nature biomedical engineering | PEER-REVIEW INFORMATION

Evoking stable and precise tactile sensations via multielectrode intracortical microstimulation of the somatosensory cortex

Corresponding author: Charles Greenspon

Editorial note

This document includes relevant written communications between the manuscript's corresponding author and the editor and reviewers of the manuscript during peer review. It includes decision letters relaying any editorial points and peer-review reports, and the authors' replies to these (under 'Rebuttal' headings). The editorial decisions are signed by the manuscript's handling editor, yet the editorial team and ultimately the journal's Chief Editor share responsibility for all decisions.

Any relevant documents attached to the decision letters are referred to as **Appendix #**, and can be found appended to this document. Any information deemed confidential has been redacted or removed. Earlier versions of the manuscript are not published, yet the originally submitted version may be available as a preprint. Because of editorial edits and changes during peer review, the published title of the paper and the title mentioned in below correspondence may differ.

The paper was initially submitted as two separate manuscripts, which were reviewed by the same three experts. The reviewer reports and decision letters for both manuscripts after one round of peer review are reproduced below. Successive rounds of peer review involved a single merged manuscript.

Correspondence

Tue 07 Nov 2023
Decision on Article nBME-23-1788

Dear Dr Greenspon,

Thank you again for submitting to *Nature Biomedical Engineering* your manuscript, "Biomimetic multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands" and for your patience in waiting for all the reports and our 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 further work you can address the criticisms and convince the reviewers of the merits of the study.

In particular, we believe that a story that includes the data and claims from both this manuscript and the other one you submitted to us, "Tesselation of artificial touch via microstimulation of human somatosensory cortex" – for which you will receive a separate email with the relative comments for the reviewers – would be more impactful than two separate manuscripts, and the findings would also be easier to interpret when placed and discussed together in the same story, so we expect a merged revised version of the two manuscripts.

In addition, please be sure to include the relevant information from the participants and all methodological details.

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 15 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)):

In their manuscript entitled, “Biomimetic multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands” Greenspon and colleagues present studies of how microstimulation in the somatosensory cortex hand representation effect can be used for providing perception of tactile force. The major new results presented here assess the number of different levels of force that can be discriminated over the safe range of microstimulation currents, the better performance of biomimetic stimulation as compared to simple, flat stimulation, and the better performance of multi-channel as compared to single-channel microstimulation. These results will find significant future application in the development of bidirectional brain-computer interfaces. The manuscript is well organized and lucidly written. It will be of considerable interest to a wide audience.

Major comments:
1. Page 6: “Natural touch thus confers far greater sensitivity to force variations than does single-channel linear ICMS.”
Can the authors make similar statements later in the paper concerning biomimetic and then multi-channel stimulation? How closely to these improvements come to natural touch? For example, Figure 5D provides a side-by-side comparison of the JNDs for single-channel linear, biomimetic, and multi-channel stimulation. Can the authors add another distribution of JNDs for natural touch? Or would this dwarf the scale for the ICMS results?

2. It would be useful if the authors could give an estimate of how many of the electrodes on a given array

would be expected to have their receptive fields contacted by their 5 mm probe. From Figure 1, it might be expected that neurons on 4 or even more electrodes would typically be responding to a 5 mm tactile stimulus. So the multi-channel ICMS would be expected to provide a closer emulation of the 5 mm probe.

3. The first paragraph of the Discussion dealing with Weber's law is a bit confusing, with apparently contradictory statements. For example, "on average, JNDs increased in proportion to the standard, consistent with Weber's law and with natural touch. At the level of single electrodes, however, Weber's law is often violated,"
Supplementary Figure 3B shows that at least 3 of 8 electrodes appeared to violate Weber's law. Were more than these 8 electrodes tested?

4. One wonders whether Weber's law would hold more consistently with mulitchannel, biomimetic ICMS. Was this tried? If not, it might be worth pointing out that this could be tried in future studies.

5. At the end of the Discussion, the manuscript points out that, "…the advantage of multi-channel ICMS is that it gives rise to a wider dynamic range of sensations." The authors might speculate on the trade-offs of using more than 4 electrodes for multi-channel stimulation, e.g. 8 or 16. Would one get a still wider dynamic range at the cost of fewer different groups of electrodes.

Minor comments:
1. Figure 1 of the present manuscript appears identical to Figure 1, subject C1 of the Tessalation manuscript. If the two manuscripts are to be published in tandem, the present Figure 1 could be omitted. Likewise for Figure S1.

2. Page 4: "...we found that perceived magnitude increased ... as a (decelerating) power function of mechanical amplitude (17) (Supplementary Figure 2C). Accordingly, the equal intensity contours also followed a power law…"
The authors might consider giving some descriptive statistics (range, median, etc.) of the power law exponents in these relationships.

3. Figure 2B: Why not use a power law to fit the data for ICMS? Was the linear fit better?

4. Figure 3B, legend: "Note that values above 40 μA are set to 40 μA for graphical purposes (n=2)."
As only two numbers are involved, please give those two values in μA in the legend.

5. Figure 3C: One cannot tell the difference between the lines and shading for the high and low standards. Perhaps color would be useful here. Also please give the values for the high and low standards in microAmps.

6. Page 10: "otheir"
typo

7. Page 12: "We selected groups of 4 electrodes, referred to as quads."
How were the groups selected? Adjacent electrodes? Overlapping projected fields? Other?

