–Computer Interfaces", and once again accept our apologies in this delay to make a decision. As you know, the manuscript has been seen by the original reviewers, but Reviewer #2 was unable at this time to provide us with another report. For this reason, we approached another expert who was willing to evaluate the improvements and your responses to the points raised by Reviewer #2, and yet they are still to provide us with their comments. Should they send to us their report, I will be sure to forward it to you, however, I am not very hopeful at this point.

You will find the reports of Reviewer #1 and #3 at the end of this message, and you will see that they acknowledge the improvements to the work and only Rev #1 raises a few additional technical criticisms that we hope you will be able to address.

As before, when you are ready to resubmit your manuscript, please upload the revised files, a point-by-point rebuttal to the comments from all reviewers, the reporting summary, and a cover letter that explains the main improvements included in the revision and responds to any points highlighted in this decision.

As a reminder, please follow the following recommendations:

* Clearly highlight any amendments to the text and figures to help the reviewers and editors find and understand the changes (yet keep in mind that excessive marking can hinder readability).

* If you and your co-authors disagree with a criticism, provide the arguments to the reviewer (optionally, indicate the relevant points in the cover letter).

* If a criticism or suggestion is not addressed, please indicate so in the rebuttal to the reviewer comments and explain the reason(s).

* Consider including responses to any criticisms raised by more than one reviewer at the beginning of the rebuttal, in a section addressed to all reviewers.

* The rebuttal should include the reviewer comments in point-by-point format (please note that we provide all reviewers will the reports as they appear at the end of this message).

* Provide the rebuttal to the reviewer comments and the cover letter as separate files.

We expect that you will be able to resubmit the manuscript within 12 weeks of receiving this message. If this is the case, you will be protected against potential scooping. Otherwise, we will be happy to consider a revised manuscript as long as the significance of the work is not compromised by work published elsewhere or accepted for publication at *Nature Biomedical Engineering*.

We look forward to receive a further revised version of the work. Please do not hesitate to contact me should you have any questions.

Best wishes,

Valeria

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Dr Valeria Caprettini
Senior Editor, *Nature Biomedical Engineering*

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Reviewer #1 (Report for the authors (Required)):

The manuscript has significantly improved. Particularly, the additional correlation analysis and the more difficult decoding experiments clearly demonstrate the benefit of high-resolution Ecog. Yet, I still have both major and minor concerns that would request further modification and clarification

Major:
1. Section of “Modularity and Scalability”. The authors stated that the system is modular, but the best data they presented that unambitiously in support is “doubly connected 529-channel modules”. I would argue scaling to 2 is not in strong support of modularity and scalability, and it was not clear if the doubly connected modules were inserted through the slit or a craniotomy. Sup. Fig. 1 showed stacked devices of four on bench top, without providing evidences that it was inserted through a slit and could record high-quality signals on all modules. Sup. Fig. 6 showed the overlay of implantations from multiple animals, if I understand it correctly, and therefore does not support modularity and scalability. Can the authors clarify: 1) in any single animal, what is the maximum number of devices and channels they implanted through a slit, and 2) show implantation images and/or recording/stimulation data in vivo from these many-module implantations. This is critical to the system’s novelty and potential impact.
Related to this, a large portion of the discussion section centered on scalability and modularity, which may need to be modified depends on the new data to be presented.
2. The manuscript presented many heat maps showing cortical activity on the array. Some of them do not have colorbar (e.g. Fig. 5d); others have color bars but do not have proper labels with units (e.g. fig. 6). In the only case I could find a color bar labeled with unit (figure 3i), it was unclear at which frequency band and under what time window of integration the heat map is generated. The authors need to correct all the heatmap plots throughout the manuscript, in both main figures and sup. Figures.
3. The Stimulation section, both the text and figure 6, are very confusing. First, not sure how cortical activity in g -j were defined (previous comment). Second, the black dots in g and h indicate very low activity – are the contacts broken, so little activity was detected, or does the device not conform on the brain surface, so fail to detect cortical activity because these regions were too far from the tissue? Please add discussions about the yield in the detection of all the arrays. In either case, please justify why these recordings are included in the downstream analyses. Third, panels e and I indicate that stimulations either suppress the cortical activity from the nearby contact or do not affect the activity much, but it does not enhance cortical activity. Why? Please also justify this is expected and not due to contamination from recording artifacts or a prolonged blank-out period in recording after stimulation.

Minor:
abstract:
“The resulting system generates 90 Gb/h of electrophysiologic data”. What really matters are how useful, independent the data is. The volume does not matter. Please revise.
Introduction:
“ (contrary to some prevailing beliefs)”, both accurate neural decoding and accuracy improve as a function of both area coverage and spatial density appear intuitive and straightforward, I am not sure what is against some prevailing beliefs. Please revise.
Figure 1: does panel d contain data? If so, please explicitly describe the data in the figure caption
Miss reference: “The overall tissue response to implantation was similar for the thin-film and control devices, with slightly less inflammation noted in response to chronic implantation of the more conformal thin-film device.” It is also unclear which has less response. Please clarify.
Fig. 2: caption stated chronic studies were at 30 days while text stated 42 days. Please clarify and correct.
Discussion: Convenient and reliable explanation is important for clinical application and can be a potential strength of this technology. Can the authors discuss this, and adding some supporting data if possible?

Reviewer #3 (Report for the authors (Required)):

The authors have candidly addressed all of my concerns, and I commend them on their important work, which I believe is a significant contribution to neural interfacing technology.

Version 2:

Decision Letter:

Dear Dr Rapoport,

Thank you for your revised manuscript, "Multimodal Neural Decoding Using Scalable Microelectrode Array Technology for Minimally Invasive Brain–Computer Interfaces" and for sending me the word file. Having consulted with Reviewers #X1, I am pleased to write that we shall be happy to publish the manuscript in *Nature Biomedical Engineering*.

We will be performing detailed checks on your manuscript, and in due course will send you a checklist detailing our editorial

and formatting requirements. You will need to follow these instructions before you upload the final manuscript files.

We welcome cover art suggestions, you will be able to submit it together with the final files.

Please do not hesitate to contact me if you have any questions.

Best wishes,

Valeria

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Dr Valeria Caprettini
Senior Editor, *Nature Biomedical Engineering*

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Reviewer #1 (Report for the authors (Required)):

The authors have addressed all the comments I have. Congratulations on the impressive body of work!

Version 3:

Decision Letter:

Dear Ben,

I am happy to inform you that your manuscript, "Minimally invasive implantation of scalable high-density cortical microelectrode arrays for multimodal neural decoding and stimulation", has now been accepted for publication in *Nature Biomedical Engineering*.

Over the next few weeks, the figures will be checked for production quality, the text edited to ensure that it conforms to house style, and the manuscript typeset.

Our Articles are published about 40 days after the acceptance date (we recommend that you inform your institutional press office of this timeframe), and you will be notified of the actual publication date a few days in advance. Articles can be published any working day of the week, and are pushed live shortly after 10 am London time.

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Springer Nature SharedIt initiative to generate a unique shareable link to the Article that will allow anyone (with or without a subscription) to read it. Recipients of the link who are subscribers will also be able to download and print the PDF.

Thank you for having submitted this work to *Nature Biomedical Engineering*.

Best wishes,

Valeria

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Dr Valeria Caprettini
Senior Editor, *Nature Biomedical Engineering*

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27 November 2024

Dear Dr. Caprettini,

Thank you for your consideration of our manuscript submission to *Nature Biomedical Engineering*, "Multimodal Neural Decoding Using Scalable Microelectrode Array Technology for Minimally Invasive Brain–Computer Interfaces," (nBME-24-0427-T, originally entitled "Multimodal Neural Decoding Using a Scalable and Minimally Invasive Brain–Computer Interface Platform") and thank you for protecting a short extension in our response timeline while we incorporated new results and analysis designed to address comments from the reviewers.

We appreciate the thoughtful and thorough comments provided by the three experts who reviewed this work on behalf of the journal. We have completed a careful and complete set of responses to your comments and theirs, and we have included the point-by-point responses as well as the revised and annotated manuscript here.

As you indicated in your original letter, we have devoted substantial additional work to addressing the criticisms, concerns, and suggestions of the reviewers. Thank you for indicating that you and the reviewers appreciate this work. We hope that our responses, modifications, and additions will be sufficient to convince you and the reviewers of the merits of the study and its suitability at this point for publication.