8. Page 15: "Network hyper-parameters network"
typo

9. Supplementary Figure 3: Can the authors please give the two standards used in mircroAmps?

10. Supplementary Figure 8: The results are reported in terms of force in Newtons, but the underlying controlled variable is skin indentation in millimeters. The calibration for conversion illustrated in Supplementary Figure 8 shows considerable variability among participants. Was a separate calibration used to convert mm of skin indentation to for each participant? Or was the mean linear fit shown in Supplementary Figure 8 used for all participants. Also, these calibration curves were obtained with a 2 mm diameter probe, whereas the current results were obtained with a 5 mm diameter probe. One might expect that more force would be required to depress the skin 1 mm using a 5 mm probe than a 2 mm probe. Is this not the case?

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

In the manuscript "Biometric multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands" Greespon and colleagues examine the range of ICMS amplitude discrimination in three participants. The perception of amplitude from ICMS is used as a surrogate for the perception of force applied to the skin. To compare the magnitude of ICMS to natural touch a participant with intact sensation on the hand was asked to rate both the magnitude of ICMS and touch sensations within blocks of trials. "Biomimetic" ICMS with an envelope of transient onset and offset was compared to ICMS without the transients on single electrodes. The biomimetic stimuli produced greater sensitivity measured by lower just-noticeable differences. Multi-electrode stimulation with the biomimetic ICMS produced stronger sensations and a greater dynamic range than biomimetic stimulation with a single electrode. One participant used biomimetic multi-electrode stimulation as feed-back for a compliance discrimination task using a robotic hand.

The manuscript is original in the sense that it capitalizes on psychophysical paradigms from the Bensmaia's lab, used with monkeys, and applies them to humans. The experimental design is sound and provides useful data. This is a short paper that overlaps with the companion paper in terms of the biomimetic stimulation and projection fields, and I would recommend combining the two.

Major technical criticisms or questions.

In comparing ICMS with actual touch, it is not reported what the participant felt. This is a missed opportunity when doing these experiments in humans. Did the participant feel sensations from ICMS and touch that were the same, making the comparison straightforward, or were the sensations different and the participant attempted to scale them in such a way that the range matched?

For the multichannel stimulation, only single biomimetic channel and biomimetic multi-channel ICMS are compared. As the authors state, it is not surprising that the sensation is more intense given the greater amount of charge for the multi-channel stimulation. What I did find missing was a comparison of mufti-channel linear stimulation and multi-channel biomimetic stimulation.

Figures 5 and 6 seem weak on data. The compliance discrimination in figure 6 with the robotic hand is what would be expected from experiments without the hand. Was this experiment only done once? There are no error bars or statistics for panel B of figure 6. Also, there are no statistics for panel D of figure 5.

Figure 4, panel C. The means do not look different. This needs some statistical analysis to make the claim that they are different.

In the companion paper, it is reported that the receptive fields are much larger than the projection fields, but the sustained part of the biomimetic stimulus matches the projection field. In this manuscript it is reported that the biomimetic stimulus increases the intensity, sensitivity, and dynamic range. it would appear that the transients of the biomimetic stimulus are necessary for this improvement but seems on the surface to contradict the results of the other manuscript. It would be useful to discuss whether these two findings are incompatible or perhaps somehow independent.

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

In the "Biomimetic …" manuscript, the Authors report a set of studies conducted with three SI implanted patients to verify fundamental properties of the modulation of intracortical microstimulation (ICMS) in SI, with the aim of refining the force feedback to be implemented into a bionic hand to improve grasp control. Central to this endeavor is to obtain a wide enough dynamic range and distinguishable evoked force sensation magnitudes. Once identified the - limited - range and – low - discriminability levels obtained with linear, flat trains of ICMS, the Authors implement biomimetic feedback and test it on single and multichannel stimulations. Multichannel biomimetic feedback largely prevails, conferring wider dynamic range and increasing the discriminability levels in passive perceptual task substantially. Ultimately, the closed-loop test demonstrates superior performance of multichannel biomimetic feedbacks - compared to linear feedback - in a compliance discrimination task implemented via a bionic hand.

The study is a major advance in the field. In a crescendo of empirical demonstrations, the manuscript reports compelling, converging, convincing evidence to support the conclusions that biomimetic multichannel ICMS may be leveraged to convey natural-like force feedback to actuate bionic hands.
I have no critical points to raise, though the Authors may want to take the following into account.

1 - I may have missed the information. It would be important to clarify whether the biomimetic type of

feedback, though improving force discriminability, would come at some cost with respect to localization ability (ref companion Tessellation … study). As the intro appropriately emphasizes, useful feedback from contact events should convey reliable information about location and force. Rough correspondence can come from somatotopically appropriate matching between electrodes and bionic force sensors. Yet, superior localization emerges from ICMS simulating the maintained stimulus dependent activity, rather than the transient evoked one. Biomimetic trains instead emphasize the transient part of the stimulus evoked activity. Would multichannel biomimetic ICMS widen the PFs' extent? While any potential cost in the localization-stability of the projected fields may be overcome by the increased range in force feedback, it may be worth clarifying whether the Authors expect any interaction – compromise to best implement both location and force via biomimetic ICMS.

2 – This study goes far beyond previous attempts in showing that multichannel ICMS not only seems more intuitive but specifically improves JNDs, thus, discriminability. As the Authors recall in the discussion, previous work in the monkey failed in showing such a superiority compared to single-channel ICMS. While fairness in acknowledging that the reasons for this discrepancy are not clear is appreciated, the Discussion may benefit from developing some tentative explanations.

Minor
I find the benchmark information about the number of discriminable levels from typical controls better positioned earlier than is in the section. 45-50 is the number one should aim at, 7 what one gets from flat ICMS. It speaks for itself.
'Discrimination of ICMS amplitudes..' section- typo: 'responses and otheir' – '.. and of their'.

Published papers are referenced in a different style compared to the companion manuscript, please check.

In Science
Alessandro Farnè

Tue 07 Nov 2023
Decision on Article nBME-23-1787

Dear Dr Greenspon,

Thank you again for submitting to *Nature Biomedical Engineering* your manuscript, "Tesselation of artificial touch via microstimulation of human somatosensory cortex" and for your patience in waiting for all the reports and our decision. The manuscript has been seen by 3 experts, whose reports you will find at the end of this message.

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In particular, we believe that a story that includes the data and claims from both this manuscript and the other one you submitted to us, "Biomimetic multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands" – for which you should have received a separate email with the relative comments for the reviewers – would be more impactful than two separate manuscripts, and the findings would also be easier to interpret when placed and discussed together in the same story, so we expect a merged revised version of the two manuscripts.

We hope that you will find the referee reports helpful when revising the work.

Best wishes,

Valeria

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Dr Valeria Caprettini
Associate Editor, *Nature Biomedical Engineering*

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

In their manuscript entitled, "Tessellation of artificial touch via microstimulation of human somatosensory cortex" Greenspon and colleagues present studies of the spatial features of the percepts evoked by microstimulation in the somatosensory cortex hand representation. The area of skin surface on which the participant experiences tactile sensation during intracortical microstimulation (ICMS) through a given electrode is referred to as the projected field (PF), to distinguish it from the area where natural stimulation evokes neural activity recorded through the electrode, i.e. the receptive field (RF). Previous publications have described that ICMS delivered through the different electrodes of an implanted array have the expected somatotopic organization. The major new results presented here show that the PF of a given electrode is stable over years, that the PF generally lies within the RF, and that ICMS delivered simultaneously through multiple electrodes with overlapping PF results in a more focal sensation. These results will find significant future application in the development of bidirectional brain-computer interfaces. The manuscript is well organized and lucidly written. It will be of considerable interest to a wide audience.

Major comments:
1. The first paragraph of the discussion reviews the stability of the projected fields over timespans of several years. It would be of interest for the authors to speculate as to how their present findings relate to previous studies showing "massive reorganization" of the somatosensory cortex following amputations/dennervations, etc. (Pons et al., 1991; Florence and Kaas, 1995). Is this a difference between inputs to S1 creating the RF versus outputs from S1 transmitting perceptions to other brain regions? Might reorganization of inputs not have occurred in patients with residual sensation? Perhaps this question is dealt with in some of the cited publications (Makin and Bensmaia, 2017), but a few sentences here would not be inappropriate.

2. Figure 1: The methods mention that the checkerboard pattern reflects interleaving electrodes wired for stimulation versus recording. Consider mentioning this in the Figure 1 legend. Perhaps more importantly, if

different electrodes were used for stimulating versus recording, please clarify whether PFs (stimulation) and RFs (recording) were obtained from the same electrode, or from adjacent electrodes.

3. Page 9: "…we assessed the relationship between PF size and sensation magnitude."

4. Please clarify how "sensation magnitude" was quantified? Subjective report of intensity? On what sort of scale?

Minor comments:
1. "Tessellation" is perhaps not the best word to describe the material presented in the manuscript, as it generally refers to a tiling that completely covers an entire area. Though such probably exists in the somatosensory cortex, that is not shown per se in the material presented here. Indeed, the word "tessellation" is used only in the title.

2. The details of each participant's SCI probably have been described elsewhere, but it would not be inappropriate to record a brief description of their sensory levels and areas of retained sensation in the present manuscript, perhaps as a supplementary figure.

3. Page 3: "sensitized" perhaps should be "sensorized"

4. Supplementary Figure 3: Consider indicating the 33% level used as the threshold in these figures.

5. Supplementary Figure 4: Consider adding a panel showing multiple hand outlines for each subject with the overlapped PFs from Figure 2B separated as time series.

REFERENCES
Florence SL, Kaas JH (1995) Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. Journal of Neuroscience 15:8083-8095.
Makin TR, Bensmaia SJ (2017) Stability of Sensory Topographies in Adult Cortex. Trends Cogn Sci 21:195-204.
Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M (1991) Massive cortical reorganization after sensory deafferentation in adult macaques. Science 252:1857-1860.

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

Overview:
The manuscript by Greenspon and colleagues, "Tesselation of artificial touch via microstimulation of human somatosensory cortex", contains a number of experiments examining various aspects of somatic sensation evoked by intracortical microstimulation (ICMS) of the hand area of S1 in human subjects. They report on stability of projection fields (PFs) defined by ICMS through electrodes over a period of 2 years in two participants and 7 years in a third. Since there is overlap of ICMS with sensate parts of the hand, correlations are made between the receptive fields of neurons and projection fields. It is also reported that ICMS of several electrodes with overlapping PFs produce more stable sensations.