In particular, you highlighted four areas requiring special attention in our revisions:

1. Extended assessment and quantification of the resolution of the micro-ECoG, as per the comments of Reviewers 1 and 2.

We have added a number of detailed, quantitative assessments related to the resolution of the micro-ECoG system, as highlighted in detail in our responses to Reviewers 1 and 2.

2. Thorough discussion about the speech decoding capabilities of the device, avoiding overstatements and clarifying the limitations of the work, as highlighted by all Reviewers.

We have added details to our discussion of the speech decoding we have performed with the system described. We have made a number of revisions in response to the suggestions of the Reviewers, taking care to eliminate overstatements, clarify limitations of the work described here, with particular emphasis on the short-duration nature of the intraoperative studies and the associated limited vocabularies. Our intention here was only to illustrate the nature of information content retrievable even from short-duration micro-ECoG recordings, not to challenge the state of the art in neural decoding.

3. Rigorous methodological and statistical reporting, as well as clear description of the array, as per the many points of Reviewers 1 and 2.

We have revised the manuscript to provide additional methodological rigor in a number of areas, as suggested by the Reviewers. We appreciate these suggestions from the Reviewers and hope they will agree that our responses to their critiques in these and other areas have strengthened the study. In particular, we refined our analysis of the inter-electrode spatial and temporal correlation. We have also provided a more detailed description of the electrode arrays together with additional images and schematics. Notably, after submitting the original draft of the manuscript for consideration we completed a detailed chronic biocompatibility study (under an externally supervised GLP protocol, with independent histopathological review), and we have included the results of that analysis in the present version of the manuscript to strengthen the analysis of histology and biocompatibility.

4. In line with the suggestions from some of the reviewers, we are also encouraging the inclusion of a draft and schematic of the array, as well as representative images or pictures of the implanted device to help the reader visualise the presented technology.

In response to these suggestions from the Reviewers and the Editor we have included a new set of figures in the Supplement that includes scaled schematics of the arrays as well as representative images of the devices both as fabricated and in situ when deployed intraoperatively.

Thank you again for your consideration, we look forward to hearing from you.

Sincerely,
Benjamin I. Rapoport, M.D., Ph.D.
(On Behalf of the Authors)

Point-by-Point Response to Reviewers

Please note that we have placed comments from the reviewers in italics, and have introduced a numbering scheme for the comments for purposes of clarity. Our responses are in roman font.

Reviewer 1

This work presents a novel approach for brain-computer interfaces (BCIs) based on high-density micro-ECOG arrays. The novelty and the impact of the work lie in its ability to achieve minimally-invasive surgical implantation while simultaneously offering high spatial and temporal resolution for bi-directional interfacing with the brain. The work has great potential to effectively address the inherent trade-off between invasiveness and resolution in neural interface. By providing a novel approach in large animal models and human that could offer an optimal compromise between invasiveness and resolution, this work holds significant promise for many clinically relevant applications. The work includes studies both in a large animal model (pig) and human intraoperative recording, providing direct clinical translation indication of the technology. In general, the concept and the data amount are impressive, the data quality could improve, and the presentation is severely lacking.

Specifically, the merit of the manuscript lies on two claims: minimally invasiveness and high resolution. While I fully appreciate the minimally invasive implantation reported in the work, I still have questions and concerns centered on the high resolution of this micro-ecog array. The authors have made considerable efforts on demonstrating the resolution, but there are still ambiguity and inconsistency that require additional analysis and discussion. Additionally, the presentation of the manuscript is sub-bar, lacks clarify, violates some of the common standards for journal publications, and needs significant improvements. My detailed comments are the following:

> We thank the reviewers for their helpful and incisive comments and have attempted to address each of the concerns raised through additional analyses, clearer writing, and more rigorous statistical analysis.

1.1 *The correlation between channels shows inconsistency likely depending on the time scale used in the analysis and the details of how correlation was computed. Short-duration snapshots, such as Fig. 1 e, 1f, and most of the panels in figure 3, show severe oversampling and high similarity among nearby several channels. This is contradicting with SFig. 4, which shows a sharp decrease of correlation coefficient even when spacing by one contact. How was the correlation coefficient computed? There was no method session. Specifically, were the signal high pass filtered to remove DC variation? Is the amplitude normalized to remove the variation of SNR on each contact? There is no errorbar or STD range in SFig. 4. Please add errors as STD and clarify how many contacts were used to compute these correlation coefficients.*

Additionally, to clarify the inconsistency, I suggest adding a plot showing correlation coefficient at a few representative distance as function of time of the recording. Please provide details of how many contacts were used and the STD of the measurements.

> We agree with Reviewer 1 that the time series signals as displayed in Figures 1 and 3 can give a misleading and potentially confusing view on the nature of the correlation across channels. Time

series representations of many channels will tend to overemphasize low-frequency signal components, which have greater channel-to-channel correlation, and underemphasize higher frequency signals, in which adjacent-channel correlation is much lower.

We have attempted to clarify this situation with a revised and more rigorous correlation analysis as suggested by Reviewer 1 (Figure 4f), as well as by slightly revising the figures to emphasize channel-to-channel divergence on shorter time scales (see subpanel 3(d)). The correlation analysis (now described more completely in the Methods section entitled "Free Recording of Spontaneous Cortical Activity") was conducted across N=6 animals using all possible electrode pairs on a 1,024 channel electrode array.

We have also conducted the analysis suggested by Reviewer 1, to calculate the correlation as a function of the time window used for the correlation analysis, as shown in Figure 4g. The figures have also been updated to show both the mean and standard deviation of the r^2 values as a function of distance, frequency band, and time window used.

We have updated the Methods section to more fully describe how the correlations among channels were calculated. Note that we did not perform any form of filtering or preprocessing of the data prior to calculating the correlation coefficients, and this has been clarified in the Methods.

1.2. *Supplemental figure 4 is very important to quantify the resolution of the micro-ECOG array but it is quite unclear. "(a) Correlation map of the Pearson correlation coefficient r2 computed for signals recorded during spontaneous cortical activity, with correlations across the entire array in each sub-plot referenced to one of 25 electrodes (white stars) distributed evenly over the array, as represented by the array of subplots." I don't understand this sentence or what the plots try to present. There is an array of black pixels in all the panels. What are they?*

All the correlation analysis is as a function of electrode number. It surprises me that no matter how big the contact size is (20 , 50, 100 um), the decay of correlation as a function of number of electrodes go down almost the same. Why? Is the separation between contacts the same no matter what is the contact size? Can the authors replot these curves as a function of distance?

We agree the quantification of the resolution of micro-ECoG is an important analysis and as a result have moved this to the main text as Figure 4f. We attempted to simplify both the visual presentation and explanation of this important analysis, which now includes an average correlation across all pairs of channels across N animals. Per the reviewer's suggestion, we have also replotted the curves as a function of distance rather than number of electrodes, with error bars to account for the fact that there are more electrode pairs at shorter distances than larger distances on the electrode array.

To reduce confusion, we have removed subpanels (c) and (d) in Supplementary Figure 4, and attempted to clarify the figure legend for the remaining panels to make it more clear. The reviewer is correct that in the 529 channel array used for those initial sub-figures, electrode spacing was kept constant regardless of contact size.

As to the question of the black pixels in the correlation plots, those correspond to electrodes wired for stimulation and not available for use in the correlation analysis. We have clarified this in the legend of the supplementary figure.

1.3. *Related to the issue above, there is no clear description throughout the manuscript about the specific pitch and dimension of the array. The only description is "The first comprises 529 electrodes of multiple sizes ranging in diameter from 20 to 200 μm, while the second version comprises 1024 channels of three different diameters (977 at 50 μm and 42 at 380 μm, with an additional 5 reference electrodes at 500 μm)." Please add a table showing the pitch of the contacts and the dimension of the array for every device in the study that provides some measurements. please also comment on the optimal electrode size and why.*

We thank the reviewer for this suggestion. We have gone ahead and added a description of the detailed features of the electrode arrays in the "System Overview" section. We describe the key characteristics for each of the two array designs used in this study (one containing 529 channels and the other containing 1,024 channels), including overall array dimensions, electrode pitch, and electrode sizing. We have also added Supplementary Figures 2 and 3 to include detailed CAD images of both electrode arrays, including a detailed diagram showing the electrode layout for the 1,024 channel array which was used for the subsequent correlation, decoding, and human pilot studies.