A number of findings are confirmatory; for instance, a good deal of the manuscript covers somatotopic organization which has already been shown for ICMS by Flesher et al. 2016. Flesher showed stable somatotopy over 6 months (in fact P2 of the current manuscript I believe may to be the same participant as in the Flesher study). The main new contribution is examining the stability of ICMS over several years.

It is certainly important from a BCI/engineering perspective that the PFs remain stable over time. It would be useful to better highlight what may account for a lack of stability in the introduction. On the one hand there may be changes in the brain representation of the body over time. This seems unlikely given that the somatotopic map remains intact even years after deafferentation from spinal cord injury (Makin and Bensmaia 2017, Flesher et al. 2016). The other source of variability would be from the electrode arrays, either becoming physically degraded or migrating across cortex.

Overall, the manuscript lacks key details and explanations, and the organization is patchy, making for a difficult read. The analysis is based on pixels, which are not defined. There is considerable text about a fourth participant R1, but no experimental data other than part of a supplementary figure showing sensate regions of the volar surface of the hand. The definition and construction of the aggregate PFs is in the results section rather than the methods. Understanding many sections requires going back and forth between the results, figure legends, and methods.

The mapping of the PFs is central to the study but appears rather qualitative. In the results "To quantitatively characterize the PF of each electrode, we repeatedly delivered through it a 1-sec long ICMS pulse train (100 Hz, 60 μA)" and in the methods "The participant could request as many repetitions of the stimulus as desired." How many repetitions? A sensation reported by ten stimulus deliveries is not the same as one reported by a single delivery. Many deliveries could be indicative of a weak sensation, or barely perceptible sensation, or one that is highly variable. Many PFs were removed from analysis because of variability in producing sensation. This may give an impression of greater stability.

I recommend streamlining the manuscript and combining it with the other Greenspon et al manuscript. The parts that are confirmatory can be reduced and participant R1 removed. The other manuscript is short, with a study that is overlapping and extending the section "the projected field is determined by the receptive e field of the activated neurons". I would recommend a change in title emphasizing stability rather than tessellation, since examining stability is the main theme of the study.

Other technical criticisms and questions.

Figure 1 has no mention of the number of repetitions, stimulation parameters or time period of data collection and assessment. Was this data collected at the beginning or end of the implantation period? Over how many sessions was this data collected?

Figure 2, the participants drew the spatial extent of the PFs, made possible by residual arm function. Was there any independent indication of how accurate these drawings were?

Figure 3. In the text:" we computed the degree to which PFs reported for an electrode on any given session matched the first ever reported PF on that electrode. We found that centroid distance between the initial PF and subsequent ones for a given electrode remained stable." The figure shows distances of 3 to 8 mm. Perhaps I am missing something, but shouldn't the distances be around 0 to be stable? In panel C, how was the subset of electrodes selected?

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

Greenspon et al,
In the "Tessellation of …" manuscript, the Authors report conglomerate studies' results with the aim of verifying a set of fundamental prerequisites for bionic hands to succeed in providing BCI's users with informative, reliable and usable feedback. Namely, hand substitutes aimed to be used via intracortical microstimulation (ICMS) in SI would require that the artificially activated neurons evoke tactile sensations that are projected at relatively small patches of skin and in a reproducible way, both at the level of their location in reference to the hand somatotopic representation and of their stability following repeated stimulation in time. To assess these and other features, the Authors report analyses of several sessions from three SI implanted patients, spanning several years. Results convincingly support the notion that such needs are fulfilled.

This manuscript reports compelling, converging, convincing evidence to support the conclusions that projected fields (PFs) evoked by ICMS are focal and stable over time. In addition, they show that their extent and location is typically within a subset of the skin area that, once touched, activates neurons recorded by implanted electrodes, that is their Receptive Field (FR), thus showing the spatial relationships between RFs and PFs in an unprecedented quantitative manner. Next, results show that ICMS of electrodes bearing overlapping PFs further refines the PFs' extent. Not last, leveraging this property, multielectrode ICMS improves implanted patients' ability to localize PFs when touching sensors on a bionic hand in finger matched arrangement, as compared to single electrode ICMS.

The study is a major advance in the field. While some previous studies already reported promising results of the stability pf PFs, none has gone this far in providing detailed quantitative examination of this phenomenon, fundamental for the successful implementation of sensing bionic hands. This study goes much further beyond that, as it provides in depth characterization, on a long-time scale, of quantitative interactions between RFs and PFs, between amplitude/frequency modulation of ICMS and their generated sensations on the skin and it identifies new avenues to keep ICMS safe and make it more efficient, to ultimately make touch sensation part of bionic hand motor control.

A few points deserve attention.

1 - The quantitative characterization of the PFs is entirely dependent upon the residual arm function of each patient. Although this is not likely to affect stability measures over time, it would be important to report these residual ability, and how they were measured, in some detail for each patient. Relatedly, was the same hand stimulated that was used for the drawing? Only right-hand figures are used to display results: were all patients right-handed before spinal cord injury?

2 - Instead, thresholding criteria for building aggregate PFs' extent may affect stability measures. It may appear that setting the reliability criterion to 33% brought to removing an important proportion of pixels concerning PFs that might have revealed a more important variability across time than presently estimated. Although Supplem Figure 3 may reassure in part (please note the legend should be added to color-code the patients in this figure), as 0,25 sets a major drop in aggregate PFs areas, it remains true that 25% of pixels for patients C1 and P2 and about 60% of pixels for patient P3 were thus excluded from all analyses. Including a larger portion of 'unreliable' pixels (i.e., analyzing results with multiple alternative threshold values) would be commendable. This seems particularly valuable as excluded pixels were still located on adjacent regions to the core of each electrode.