Per the reviewer's suggestion, we have also added a brief description on how we selected the optimal recording electrode size of 50 μm for the 1,024 channel device:

"We designed the 529 channel array with multiple electrode sizes and 300 μM pitch to help determine the optimal inter-electrode spacing and recording electrode size for the larger 1,024 channel array, based on a combination of manufacturing reliability, electrode impedance, and analysis of inter-electrode correlation. As expected, smaller electrodes captured more unique high-frequency information across adjacent channels, but at the cost of higher impedance and greater manufacturing variability; and tighter pitch results in increased inter-electrode correlation across all spectral bands, but in a frequency-dependent manner. The choices of 400 μM pitch and 50 μM recording electrode diameter for the 1,024 channel array were made after weighing the results of these analyses."

1.4. *Fig. 2 cosmetic issue: the letter labeling in panel d and e are very confusing. Please move all panel label out of the figure if authors would like to stick with single letter labeling. g, h: please add an arrow pointing to the implants. Why is h so blurry? I cannot find the device.*

Other issue: k, l: "Histologic analysis demonstrated microscopic preservation of the cortical surface architecture and no systematic differences between implanted and non-implanted control regions (k and l, respectively, hematoxylin and eosin)."

where is the implantation region? and where is the non-implanted control regions? with no device how did the authors identified the implantation region?

We have updated Figure 2 with the requested changes, including moving the figure labels outside the panels, annotating the microscopic and radiographic images, adding scale bars, and more clearly marking the location of the implants in each section. Note that at the request of Reviewer 2, we have substantially increased the amount and rigor of the histology data being used for our biocompatibility analysis; in addition to comparing implanted to unimplanted cortex in the same animal, we also compare implantation of the Layer 7 electrode to that of a standard 4-contact AdTech subdural strip electrode.

To answer the question on how we distinguish implanted from non-implanted cortical regions: At the time of gross dissection, gross photographs were taken to identify array location and sections were taken through the cortex in both implanted and non-implanted regions. The electrode arrays are removed prior to further histologic processing, so no implant is visible in these microscopic images, but we can compare histologic changes across tissue blocks to identify changes induced by implantation. We have added a section to the Methods ("Implantation Test") describing the protocol and methods in more detail.

1.5. *Fig. 3. The panel number are not ordered properly. e. g. b comes before a. they need to be ordered according to the journal's requirement.*

Thank you for pointing this out. The panels are now in the proper order.

1.6. *Fig. 4 is critical to demonstrate resolution. it needs some clarification. First, how many animals were used in the experiment of rostrum stimulation? The errorbar appears to be defined from one animal's data using 25 different deep learning models. Can you define the errorbar as STD or SE using animal as independent sample? This is the most critical piece of data for resolution and need more than one animal to be convincing.*

What is the chance level? What is Ctrl?

The decrease of decoding accuracy from complete to sparse array is very small. can the authors provide more sparse arrays (e.g. ¼ of the density, 1/8 of the density) and quantify how the decoding accuracy decrease with the sparsity? This will be very useful to evaluate resolution and guide future technological development.

We agree that the decoding analysis presented in Figure 4 is critical to demonstrate the benefits of high-resolution electrocorticography. We have therefore substantially updated and improved the analysis used to demonstrate this point. The results presented now demonstrate real-time somatosensory decoding of 8 rostrum locations in 4 consecutive animals. In these studies, models were trained intraoperatively using between 10-30 minutes of training data and then tested on unseen, prospectively collected validation data. Across these 4 animals, we obtained an average accuracy of 93% +/- 6%, where the chance accuracy is 12.5% (1 out of 8); control indicates that no stimulation is applied to the rostrum.

In addition, we have conducted a more thorough analysis of the impact of array subsampling on decoding accuracy, now shown in Figure 4e. These results indicate that decoding accuracy increases monotonically with increasing channel number. For the 8-class problem, >95%

accuracy was achieved at a 1:4 channel downsampling (representing an effective 2x increase in electrode spacing), making it difficult to demonstrate increasing value to even higher resolutions. Therefore, in three animals, we increased the difficulty of the decoding problem by increasing the number of simultaneously decoded locations to 14, 24 and 30, respectively. As we made the decoding problem progressively harder, the value of increasing resolution became more clear; the highest decoding accuracy in these cases was achieved with 1,024 channels, with no evidence of performance saturation. Thus, while it would be possible to do lower-class somatosensory decoding using lower resolution surface arrays, higher resolution arrays enable increasingly complex decoding capabilities.

1.7. *Panel l and m is not clear. Please provide x y scale bar and colorbar.*
Why is the motor decoding relatively low accuracy? These are big movements. What is the chance level?

In our awake motor decoding experiments, the animals were untrained, movements were natural, unconstrained, heterogeneous, and spontaneous, and thus the training data sets were much smaller than those typically used in the literature, for example, involving trained nonhuman primates. The decoding results here were trained on only 127 separately observed gross motor events of each type, and tested on a balanced dataset of 32 events; the chance accuracy is 33%.

The intent of this section was not to demonstrate optimal motor decoding in an untrained animal, but rather to show the feasibility of multimodal decoding from high-resolution cortical surface arrays. While we believe these results are additive to the overall validation of the system, we have moved these panels to Supplementary Figure 9 to avoid overstating the importance of these unoptimized results and to make room for the more detailed correlation analysis and somatosensory decoding results that were requested.

1.8. *human study should be its own section.*
I was super excited to see the manuscript included human studies but was somewhat disappointed by the result. The decoding was limited to only the speech onset, instead of being able to decode specific words. The patients were apparently given repeated words as shown in the S. Video. Is it that the recording could not decode these words? If not, the results can not be named as "speech decoding", because there was no speech to be decoded. It can be the arrays were recording an arousal state change. Please articulate why individual words could not be decoded. What limitation did this study reveal about the technology?

We thank the reviewer for the feedback. We believe the inclusion of the human data is important as it demonstrates the safety and feasibility of the electrode array for use in human intraoperative recordings. However, for several reasons, the present data were not optimized for high-accuracy speech decoding of individual words; recording of speech was limited to <4 minutes in each patient, and from several different speech-related cortical areas.

Since our original submission, and as described in more detail in our response to Reviewer 2, we have now increased the total number of intraoperative recordings to 26 total patients across 3

institutions, including multiple additional cases of awake language mapping. In these additional studies, we have demonstrated accurate hand fine-motor and speech decoding at the speech-onset and individual-word levels. We believe a full description of these methods and results goes well beyond the scope of the current manuscript, and thus are planning additional manuscripts describing these results in greater detail.

For the present manuscript, we agree with de-emphasizing the limited speech decoding results obtained in these first few cases, which are not reflective of the accuracy of speech decoding which can be obtained with proper array placement and language protocols. The in-human data collected in this study demonstrate that electrocortical signals associated with speech onset can be detected intraoperatively, supporting both the more detailed language decoding studies and with potential application for intraoperative mapping of language-associated cortical regions. However, we do not claim the present results represent state-of-the-art speech decoding as has been described by others in the recent literature (Metzger et al, Nature 2023; Willet et al, Nature 2023; Card et al, NEJM, 2024). We have edited the corresponding text to more properly put these limited results into context.

1.9. *Fig.6. many panels were not discussed in the text. The "near" electrode were not properly defined – is it just that single random red ring in g that were a random number of electrode away from the stimulation electrodes? why that seemingly random distance away from the stimulation electrode? The discussion section seems to indicate this is "precision neuromodulation". I don't get what is precise here. temporally it takes more than 2s for the stimulation effect to go away; spatially its affects a relatively large area. Please articulate either in the result section or discussion*

We thank the reviewer for these questions and have attempted to improve both the description and explanation of these results in the revised manuscript. We have clarified that the "near" electrode highlighted for exemplary traces was selected for its 1 mm distance from the stimulating electrode. We have also clarified that the group of electrodes highlighted in the analysis as being within a 5-electrode distance from the stimulus corresponds to those electrodes located at most 2 mm from the stimulating electrode.