3 - As a relatively minor point, the suggestion is made that since transient and sustained contact activate areas of cortex at different scales (much larger for transient), ICMS is rather comparable to sustained contact. This would indeed be appropriate for prolonged contact, for example during object holding and manipulation. Yet, the reasoning is proposed that responses to contact transients cannot determine the spatial extent of touch perception as touching a single digit would evoke sensations in multiple digits (by the larger scale of neuronal response). Yet again, brief transient touches with small indentation (like von Frey filaments) do evoke subjectively well localized tactile perception on single digits, in absence of prolonged contact. The authors may want to take this in consideration to clarify this apparent paradox further, also in regard of the companion manuscript, as biomimetic ICMS actually emphasizes contact transients compared to prolonged contact.

Minor

'Residual sensation' section- typo: van Frey, should read von Frey.
This section would benefit from being completed by adding information about participant R1.

In Science
Alessandro Farnè

Mon 10 Jun 2024
Decision on Article NBME-23-1788A

Dear Dr Greenspon,

Thank you for your revised manuscript, "INTRACORTICAL MICROSTIMULATION OF SOMATOSENSORY CORTEX EVOKES STABLE AND PRECISE TACTILE SENSATIONS", which has been seen by the original reviewers, and thank you for your patience in waiting the final report. One of the reviewers found difficult to navigate the changes and needed additional time to provide a thorough assessment. In their reports, which you will find at the end of this message, you will see that the reviewers acknowledge the improvements to the work, and raise a few additional technical criticisms that we hope you will be able to address. In particular, we would expect that the next version of the manuscript to provide a more cohesive narrative of the findings to improve accessibility, as highlighted by Reviewer #2.

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).

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* 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 12 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 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
Associate Editor, *Nature Biomedical Engineering*

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

In their manuscript entitled, “INTRACORTICAL MICROSTIMULATION OF SOMATOSENSORY CORTEX EVOKES STABLE AND PRECISE TACTILE SENSATIONS” Greenspon and colleagues have done an admirable job of combining their tandem manuscripts on “tessellation” and force perception. The combined manuscript now assesses both the stability of projected fields over time and the number of different levels of force that can be discriminated over the safe range of microstimulation currents. In addition biomimetic stimulation as compared to “linear,”flat stimulation, and multi-channel stimulation is shown to provide advantanges as compared to single-channel microstimulation. The findings are convincing and useful. These results will find significant future application in the development of bidirectional brain-computer interfaces. The manuscript is well organized and lucidly written. It will be of considerable interest to a wide audience. I have only a few minor comments.

Major comments:

None

Minor comments:

1) Abstract, line 3:
Because there is a secondary somatosensory cortex and you are using the abbreviation "S1", consider adding the word "primary” before somatosensory cortex (S1)

2) Figure 1 and Methods on Cortical Implants:
Although I recognize that the present work focusses on S1, referring to the crown of the human precentral gyrus as M1, primary motor cortex, is incorrect. A number of studies have shown that in humans, at the level of the hand knob, area 4 lies buried entirely in the anterior bank of the central sulcus (Geyer et al., 1996; White et al., 1997; Binkofski et al., 2002).

3) page 12:
"C1’s (fully sensate left hand)" perhaps should be "C1’s (fully sensate) left hand"

4) page 17:
"Consistent with this, increases in ICMS amplitude or frequency led to increases in the volume of activated neurons and/or density of activated neurons within a volume (20–22,32) and concomitant increases in PF area."
This sentence makes it sound as if the increase in volume and density of activated neurons had been assessed in the present study. This inaccurate implication could be corrected by changing the word "led" to "would lead" and changing "and concomitant” to "producing concomitant".

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Binkofski F, Fink GR, Geyer S, Buccino G, Gruber O, Shah NJ, Taylor JG, Seitz RJ, Zilles K, Freund HJ (2002) Neural activity in human primary motor cortex areas 4a and 4p is modulated differentially by attention to action. J Neurophysiol 88:514-519.
Geyer S, Ledberg A, Schleicher A, Kinomura S, Schormann T, Burgel U, Klingberg T, Larsson J, Zilles K, Roland PE (1996) Two different areas within the primary motor cortex of man. Nature 382:805-807.
White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, Purves D (1997) Structure of the human sensorimotor system. I: Morphology and cytoarchitecture of the central sulcus. Cereb Cortex 7:18-30.

- Marc H. Schieber

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

This is a resubmission in which two original submissions were combined into one to reduce repetition and produce a more concise report. The study reports several new findings using intracortical microstimulation (ICMS) in humans with the goal of providing tactile feedback to spinal cord injured patients. It documents stability of ICMS over periods of years, the alignment of the ICMS sensations with neural receptive fields, somatotopy, effects of increasing ICMS intensity, advantages of multielectrode stimulation, and biomimetic shaping of the stimulus parameters.

Major criticism.
There is a lot of valuable data in the paper and the authors have added to the biometric part of the study since the previous submission. However, the paper reads like a list of new findings or corroborations of prior research without a common theme. Rewriting parts of the paper to have a more overarching conceptual framework would improve its accessibility.

Minor criticisms.
The authors respond to some of my comments but not all. Pinpointing changes is difficult in the new submission since the locations of the changes are not indicated.

In the abstract, ‘projection field’ is not defined. The abstract, like the paper, seems to be a list of results without a cohesive theme.

Pixels are mentioned throughout the paper but not explicitly defined.

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R1, the fourth subject, does not add much to the paper and the response to reviewers is vague. Three participants are mentioned in the abstract, introduction, and most of the paper so it is a bit confusing when R1 is introduced briefly in the results. I still recommend removing R1.

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

I congratulate the authors for the successful merge and trim of their manuscripts into a single paper. The manuscript has gained in clarity and readability without losing any important analytic information.

All the previous points I raised have been dealt with fully satisfactorily, no further requests.

There is a typo in the "Projected fields are contained..” section: “.. projected verses receptive fields ..” should read “versus”.

In Science
Alessandro Farnè

Mon 05 Aug 2024
Decision on Article NBME-23-1788B

Dear Dr Greenspon,

Thank you for your revised manuscript, "INTRACORTICAL MICROSTIMULATION OF SOMATOSENSORY CORTEX EVOKES STABLE AND PRECISE TACTILE SENSATIONS". Having consulted with Reviewers #1 and #2 (whose comments you will find at the end of this message), 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 carefully follow these instructions before you upload the final manuscript files.

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

Best wishes,

Valeria

—
Dr Valeria Caprettini
Associate Editor, *Nature Biomedical Engineering*

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

In their revised manuscript entitled, "INTRACORTICAL MICROSTIMULATION OF SOMATOSENSORY CORTEX EVOKES STABLE AND PRECISE TACTILE SENSATIONS" Greenspon and colleagues have done an admirable job of combining their tandem manuscripts on "tessellation" and force perception. The combined manuscript now assesses both the stability of projected fields over time and the number of different levels of force that can be discriminated over the safe range of microstimulation currents. In addition, biomimetic stimulation as compared to "linear," flat stimulation, and multi-channel stimulation is shown to provide advantanges as compared to single-channel microstimulation. The findings are convincing and useful. These results will find significant future application in the development of bidirectional brain-computer interfaces. The manuscript is well organized and lucidly written. In particular, the revisions to the Abstract and Introduction have clarified what has been done previously and what are the new contributions of the present report. The addition of topic sentences at the beginning and concluding sentences at the end of many paragraphs also clarifies the motivation underlying the various analyses. This paper will be of considerable interest to a wide audience. The authors have addressed the concerns raised by the previous review appropriately and thoroughly. I have no further concerns or comments.

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

The authors have done a good job responding to my comments. I have no remaining concerns.

Rebuttal 1

Response To Reviewers

We'd like to thank each of the authors for reading both of our papers and giving their feedback. Based on some comments and discussion with the editor we have merged the two papers into one. This has, unsurprisingly, resulted in extensive changes to the paper. We have broadly tried to streamline the story to focus on the benefits of multi-channel stimulation for localization and force feedback while emphasizing that this approach is only possible due to the stability of the projected fields.

Additionally, we have addressed each of the comments as best possible, below is a description of each of the changes implemented in response to each comment. Thank you again for your time and assistance with this paper!

23-1788 "Biomimetic multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands"

Reviewer #1:

Can the authors add another distribution of JNDs for natural touch? Or would this dwarf the scale for the ICMS results?

As JNDs are in the units of the delivered stimulus, it would be misleading to compare units of microamps and force/depth. Furthermore, as the exact value of the JND depends on the reference stimulus (following Weber's law), it is also dependent upon the exact intensity used. The number of discriminable levels metric that we use attempts to solve this problem by addressing the number of intervals that could be expected within a given range and, we believe, is more appropriate than attempting to directly compare JNDs.

"It would be useful if the authors could give an estimate of how many of the electrodes on a given array would be expected to have their receptive fields contacted by their 5 mm probe"

This is an interesting question, however if you look at the electrode PF maps you'll notice that the number of electrodes 'dedicated' to each digit varies – likely a result of differential cortical magnification. Consequently, the number would be highly variable, depending on where the probe is contacting. Furthermore, it also appears to vary depending on the subject, perhaps due to the digit vs palmar localization of each array. Consequently, though we are proud of the fact that we are able to use 3 participants for the study, we do not believe we could give an accurate number that would generalize across participants or even within a single participant across digits.

The first paragraph of the Discussion dealing with Weber's law is a bit confusing, with apparently contradictory statements

We have attempted to clarify the relevant text and updated the figure to make the colors clearer.

One wonders whether Weber's law would hold more consistently with multi-channel, biomimetic ICMS. Was this tried? If not, it might be worth pointing out that this could be tried in future studies

We have added a section suggesting this to the discussion.

At the end of the Discussion, the manuscript points out that, "…the advantage of multi-channel ICMS is that it gives rise to a wider dynamic range of sensations." The authors might speculate on the trade-offs of using more than 4 electrodes for multi-channel stimulation, e.g. 8 or 16.Would one get a still wider dynamic range at the cost of fewer different groups of electrodes

We have added a section addressing this point in the discussion. Briefly, we believe that as electrodes are additive when the projected field overlaps this should occur with any combination of overlapping electrodes, however we also point out that as the magnitude interaction is sub-linear the effect likely saturates quickly. Additionally, per another comment, we discuss the effect this might have on the PF size/extent.