In addition, all subpanels are now referenced in the main text, and we have attempted to clarify both the spatial and temporal response to cortical stimulation. We recognize that what constitutes "precision neuromodulation" may be open to interpretation. These results are presented primarily to demonstrate the ability to provide spatially controllable cortical stimulation through the described microelectrode array and to measure evoked cortical responses at high spatial and temporal resolution. The physiological or clinical significance of cortical microstimulation on these scales is as yet not fully defined, so we have removed the term "precision neuromodulation" from the discussion to avoid overstating the claims. We think this is an important technical capability whose physiological and clinical relevance can be studied in future scientific and clinical investigations.

1.10. *some of the discussion will be changed in response to my comments so I will not comment much on the current version of the discussion.*

We appreciate that Reviewer 1 may have additional comments on the Discussion section. As mentioned in our response to Reviewer 3, among other modifications to the text softening certain claims, we have also added comments in the Discussion regarding the limitations of the study. Please see the second-to-last paragraph of the Discussion.

Reviewer 2

2.1 *This manuscript by Hettick and many co-workers at Precision Neuroscience describes the company's flexible micro-ECoG interface. While the device appears to be a nice addition to the already large space of recording devices under development and does seem to be fairly robust (with high potential for translational use), it does not seem particularly novel, given the many different micro-ECoG solutions that have been described previously. There is great emphasis on the meaningless buzz-phrase "minimally invasive" (which appears in the article 15 times), which one assumes is meant to establish a marketing position as somehow superior to competitors. Most of the mentions do not add substantively to the manuscript and should be deleted, although keeping the phrase in the title is probably okay. Similarly, there is emphasis on the speed of implantation, again presumably to contrast against competitor devices which may require more surgical time for implantation. These claims should be de-emphasized, and the "Results: Minimal Invasiveness and Speed" section could be completely removed. If the authors are focusing on implant technique, the manuscript may be more appropriate for a surgical specialty journal and should include a full-length video of the entire implant to bolster their claims of speed.*

We appreciate the encouragement of Reviewer 2 to avoid overusing the term "minimally invasive," which the Reviewer characterizes as a "meaningless buzz-phrase." We have modified the manuscript accordingly, as detailed below. We would like to point out, though, that in surgical practice, including neurosurgical practice, "minimally invasive" is not a "meaningless buzz-phrase" but rather a term that carries specific meaning. There is an extensive surgical literature on this subject. In the context of neurosurgery, please see, for example, the October 2010 special issue of *Neurosurgery Clinics of North America*, "Minimally Invasive Intracranial Surgery" edited by Sughrue and Teo, two surgeons of international stature: "Minimally invasive neurosurgery has developed from technological innovations, including endoscopy, instrumentation, neuroimaging, stereotaxy, and others" and refers to neurosurgical approaches and techniques that "minimize collateral damage without compromising the intended goal of surgery." We feel that such technological advances and clinical goals apply in the translation of brain–computer interfaces to clinical practice, and it is in that context that we use the term in this manuscript.

The quotations above are drawn from the following articles in the above-cited special issue:
The Concept of Minimally Invasive Neurosurgery, Charles Teo, Neurosurgery Clinics of North America 21(4): 583-584 (2010).
Application of Technology for Minimally Invasive Neurosurgery, Masaru Ishii and Gary L. Gallia, Neurosurgery Clinics of North America 21(4): 585-594 (2010).

In keeping with the recommendations of Reviewer 2, we have removed 4 of the instances of the term "minimally invasive" from the manuscript (outside of the title and References section, the term originally appeared 12 times). We have also changed the title of the section previously labeled "Minimal Invasiveness and Speed" to "Feasibility of Insertion Technique," and have revised the text in that section to de-emphasize claims related to speed of implantation. We have included a supplemental video (Supplementary Video 1) demonstrating the critical portions of the implantation technique (omitting portions such as skin incision and closure).

2.2 *The authors appear to be attempting to portray intracortical recording electrodes as an inferior alternative due to safety concerns with statements like the following: "Microelectrode arrays that penetrate the brain have facilitated high-spatial-resolution recordings for brain–computer interfaces, but at the cost of invasiveness and tissue damage that scale with the number of implanted electrodes" (none of the citations listed for this statement addresses scaling of tissue damage with number of implanted electrodes); "Such systems are also difficult to remove or replace without causing damage to surrounding brain tissue, and signals from penetrating electrodes are less stable over time than those from surface electrodes" (no citations for this claim) and "Clinically useful neural interfaces must balance the need for improved function, achieved through increasing channel counts and spatial resolution, against the invasiveness of the surgical procedure and damage to brain tissue associated with penetrating intracortical electrode arrays" (again the meaningless "invasiveness" term, and no citations for this statement). It is certainly true that there are trade-offs in terms of performance vs. longevity / stability, but there is no evidence currently that chronic ECoG is any safer than chronic intracortical recording. Given that this is a commercial device being presented by the company that makes it, readers should be wary about straw man arguments meant to possibly bolster marketing claims.*

We thank Reviewer 2 for detailed attention to certain citations and for advocating a more balanced portrayal of the tradeoffs inherent in use of any particular microelectrode technology. We have moved certain citations within the text to indicate more clearly which statements they were intended to support, and we have added additional citations where Reviewer 2 indicated inadequate support from the literature had not been provided. With respect to our portrayal of various microelectrode modalities, it is not our intention to suggest that one type is categorically inferior to another. The contributions of intracortical microelectrodes to the field of brain–computer interfaces is certainly well established. Nevertheless, there are tradeoffs involved in the selection of any microelectrode modality, and intracortical microelectrodes also have certain drawbacks. We point these out in order to explain our rationale for making the particular set of design tradeoffs inherent in developing the micro-ECoG electrodes described in this study.

In the first instance referenced here by Reviewer 2, we agree that we should have chosen a more directly supportive group of citations. We have now cited a number of well known papers in the field (already cited elsewhere in the manuscript) to support the statement in the first part of the sentence: "Microelectrode arrays that penetrate the brain have facilitated high-spatial-resolution recordings for brain–computer interfaces" and we have moved the citations earlier in the sentence to make this clear.

We have also added additional references (to explant and autopsy studies examining subjects implanted with intracortical microelectrodes) to substantiate the second part of the sentence, "but at the cost of invasiveness and tissue damage that scale with the number of implanted electrodes." In particular, we have cited the following studies by well known groups in the field:

Explant Analysis of Utah Electrode Arrays Implanted in Human Cortex for Brain-Computer-Interfaces.
Frontiers in Bioengineering and Biotechnology (9):759711 (December 2021).

Kevin Woeppel, Christopher Hughes, Angelica J Herrera, James R Eles, Elizabeth C Tyler-Kabara, Robert A Gaunt, Jennifer L Collinger, Xinyan Tracy Cui.

Utah array characterization and histological analysis of a multi-year implant in non-human primate motor and sensory cortices.
Journal of Neural Engineering 20(1):10.1088/1741-2552/acab86 (January 2023).
Paras R Patel, Elissa J Welle, Joseph G Letner, Hao Shen, Autumn J Bullard, Ciara M Caldwell, Alexis Vega-Medina, Julianna M Richie, Hope E Thayer, Parag G Patil, Dawen Cai, Cynthia A Chestek.

Neuropathological effects of chronically implanted, intracortical microelectrodes in a tetraplegic patient.
Journal of Neural Engineering 18(4):0460b9 (July 2021).
Linda J Szymanski, Spencer Kellis, Charles Y Liu, Kymry T Jones, Richard A Andersen, Deborah Commins, Brian Lee, Douglas B McCreery, Carol A Miller.

The above references graphically illustrate that the nature and extent of tissue damage inherent in the use of penetrating microelectrodes scales with the number of electrodes. See, for example, Figures 1, 5, 6, and 7 in the Szymanski paper, which also concisely summarizes observations from the literature related to such electrodes:

"Previous animal studies have shown that variability in MEA performance is mostly attributed to biological factors including tissue damage rather than to device failure per se [11–13]. … Acute injury and long-term exposure to a foreign body [12, 14–20] may trigger progressive inflammatory and fibrogenic responses that are characterized by an influx of astrocytes and microglia that encapsulate the electrodes [14, 18]. These processes lead to the formation of a glia scar around microelectrodes that can directly affect neuronal recordings by increasing the electrical impedance of the recording tip [11, 21], and degrading signal quality over time [22, 23]. Moreover, a progressive and sustained inflammatory response and neurovascular damage can lead to localized neuronal loss [12, 17, 19, 24]."

The facts that intracortical electrodes irreversibly damage the brain, and that the amount of tissue injury depends to a certain extent on the number of electrode penetrations, are not in question. By calling out these properties of intracortical electrodes we are not attempting to claim to have developed a superior electrode array, particularly as the safety profile of Utah arrays in particular is well known at this point, and such arrays are well tolerated in humans, at least at the scale of several hundred microelectrodes. However, these issues of tissue disruption must at least be considered for brain–computer interface systems designed to scale to thousands of electrodes or more, and in this context micro-ECoG is a natural approach to investigate.

Reviewer 2 requested support for the statement "Such systems are also difficult to remove or replace without causing damage to surrounding brain tissue." This was not intended to be a controversial statement. It is well established that the precise anatomic location of microelectrodes influences the nature of the electrophysiologic information they provide. In

clinical context, the positions of depth and surface electrodes are often modified (sometimes using micromanipulators) to optimize the electrophysiologic output for these reasons. The ability to reposition surface electrode arrays without trauma to the underlying brain is a well known feature of such arrays when used clinically for electrophysiologic mapping. Penetrating microelectrode arrays such as the Utah array cannot be repositioned once implanted. This is a known drawback of such arrays. Changing the position of such an array after implantation requires additional surgery for hardware explantation and reimplantation of a new array (in such cases, the tissue disruption of the original implant cannot be reversed). Indeed, this has sometimes been required in research studies involving human participants, even when extremely experienced groups are involved—the study cited above by Collinger, Cui, and colleagues, is an example: "Following implantation of the arrays into [participant] P2, it was discovered that the implant locations were posterior to the intended sites. Following which, the pedestals were removed, and a second implantation was performed 2 months later. This second set of implants are not within the scope of this study."

Reviewer 2 requested support for the statement "Signals from penetrating electrodes are less stable over time than those from surface electrodes." Perhaps this statement was not sufficiently specific. We intended this as a reference to stability from the standpoint of neural decoding performance, as neural decoders based on state-of-the-art intracortical systems (Shenoy and Henderson and colleagues, Nature 2023) have typically required recalibration due to signal drift on timescales on the order of days, whereas state-of-the-art ECoG-based decoding performance has been shown to be stable over many months without requiring recalibration (Chang and colleagues, Nature 2023). We have rephrased the statement accordingly in the text, and have inserted these citations: "In the context of brain–computer interfaces, neural decoding performance from penetrating electrodes has been shown to be less stable over time than neural decoding based on surface electrodes."

We agree with Reviewer 2 that "It is certainly true that there are trade-offs in terms of performance" and other properties of microelectrodes used for brain–computer interfaces. The system presented here has adopted one set of trade-offs, and we have attempted to explain the contexts in which such trade-offs could be well justified, particularly in brain-computer interface systems that might require many thousands of microelectrodes spanning wider functional areas of human neocortex. We do not intend to assess in this study the relative clinical safety of different electrodes or approaches; a number of approaches have been used with apparent safety in numerous studies.

As to the comment from Reviewer 2, "Given that this is a commercial device being presented by the company that makes it, readers should be wary about straw man arguments meant to possibly bolster marketing claims" we would point out that the devices described are not commercially available, and we have not made "marketing claims" here or elsewhere. We have performed a full battery of studies to characterize array longevity, biocompatibility, and other properties in keeping with international and FDA standards for electrode arrays intended for clinical use, and, as mentioned elsewhere in this set of responses, we have incorporated the results of these studies into the revised manuscript.

2.3 *The authors claim to "demonstrate accurate neural decoding of somatosensory, visual and volitional walking activity," although the decoding is rather rudimentary (essentially merely differentiating between different sensory stimulation localities with ~75% accuracy and differentiating between head and limb movement with 68% accuracy). In their "speech decoding" example, they merely decode voice onset; this is far below the capability reported by, e.g., the Chang group using a much sparser array to do accurate, large-vocabulary speech decoding. Although there certainly is finer-scale resolution obtainable with these arrays, it's unclear what actual benefit they will have for BCI, given these modest results.*

Reviewer 2 was correct to point out that in our manuscript as originally submitted the decoding performance in certain examples was suboptimal. We have since demonstrated and multiply replicated significantly improved results, with decoding performance reliably in the range of >95% accuracy on complex problems, and with clear dependence of accuracy on electrode number and electrode spacing. We have added these results to the section entitled "Multi-Modal Neural Decoding" and encapsulated them in a new version of Figure 4 as well as a new Supplementary Figure 10.

In the context of awake motor and speech decoding, our intention here was to demonstrate feasibility across multiple modalities. We have attempted to soften the presentation in a number of locations throughout the revised manuscript to avoid any appearance of overstating results. To this end, we have emphasized in the primary figures the highest-accuracy neural decoding as well as the dependence of accuracy on electrode number and spacing. We have shifted some of the decoding results to the supplement as new Supplementary Figure 9.

However, we do wish to emphasize the contexts here. In our awake motor decoding experiments, the animals were untrained, movements were natural, unconstrained, heterogeneous, and spontaneous, and the training data sets were much smaller than those typically used in the literature, for example, involving trained nonhuman primates. Similarly, in our initial human speech decoding work, models were constrained to be trained on a maximum of 4 minutes of data obtained while participants were awake during neurosurgical procedures. These contexts are not directly comparable to those in which state-of-the-art neural decoding performance has been demonstrated (after hours and days of training and optimization). We present neural decoding under highly constrained conditions to demonstrate feasibility and what we know to be an important starting point.

We believe that the results presented in our revision of this manuscript should address the criticisms of Reviewer 2. Since submitting our initial manuscript, we have performed intraoperative studies involving an additional 20 patients across 3 major clinical centers, with accurate hand fine-motor decoding and speech detection at the speech-onset and individual-word levels. The protocols involved in those studies are more complex than those described here and were conducted with other collaborators. We are preparing those results, together with our clinical collaborators, for peer review, together with the underlying electrophysiologic data, which we hope will be of interest to the broader scientific community. The present manuscript,

describing the device, surgical techniques, and feasibility of neural decoding across several sensory and motor modalities, will be referenced by our subsequent studies.

2.4 *The surgical technique is clever and does appear to have been successful, although it is impossible to fully assess since there is no mention of the number of pigs used for the study, and what the variations in implant technique might have been. Under "Results: Safety and Reliability" the authors state that "Histologic evaluation of cortical sections immediately beneath implantation sites following acute (≤8 h) and chronic (>30 day) implants revealed no evidence of acute or chronic tissue injury." How many animals were in the chronic cohort? What did recordings look like at 30 days? They claim this system is easy to explant – what did the 30-day explant procedure look like? Did it require a full craniotomy, or could the arrays simply be pulled free from the epidural space? Much more data are needed to assess these claims.*

We agree with Reviewer 2 that these important claims should be better supported than the evidence that was presented in the initial submitted draft of the manuscript. Since the manuscript was submitted, we have completed a formal implantation study (conducted in accordance with the FDA's Good Laboratory Practices as outlined in 21 CFR Part 58) in 16 Gottingen minipigs implanted with either 2 Layer 7 electrode arrays ("Test") or 2 AdTech subdural electrodes ("Control"). The cohorts were further split into two time points to assess the subacute (7 days) and chronic (42 days) responses to device implantation. All animals were clinically assessed throughout the duration of the implant, and following euthanasia, the calvaria and brains of each animal were sent to an independent, board-certified veterinary neuropathologist who grossed each specimen while maintaining complete photographic records, and reviewed multiple histologic sections stained with traditional H&E and immunohistochemical stains (Iba1, GFAP).

Please note that this study was not designed to assess recording function at 30 days.

We have described the additional analysis in the Methods under "Implantation Test," and have incorporated the results of this additional analysis into the revised manuscript in the Section titled "Safety and Reversibility." Note that these results, while more rigorous than those presented in the initial version of the manuscript, do not fundamentally change the conclusions presented in the original draft regarding the safety and reversibility of the Layer 7 device.

In answer to Reviewer 2 regarding the question of array removal, the procedure for formal pathologic and histologic analysis required a craniotomy in every animal studied. It was noted that array removal at chronic timepoints was feasible using gentle traction from the epidural portion of the array after clearance of a small amount of epidural granulation tissue.