The authors might consider giving some descriptive statistics (range, median, etc.) of the power law exponents in these relationships. … Was the linear fit better

We have added these metrics.

As only two numbers are involved, please give those two values in μA in the legend

Done

How were the groups selected? Adjacent electrodes? Overlapping projected fields? Other?

We have clarified this in the text. Selection was based on overlapping projected fields.

"One might expect that more force would be required to depress the skin 1 mm using a 5 mm probe than a 2 mm probe. Is this not the case?"

We have added a section to the methods explaining that we convert the units appropriately taking into consideration the different amount of pressure required to displace the surface of the skin depending on the probe tip diameter.

Reviewer #2

Did the participant feel sensations from ICMS and touch that were the same, making the comparison straightforward, or were the sensations different and the participant attempted to scale them in such a way that the range matched?

We have added text to explain that we selected electrodes that the participant reported evoked sensations similar to those evoked by the indenter.

"What I did find missing was a comparison of mufti-channel linear stimulation and multi-channel biomimetic stimulation."

We completely agree! We had actually started collecting this data but hadn't finished yet at the time of submission. After finishing collection and analyzing the data we found that multi-channel biomimetic and linear were approximately equivalent. We have added this to the paper and – as part of the merge – de-emphasized the biomimetic aspects of the paper accordingly.

There are no error bars or statistics for panel B of figure 6. Also, there are no statistics for panel D of figure 5.

The means do not look different. This needs some statistical analysis to make the claim that they are different.

We have updated the figure and the text to include these.

Reviewer #3

This study goes far beyond previous attempts in showing that multichannel ICMS not only seems more intuitive but specifically improves JNDs, thus, discriminability. As the Authors recall in the discussion, previous work in the monkey failed in showing such a superiority compared to single-channel ICMS. While fairness in acknowledging that the reasons for this discrepancy are not clear is appreciated, the Discussion may benefit from developing some tentative explanations.

We have added text to the discussion. Broadly, we believe that it is imperative that the range of stimuli given change for each comparison. In the previous work the same stimuli were given but the reference changed. However, from an individuals perspective 20 vs 80 where 20 is the standard and 20 vs 80 where 80 is the standard are identical. This meant that the perceptual scaling was constant across conditions.

1787 " Tesselation of artificial touch via microstimulation of human somatosensory cortex"

Reviewer #1

Might reorganization of inputs not have occurred in patients with residual sensation?

We have added text to the discussion on this point.

Perhaps more importantly, if different electrodes were used for stimulating versus recording, please clarify whether PFs (stimulation) and RFs (recording) were obtained from the same electrode, or from adjacent electrodes.

We have clarified that these were the same electrodes.

Please clarify how "sensation magnitude" was quantified? Subjective report of intensity? On what sort of scale?

We have added text to make it clear that these were free rating of subjective intensity.

The details of each participant's SCI probably have been described elsewhere, but it would not be inappropriate to record a brief description of their sensory levels and areas of retained sensation in the present manuscript, perhaps as a supplementary figure.

We have added text and a supplementary figure. Please let us know if extra details would be desired.

Consider indicating the 33% level used as the threshold in these figures.

Done.

Consider adding a panel showing multiple hand outlines for each subject with the overlapped PFs from Figure 2B separated as time series.

We made a mockup of this but did not find it more compelling than the existing figures. Happy to add this or send an example directly if desired.

Reviewer #2

The parts that are confirmatory can be reduced and participant R1 removed

While we appreciate that the addition of R1 is minor, we believe that the field of BCI strongly suffers from a reproducibility crisis as most are only able to publish data with one subject or from one site. We believe that promoting collaboration, even when minor, is important to the field and would prefer to leave participant R1 in the paper.

“How many repetitions? A sensation reported by ten stimulus deliveries is not the same as one reported by a single delivery. Many deliveries could be indicative of a weak sensation, or barely perceptible sensation, or one that is highly variable. Many PFs were removed from analysis because of variability in producing sensation. This may give an impression of greater stability.”

We have added text to address these points. One goal is to separate electrodes that evoke weak sensations (that are inherently difficult to localize) from the stability of the evoked response. To include these electrodes in the stability analysis risks conflating the two points. Crucially, however, the stability analyses are not substantially dependent on the threshold as can be seen in the supplementary figures.

Including a larger portion of ‘unreliable’ pixels (i.e., analyzing results with multiple alternative threshold values) would be commendable.

I believe this is addressed in the above point but please clarify if this is not the case.

The figure shows distances of 3 to 8 mm. Perhaps I am missing something, but shouldn’t the distances be around 0 to be stable?

Please note that the distances are Euclidean and thus are always positive. For the values to be centered around 0, we would have to project onto an axis. To make it clearer that the movements are random we have computed the vector strength of sequential movements for each electrode and this is shown in the supplement now.

Reviewer #3

The quantitative characterization of the PFs is entirely dependent upon the residual arm function of each patient. Although this is not likely to affect stability measures over time, it would be important to report these residual ability, and how they were measured, in some detail for each patient. Relatedly, was the same hand stimulated that was used for the drawing? Only right-hand figures are used to display results: were all patients right-handed before spinal cord injury?

We have added text to clarify each of these details.