2.5 *In the caption of figure 2, the authors state that "Safety was also assessed using standard, semi-quantitative histology techniques following 30-day chronic array implantation." However, these techniques are not described in the methods section, other than routine H&E staining, which is not a particularly sensitive indicator of local damage. Again, how many animals were sacrificed, and what was the variation? What assurances are there that the data were not "cherry picked" to illustrate this device and implant technique in the most favorable light?*

This is a reasonable question from Reviewer 2. Please see our response to the preceding question, and in particular our completion of a full GLP study with independent analysis and complete gross photographic and histologic documentation to avoid a biased analysis and presentation of results of the type implied by Reviewer 2.

2.6 *Under "Results: System overview," it would be helpful to have a photograph of the complete system as implanted in the awake, behaving animal. This would allow for a better comparison with BCI systems currently used in human clinical trials.*

We appreciate this request from Reviewer 2 and we have added images, including Supplementary Figures 2 and 3, to ensure that the electrode arrays are clearly presented, both in terms of feature dimensions, fabricated form, and *in situ* appearance. We have ensured throughout the Methods that the structures of the systems used in awake behaving animals and intraoperatively are clearly described, and have made a number of updates and clarifications to the Methods in this revised manuscript. The systems used in the studies described here were not intended for chronic use (except in the context of the chronic biocompatibility studies described above), so we prefer to use the system schematics presented in Figure 1 and Figure 3, for example, to describe the awake-behavior setup, which, as described, includes some standard and commercially available components. In keeping with our response to related comments from Reviewer 3, we have modified the title of the manuscript and softened certain of our claims regarding the "System" in favor of emphasizing the electrode array, insertion technique, and aspects of microelectrocorticography related to neural decoding and brain–computer interfaces. Our fully implantable system, which will be more appropriate to compare with other such systems, will be described in more detail in subsequent publications.

2.7 *In the Discussion section, the authors state that "our early experience in human patients substantiates the clinical utility and usability of the system." However, they don't demonstrate the full end-to-end microslit technique in this setting, which presumably forms the basis of the "clinical utility and usability" claim. Micro-ECoG recordings are hardly novel and nearly any of these devices would be expected to provide similar "utility and usability."*

Reviewer 2 makes a nuanced point here, and we have revised this statement to: "Our early experience in human patients substantiates the clinical usability of the system," as we certainly have demonstrated that the system is straightforward to use in a human clinical intraoperative setting. Perhaps the "utility" is more subjective at this point, though high-resolution somatosensory evoked potentials in human patients, as demonstrated in this study, have the potential to assist in more precise localization of function intraoperatively in patients undergoing surgery in eloquent regions near primary motor cortex.

We demonstrate the "end-to-end microslit technique" in the large animal model and in human cadavers for regulatory reasons at this point. At the time of our initial submission of this manuscript the novel device had only been used in the setting of open craniotomies. In subsequent work with other collaborators the device has been used in a more minimally invasive

fashion (in a series of awake patients), using the tools and features designed for the microslit technique. As mentioned in response to an earlier question, we are preparing those results, together with our clinical collaborators, for peer review, together with the underlying electrophysiologic data, which we hope will be of interest to the broader scientific community. The present manuscript will be referenced by our subsequent studies.

2.8 *In summary, this manuscript describes a nice design which is incremental in nature and will likely at some point form the basis of a BCI system, given the resources the company has invested in development. However, the authors provide little convincing evidence that safety, decoding accuracy, or ease of use are better than devices currently being widely used to advance the state of the art in BCI.*

We appreciate the critique of Reviewer 2. As to the nature of the micro-ECoG array design, we respectfully disagree with Reviewer 2. Reviewer 2 references "devices currently being widely used to advance the state of the art in BCI," but to our knowledge there is no microfabricated micro-ECoG array widely available to the scientific community. To the best of our knowledge, this is the first microfabricated micro-ECoG system that has been implemented in scaled production under a human implant-grade quality control system and demonstrated in human intraoperative use in a manner that could facilitate clinical use of micro-ECoG in practice. Please recall that the Utah array was far from the only or the first penetrating microelectrode array, but the consistency and control of its manufacturing processes and its availability for use at modest scale resulted in more than incremental contributions to neuroscientific research and the development of brain–computer interfaces. The system reported here is presented in a similar spirit but for micro-ECoG-based systems rather than those based on penetrating intracortical electrodes.

As to the questions of safety, decoding accuracy, and ease of use, we have added substantial content to the manuscript in response to related comments from Reviewer 2, as described above. Questions of safety and biocompatibility have been addressed with a rigorous study adhering to GLP protocols, with all pathological and histological analysis performed by an independent assessor. We have also demonstrated substantially higher-quality decoding performance in this revised version of the manuscript, with clear dependence on electrode number and inter-electrode spacing, as described in response to earlier questions from Reviewer 2.

We respectfully hope that these modifications and additions and responses adequately address the concerns Reviewer 2 raised regarding the initially submitted manuscript.

Reviewer 3

The work by Hettick and colleagues describes a novel high-channel count, high-density, electrocorticography platform. They illustrate its practical aspects in terms of minimally-invasive footprint to insert it onto the cortical convexity of an animal model. They additionally demonstrate its use during intraoperative recordings with human patients undergoing neurosurgery for other reasons.

In the animal model, they illustrate in-vivo signal viability during awake behavior, sensory physiology, decoding of behavioral state, and high-fidelity & spatially complex microstimulation.

In the human patients, they show signal viability and usability for (offline) speech decoding.

The primary content is supported by a rich set of supplemental material.

I believe that this is extremely important technological advancement that will be useful to the entire neuromodulation community, and may have real impact in human therapies. Provided that a few minor concerns are addressed, I believe that Nature Biomedical Engineering would be the perfect place for it, and I recommend publication.

We thank Reviewer 3 for these comments and for this overall positive assessment of the work. We also appreciate the detailed comments and suggestions for improving the manuscript, which we have addressed and attempted to incorporate, as described in detail below.

General (major) comments:

3.1 *It would be helpful to know what the relative in-vivo filtering and signal to noise properties of the recording ecosystem are. These are very important to ascertain what the resolvable behaviorally-associated signals are. These might be characterized along the lines shown in the manuscript and supplement to Miller, et al, "Power-Law Scaling in the Brain Surface Electric Potential", PLoS Comp Biol, 2009. Particularly along the lines of Figs. 1B, 4, and supp Figs 13-17.*

Reviewer 3 is correct to note that we should have included data more clearly characterizing the intrinsic filtering, signal-to-noise, and noise floor properties of the micro-ECoG recording system. We thank Reviewer 3 for referencing the exemplary work along these lines in Miller and colleagues, PLoS Computation Biology 2009, which we have cited in the section we have added to address this comment.

We have added a statement to the Results subsection “Electrode Array Characterization” discussing these characteristics of the system, and we present the power spectral density as measured from the 50-micron and 380-micron electrodes in the micro-ECoG array physiologic conditions. We also show the power spectral density for rejected (high-impedance) channels, an analysis similar to the ones presented by Miller and colleagues in the reference cited here by Reviewer 3. We have added a new Supplementary Figure 3 illustrating these analyses.

3.2 *I am not certain that the work really constitutes a full BCI platform. A) There is a novel ECoG array, with a novel, minimally-invasive, delivery mechanism for this array. These are impressive. B) The amplifier setup appears to be a customized intan-based system, but this is not described in sufficient detail in text or figures for me to understand what is important about this. C) The analyses appear to*

appropriate to address and interpret the recorded data. However, it is not clear what new contribution this is, what is decoded online (i.e. what is actually BCI), and how it is uniquely suited to the array or the amplifier. Items A, B, and C combined constitute a platform. However, the manuscript is primarily concerned with the array and its novel implantation. Therefore, I would propose that either the concept of this being a platform be expanded, or the title and text should be centered around the array, but not a new BCI platform. To be clear, I do believe that the array component (A) is sufficiently important and novel to merit publication in this journal on its own.

> We appreciate this perspective from Reviewer 3. We agree that the title should reflect the scope of the work and that the text should emphasize this scope without appearing to overstate what has been presented in the present work. We have therefore removed the word "Platform" from the title, which we have revised to "Multimodal Neural Decoding Using Scalable Microelectrode Array Technology for Minimally Invasive Brain–Computer Interfaces". Among other modifications to the text softening the claims (while also demonstrating improved on-line neural decoding, addressing concern "C" from Reviewer 3, as described in detail in responses to the other Reviewers above), we have also added comments in the Discussion regarding the limitations of the study. Please see the second-to-last paragraph (newly added, highlighted, and reproduced here):
>
> This work has a number of limitations. In particular, we have not demonstrated the performance of the thin-film electrode interface in the context of a fully integrated package designed for chronic implantation and wireless data transfer. A full system of this nature is under development and will be described in future studies. We have also focused on demonstrating the decodability of neural data obtained from the thin-film arrays, but given constraints imposed by our animal models (untrained, freely behaving Gottingen mini-pigs) and limited duration of our intraoperative recordings, but have have not optimized decoding performance for any specific clinical indication. Finally, the clinical data reported in this study were gathered as part of a feasibility study to demonstrate the safety and functionality of our system for short-term, intraoperative recordings; future studies will be needed to demonstrate the clinical utility of our thin-film microelectrode array for specific indications, including intraoperative mapping and restoring motor or speech function in paralyzed patients.

3.3 *Both human and animal data should be made available. As a neurosurgeon, I would like to be able to ensure - myself - that the quality of the data is sufficient to resolve for the applications I would use the system for before I would feel comfortable moving to implant it into a patient.*

> We appreciate the interest of Reviewer 3 in the human and animal data. We share an interest in ensuring that the community is able to assess the data quality and potentially conduct additional analyses beyond those presented here. We fully intend to make the data available with publication of the study. The statement regarding Data Availability has been revised to reflect this.

Focused (minor, optional) comments:

3.4 *Figures 1,2, 3, 5, 6b-f, - If acceptable, I think it would be helpful if a small amount of text were embedded in the figure so that it is clear what the purpose of each panel is (rather than having to learn this going back and forth to the caption).*

We appreciate these comments from Reviewer 3 regarding figure clarity and have made numerous modifications to the figures in the revised manuscript in an attempt to improve them along these lines.

3.5 *Figure 1 - There are several 'pale gray lines' throughout the figure that should be removed.*

We have addressed this issue. Thank you.

3.6 *Figure 3 general - panels b, e, f, g, and i do not have a scale. This should be remedied.*

We have added scale bars wherever possible.

3.7 *Figure 3f - do the flat traces correspond to no response at all? Or are they artifactually flat? If they are non-physiologic, I would omit the traces.*

We appreciate this comment and have omitted high-impedance (>4 MOhm) traces from figures in the revised manuscript. Some traces may appear relatively low-amplitude in array grid plots due to the small size of each trace in these 1024-trace plots.

16 March 2025

Dear Professor Caprettini and Colleagues,

Thank you for your consideration of our revised manuscript submission to *Nature Biomedical Engineering*, "Multimodal Neural Decoding Using Scalable Microelectrode Array Technology for Minimally Invasive Brain–Computer Interfaces," (nBME-24-0427-T, originally entitled "Multimodal Neural Decoding Using a Scalable and Minimally Invasive Brain–Computer Interface Platform").

We appreciate the additional comments provided by the experts who re-reviewed this work on behalf of the journal, after our initial revision of the manuscript in response to the first round of reviewer comments. We have completed a careful and complete set of responses to these comments, and we have included the point-by-point responses as well as the revised and annotated manuscript here.

We have devoted substantial additional work to addressing the criticisms, concerns, and suggestions of the reviewers. We hope that our responses, modifications, and additions will be sufficient to convince you and the reviewers of the merits of the study and its suitability at this point for publication.

Thank you again for your consideration, we look forward to hearing from you.

Sincerely,

Benjamin I. Rapoport, M.D., Ph.D.
(On Behalf of the Authors)

Point-by-Point Response to Reviewers

Please note that we have placed comments from the reviewers in italics, and have introduced a numbering scheme for the comments for purposes of clarity. Our responses are in roman font.

Reviewer 1

1.0. ***[Overall Comments]*** *The manuscript has significantly improved. Particularly, the additional correlation analysis and the more difficult decoding experiments clearly demonstrate the benefit of high-resolution Ecog.*

We thank Reviewer 1 for this acknowledgement.

Yet, I still have both major and minor concerns that would request further modification and clarification.

Please see our responses below.

1.1. ***Section of "Modularity and Scalability"*** *[Major]. The authors stated that the system is modular, but the best data they presented that unambitiously in support is "doubly connected 529-channel modules". I would argue scaling to 2 is not in strong support of modularity and scalability, and it was not clear if the doubly connected modules were inserted through the slit or a craniotomy. Sup. Fig. 1 showed stacked devices of four on bench top, without providing evidences that it was inserted through a slit and could record high-quality signals on all modules. Sup. Fig. 6 showed the overlay of implantations from multiple animals, if I understand it correctly, and therefore does not support modularity and scalability. Can the authors clarify: 1) in any single animal, what is the maximum number of devices and channels they implanted through a slit, and 2) show implantation images and/or recording/stimulation data in vivo from these many-module implantations. This is critical to the system's novelty and potential impact.*
Related to this, a large portion of the discussion section centered on scalability and modularity, which may need to be modified depends on the new data to be presented.

Reviewer 1 highlights an important feature of the system presented here in requesting clarification and additional evidence related to modularity.

In answer to the first question posed by Reviewer 1, regarding the maximum number of devices and channels we have implanted through slit osteotomies, the maximum number of devices we have placed in a single animal using the slit insertion technique to date is four, two 529-channel devices in each of two cranial slit osteotomies, one per hemisphere, for a total of 2,116 channels. The electrode array locations correspond schematically to the light blue regions in Supplementary Figure 6. We have clarified this point in the revised manuscript, adding the following comment to the section "Modularity and Scalability": "The maximum number of devices we have placed in a single animal using the slit insertion technique to date is four, two 529-channel devices in each of two cranial slit osteotomies, one per hemisphere, for a total of 2,116 channels. The electrode array positions correspond schematically to the light blue regions in Supplementary Figure 6."

In answer to the second question posed by Reviewer 1, requesting that we show electrophysiologic data from modular implants, please note that the data presented in Figure 3, Supplemental Figure 11, and Supplemental Video 3 all relate to modular deployments. Subfigures 3g and 3h show somatosensory and visual evoked potentials obtained from electrode arrays placed in different cortical locations in the same animal, as shown in the inset of Subfigure 3c. We have modified the Figure 3 caption as follows to clarify this point: "(c) Schematic of the Göttingen minipig brain showing color-coded areas corresponding to placement of thin-film subdural microelectrode arrays in different functional regions in the same animal." Additionally, the "Neural Stimulation" section provides an example of multiple arrays being used simultaneously, with propagation of electrophysiologic activity across the arrays.

Additionally, we explain in the manuscript that the 1024-channel electrode array was used in modular fashion in the context of our awake and spontaneously ambulatory animal work, as described in the section entitled "Multi-Modal Neural Decoding." In these experiments, two 1024-channel arrays were implanted in each animal, one over the sensorimotor region of each hemisphere. We have added an explicit comment now in the revised manuscript, in the final paragraph of the "Multi-Modal Neural Decoding" section: "This approach was designed to use the modular nature of the electrode arrays to maximize data acquisition over the relevant functional areas."

Furthermore, since submitting the original version of this manuscript, we have expanded our clinical collaborations to include additional centers. Much of the associated work is in preparation for publication, but one center has reported intraoperative deployment of four 1024-channel electrode arrays, for a total of 4,096 electrodes placed in a single patient during a craniotomy for a tumor involving intraoperative mapping of motor and sensory regions. We have added an explicit reference to this work now in the Discussion section of the revised manuscript, at the end of the first paragraph of the Discussion: Fink and Colleagues, "Functional Localization of the Human Sensorimotor Cortex Using High Resolution 4096 Channel Intraoperative Cortical Recordings: A Case Report" [Poster Abstract], North American Neuromodulation Society Annual Meeting (2025). We have modified the final sentence of the first paragraph of the Discussion section, in which we reference this work, to read as follows: "Our early experience in human patients substantiates the clinical usability and modularity of the system."

Beyond adding this additional comment and citation to the Discussion section, given these responses to Reviewer 1 substantiating multiple examples of modular deployment of the system in the ways Reviewer 1 has requested, we do not believe further modifications to the Discussion section are indicated relating to the subject of modularity.