Instead, thresholding criteria for building aggregate PFs’ extent may affect stability measures. It may appear that setting the reliability criterion to 33% brought to removing an important proportion of pixels concerning PFs that might have revealed a more important variability across time than presently estimated. Although Supplem Figure 3 may reassure in part (please note the legend should be added to color-code the patients in this figure), as 0,25 sets a major drop in aggregate PFs areas, it remains true that 25% of pixels for patients C1 and P2 and about 60% of pixels for patient P3 were thus excluded from all analyses. Including a larger portion of ‘unreliable’ pixels (i.e., analyzing results with multiple alternative threshold values) would be commendable. This seems particularly valuable as excluded pixels were still located on adjacent regions to the core of each electrode.

We have added some text to explain the surprisingly small effect of the threshold on analyses. Briefly, as each of the analyses is weighted based on pixel frequency, they are heavily weighted towards the pixels that pass the threshold already. Consequently, inclusion of these low frequency pixels would have negligible effects. Additionally, from the perspective of trying to combine multi-electrode sensations, it is crucial to be able to reliably predict locations on the hand.

As a relatively minor point, the suggestion is made that since transient and sustained contact activate areas of cortex at different scales (much larger for transient), ICMS is rather comparable to sustained contact. This would indeed be appropriate for prolonged contact, for example during object holding and manipulation. Yet, the reasoning is proposed that responses to contact transients cannot determine the spatial extent of touch perception as touching a single digit would evoke sensations in multiple digits (by the larger scale of neuronal response). Yet again, brief transient touches with small indentation (like von Frey filaments) do evoke subjectively well localized tactile perception on single digits, in absence of prolonged contact. The authors may want to take this in consideration to clarify this apparent paradox further, also in regard of the companion manuscript, as biomimetic ICMS actually emphasizes contact transients compared to prolonged contact.

We have added extra text to the discussion to address this. Indeed, macaque data shows a similar phenomenon with natural touch as does some of our human data. Additionally, we have begun to experiment with greater numbers of combinations of electrodes and have observed that transient stimulation of electrodes for the whole hand followed by sustained stimulation of electrodes specific to a digit do not interfere with our participants ability to localize sensations.

Rebuttal 2

Response To Reviewers

We'd again like to thank the reviewers for reading the consolidated paper and giving their feedback. We understand that merging the two papers resulted in a particularly long paper and appreciate the effort and time taken to give comments on it. We have addressed all of the comments to the best of our abilities and hope that everyone will be satisfied with it!

Sincerely,

Charles Greenspon

Because there is a secondary somatosensory cortex and you are using the abbreviation "S1", consider adding the word "primary" before somatosensory cortex (S1)

Thank you for noticing this. We have added this throughout.

Although I recognize that the present work focusses on S1, referring to the crown of the human precentral gyrus as M1, primary motor cortex, is incorrect. A number of studies have shown that in humans, at the level of the hand knob, area 4 lies buried entirely in the anterior bank of the central sulcus (Geyer et al., 1996; White et al., 1997; Binkofski et al., 2002).

We have also changed the figure to address this, thank you for your comment.

"C1's (fully sensate left hand)" perhaps should be "C1's (fully sensate) left hand"

Done, thanks!

"Consistent with this, increases in ICMS amplitude or frequency led to increases in the volume of activated neurons and/or density of activated neurons within a volume (20–22,32) and concomitant increases in PF area."

This sentence makes it sound as if the increase in volume and density of activated neurons had been assessed in the present study. This inaccurate implication could be corrected by changing the word "led" to "would lead" and changing "and concomitant" to "producing concomitant".

W we have changed this accordingly.

There is a lot of valuable data in the paper and the authors have added to the biometric part of the study since the previous submission. However, the paper reads like a list of new findings or corroborations of prior research without a common theme. Rewriting parts of the paper to have a more overarching conceptual framework would improve its accessibility.

Thank you for this comment, we have attempted to make edits throughout the abstract (regarding the below comment) as well as the introduction and several parts of the results to try and produce a more coherent story. I will add that we considered re-ordering the manuscript such that we presented all the single-electrode results and then the multi-electrode results but found that swapping between types of experiments was less coherent than the current format.

In the abstract, 'projection field' is not defined. The abstract, like the paper, seems to be a list of results without a cohesive theme.

We have both added a definition and substantially edited the abstract to make it flow better.

Pixels are mentioned throughout the paper but not explicitly defined.

We have added a definition to the methods section to clarify this.

How many PFs were used for the panels in Figure 2?

We have clarified this in the figure caption.

Was there any measure of similarity in perception between ICMS and tactile stimulation for PFs that included sensate locations? If the sensations were different did the participants scale them to match?

We have clarified that the participants reported that the ICMS-evoked sensations felt like the mechanical stimuli but that no explicit metric was used.

R1, the fourth subject, does not add much to the paper and the response to reviewers is vague. Three participants are mentioned in the abstract, introduction, and most of the paper so it is a bit confusing when R1 is introduced briefly in the results. I still recommend removing R1.

To expand upon our earlier response, while we agree that adding the data from participant R1 does not change the story of the paper, we believe that being able to present independent validation of a result is extremely compelling for a result that many members of the team were initially surprised about. The fact that they performed the experiments before knowing about this paper, used a different method to map the results, and collected data from a subject with a different implant all come together to make the admittedly minor addition a compelling piece of extra evidence to support the claim that receptive fields in Brodmann's Area 1 tend to be larger than the ICMS-evoked percepts.

There is a typo in the "Projected fields are contained.." section: ".. projected verses receptive fields .." should read "versus".

Thank you for catching this typo!