*1.2. **Legends** [Major]. The manuscript presented many heat maps showing cortical activity on the array. Some of them do not have colorbar (e.g. Fig. 5d); others have color bars but do not have proper labels with units (e.g. fig. 6). In the only case I could find a color bar labeled with unit (figure 3i), it was unclear at which frequency band and under what time window of integration the heat map is generated. The*

authors need to correct all the heatmap plots throughout the manuscript, in both main figures and sup. Figures.

We thank Reviewer 1 for pointing out some omissions related to legends, labels, and units in figures throughout the manuscript. We have corrected all of the issues identified in this comment from Reviewer 1, as follows:

The captions in Figure 3i have been updated to clarify that the "dot plot" represents one frame from the 20 kHz recording.

Figure 5d now has an updated color bar with appropriate labeling of the voltage measurements.

The measure of "activity" used in Figure 6 is the Hjorth activity parameter, which has dimensions of voltage-squared. We have added a color bar to panel 6h for clarity, and have updated all color bars with proper units.

Proper units and labels have now been added to the color bars in Supplemental Figures 4, 8, and 9.

In addition to descriptions in the Methods section, we have also added information about the time windows in the captions of Supplemental Figure 7 to enhance readability.

1.3. ***Stimulation Section*** *[Major]. The Stimulation section, both the text and figure 6, are very confusing. First, not sure how cortical activity in g -j were defined (previous comment). Second, the black dots in g and h indicate very low activity – are the contacts broken, so little activity was detected, or does the device not conform on the brain surface, so fail to detect cortical activity because these regions were too far from the tissue? Please add discussions about the yield in the detection of all the arrays. In either case, please justify why these recordings are included in the downstream analyses. Third, panels e and I indicate that stimulations either suppress the cortical activity from the nearby contact or do not affect the activity much, but it does not enhance cortical activity. Why? Please also justify this is expected and not due to contamination from recording artifacts or a prolonged blank-out period in recording after stimulation.*

We appreciate that Reviewer 1 has requested additional refinement to and clarification in the section on stimulation. We have addressed all of the questions in this area, as follows:

Here, "activity" refers to the Hjorth parameter commonly used in EEG analyses, which is the variance of the signal. We have updated the captions and the Methods section to clarify that we are using a familiar and precisely defined measure of electrophysiologic activity.

As for the black dots, these correspond to electrodes that are defective as a result of defects in fabrication or damage during handling, leading to measurements with low variance in the signal and therefore low Hjorth activity. In the cortical stimulation experiments, while we made no attempt to reject electrodes, it was interesting to see that the electrodes exhibiting low activity

were predominantly those with high impedance (>4 MOhm). We agree with Reviewer 1 that a discussion of electrode yield would improve the manuscript, and we have now explicitly included electrode yield in the text in figure captions and in the Methods section. Briefly, with a selection criterion of <4 MOhm, all electrode arrays used for decoding tasks had over 95% yield, and the two electrode arrays used for cortical stimulation had 86% and 90% yield, respectively.

We did not apply blanking at the time scale that was analyzed, and excessive stimulation artifacts should only lead to an erroneous increase in activity rather than a decrease. In addition, the spatial distribution and continuity across adjacent arrays also confirm that the analyzed signal was indeed physiological and not artifactual. Finally, artifacts of the type referenced by Reviewer 1 would not be expected to change with the level of anesthesia, so the observed differential response to light versus deep anesthesia further supports the interpretation of a physiological rather than an artifactual response.

As to the question of whether this is an expected result, we believe the field of cortical microstimulation is relatively underexplored and merits further investigation. Our results are intended to demonstrate the feasibility of modulating cortical activity through the thin-film cortical array, and we have designed controlled studies to show that we can reproducibly modulate cortical activity in a way that reflects true physiological modulation. However, we feel it is premature to say definitively whether the results presented in this manuscript are expected and to speculate as to the physiologic mechanisms by which such modulation occurs. We have added a comment to the Discussion clarifying this limitation: “While the present work demonstrates the feasibility of delivering focal cortical stimulation and modulating physiologic activity through a high-density cortical surface array, while also observing the effects of the stimulation at high spatiotemporal resolution, further work will be required to determine the physiological significance of the modulation demonstrated here in different experimental and clinical contexts.”

1.4. [Minor] ***Abstract:*** *“The resulting system generates 90 Gb/h of electrophysiologic data”. What really matters are how useful, independent the data is. The volume does not matter. Please revise.*

We have eliminated the wording “generates 90 Gb/h of electrophysiologic data, and” so that the sentence in question now reads as follows: “The resulting system demonstrates the highly scalable nature of micro-electrocorticography and its utility for next-generation brain-computer interfaces that may expand the patient population that could benefit from neural interface technology.”

1.5. [Minor] ***Introduction:*** *“(contrary to some prevailing beliefs)”, both accurate neural decoding and accuracy improve as a function of both area coverage and spatial density appear intuitive and straightforward, I am not sure what is against some prevailing beliefs. Please revise.*

We have eliminated the parenthetical “(contrary to some prevailing beliefs)” so that the sentence in question now reads as follows: “We characterize the spatial scales over which electrophysiologic information is represented at the cortical surface, and show not only that

accurate neural decoding can be achieved, but also that accuracy improves as a function of both area coverage and spatial density."

1.6. [Minor] ***Figure 1:*** *does panel d contain data? If so, please explicitly describe the data in the figure caption*

The initial caption, which stated "This schematic illustration shows how neural activity is acquired from and stimulated by the thin-film cortical interface," was meant to emphasize that this figure is conceptual in nature only, demonstrating the system configuration and approach to data acquisition used in this study. The sub-panels are conceptual illustrations and do not contain physiologic data. As a point of clarification in response to this question from Reviewer 1, we have added a sentence to the end of the caption of Figure 1: "(Subfigures e, f, and g are conceptual illustrations and do not contain physiologic data.)"

1.7. [Minor] ***Miss[ing] Reference:*** *"The overall tissue response to implantation was similar for the thin-film and control devices, with slightly less inflammation noted in response to chronic implantation of the more conformal thin-film device." It is also unclear which has less response. Please clarify.*

We have revised the corresponding sentence in the text to read as follows: "The overall tissue response to implantation was similar for the thin-film and control devices, with slightly less inflammation noted in response to chronic implantation of the more conformal thin-film device relative to that observed in implantation of the control device."

1.8. [Minor] ***Fig[ure] 2:*** *caption stated chronic studies were at 30 days while text stated 42 days. Please clarify and correct.*

We thank Reviewer 1 for identifying this oversight. In the revised manuscript we updated the chronic histology data to include a larger study in which our chronic timepoint was 42 days; however, we neglected to update the corresponding figures which were from a smaller study for which the chronic timepoint was 30 days. We have updated Figure 2 (panels k and l) to include images from implantations of both the thin-film electrode and the control cortical surface array at 42 days, and updated the figure caption to be consistent with the main text. Specifically, the final portion of the caption for Figure 2 now reads as follows: "(k-l) Safety was also assessed using standard, semi-quantitative histology techniques following 42-day chronic array implantation. Histologic analysis demonstrated microscopic preservation of the cortical surface architecture and no systematic differences between cortical regions implanted with (k) the thin-film microelectrode array and (l) a standard 4-contact subdural strip electrode (HE, hematoxylin and eosin; D, dura mater; dotted blue line, region of cortical surface in contact with array prior to explantation; green arrows, cortical surface; yellow arrows, subcortical white matter)."

1.9. [Minor] ***Discussion:*** *Convenient and reliable explan[t]ation is important for clinical application and can be a potential strength of this technology. Can the authors discuss this, and adding some supporting data if possible?*

We thank Reviewer 1 for this comment and we agree that convenient and reliable explantation is important for clinical applications and may be a potential strength of our technology. We have added a comment on this point in the Discussion: “One potential benefit of a non-penetrating, cortical interface is the ability to reliably explant the device after chronic implantation in humans without causing tissue damage. Our chronic implantation study demonstrated straightforward and atraumatic explanation of the device after 42-day implants, supporting potential for long-term interfaces that may eventually be removed or upgraded. However, human clinical studies with long-term implantation will be required to fully substantiate this claim.”

Reviewer 3

The authors have candidly addressed all of my concerns, and I commend them on their important work, which I believe is a significant contribution to neural interfacing technology.

We thank Reviewer 3 for this comment.