## Intracortical Somatosensory Stimulation to Elicit Fingertip Sensations in an Individual With Spinal Cord Injury

Matthew S. Fifer, PhD,\* David P. McMullen, MD,\* Luke E. Osborn, PhD, Tessy M. Thomas, PhD, Breanne Christie, PhD, Robert W. Nickl, PhD, Daniel N. Candrea, BS, Eric A. Pohlmeyer, PhD, Margaret C. Thompson, PhD, Manuel A. Anaya, MD, Wouter Schellekens, PhD, Nick F. Ramsey, PhD, Sliman J. Bensmaia, PhD, William S. Anderson, MD, PhD, Brock A. Wester, PhD, Nathan E. Crone, MD, Pablo A. Celnik, MD, Gabriela L. Cantarero, PhD, and Francesco V. Tenore, PhD

Neurology® 2022;98:e679-e687. doi:10.1212/WNL.00000000013173

## Abstract

### **Background and Objectives**

The restoration of touch to fingers and fingertips is critical to achieving dexterous neuroprosthetic control for individuals with sensorimotor dysfunction. However, localized fingertip sensations have not been evoked via intracortical microstimulation (ICMS).

#### **Methods**

Using a novel intraoperative mapping approach, we implanted electrode arrays in the finger areas of left and right somatosensory cortex and delivered ICMS over a 2-year period in a human participant with spinal cord injury.

#### Results

Stimulation evoked tactile sensations in 8 fingers, including fingertips, spanning both hands. Evoked percepts followed expected somatotopic arrangements. The subject was able to reliably identify up to 7 finger-specific sites spanning both hands in a finger discrimination task. The size of the evoked percepts was on average 33% larger than a finger pad, as assessed via manual markings of a hand image. The size of the evoked percepts increased modestly with increased stimulation intensity, growing 21% as pulse amplitude increased from 20 to 80  $\mu$ A. Detection thresholds were estimated on a subset of electrodes, with estimates of 9.2 to 35  $\mu$ A observed, roughly consistent with prior studies.

#### Discussion

These results suggest that ICMS can enable the delivery of consistent and localized fingertip sensations during object manipulation by neuroprostheses for individuals with somatosensory deficits.

#### **ClinicalTrials.gov Identifier**

NCT03161067.

**Correspondence** Dr. Fifer matthew.fifer@jhuapl.edu

#### **RELATED ARTICLE**

**Editorial** Selective Induction of Fingertip Sensations for Better Neuroprosthetic Control Page 261





From the Research and Exploratory Development Department (M.S.F., L.E.O., B.P.C., E.A.P., M.C.T., F.V.T.), Johns Hopkins University Applied Physics Laboratory, Laurel; National Institute of Mental Health (D.P.M.), NIH, Bethesda; Department of Biomedical Engineering (T.M.T., D.N.C.), Department of Physical Medicine and Rehabilitation (R.W.N., M.A.A., P.A.C., G.L.C.), Department of Neurosurgery (W.S.A.), and Department of Neurology (B.A.W., N.E.C.), Johns Hopkins University, Baltimore, MD; UMC Utrecht Brain Center (W.S., N.F.R.), the Netherlands; and Department of Organismal Biology and Anatomy (S.J.B.), University of Chicago, IL.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

## Glossary

**BiCNS** = Investigation on the Bidirectional Cortical Neuroprosthetic System; **ECoG** = electrocorticographic; **FDA** = Food and Drug Administration; **ICMS** = intracortical microstimulation; **IQR** = interquartile range; **NHP** = nonhuman primate; **SCI** = spinal cord injury; **3D-1U** = 3 down–1 up; **2AFC** = 2-alternative forced-choice.

The loss of touch contributes to the loss of independence experienced by patients with spinal cord injury (SCI). Beyond the inability to directly sense the physical properties of objects, the loss of cutaneous sensation impairs patients' ability to manipulate objects<sup>1-4</sup> because information about object contact is often not available visually. Loss of fingertip sensation is especially detrimental to motor control given the outsized involvement of the fingertips in contact events<sup>5</sup> and dexterous object manipulation.<sup>6</sup>

Intracortical microstimulation (ICMS) of somatosensory cortex has the potential to restore touch. Indeed, ICMS has been shown to evoke tactile sensations in nonhuman primates (NHPs), and these sensations can be systematically manipulated by variation of the stimulation parameters, including frequency<sup>7–10</sup> and intensity.<sup>9,11</sup> NHPs can use ICMS as movement direction instruction cues<sup>12–14</sup> to detect and discriminate indentations delivered to a prosthetic finger,<sup>9,15</sup> to discriminate virtual objects,<sup>8,16</sup> and to discriminate textures.<sup>17</sup>

In 2 recent studies, human subjects reported ICMS-evoked sensations, but they were not localized on the fingertips. One study reported cutaneous sensations projected to the palm, with additional percepts on the base of the index finger,<sup>18</sup> while the other reported percepts distributed over the arm and hand.<sup>19</sup> Stimulation through electrocorticographic (ECoG) electrodes in humans has also elicited hand sensations,<sup>20–22</sup> although these sensations are poorly localized and are often accompanied by hand movements. Despite these promising results, it remained unclear whether localized fingertip percepts could be elicited in human somatosensory cortex given existing Food and Drug Administration (FDA)–approved electrode technology, which allows interfaces only with superficial cortex.

In the present study, we elicited fingertip sensation via delivery of ICMS to somatosensory cortex in both hemispheres in a patient with incomplete SCI. After implantation of microelectrode arrays, we characterized the location and detectability of the ICMS-evoked percepts via blinded assessments of the patient's spatial distribution and detection thresholds. Our results demonstrate that fingertip percepts can be elicited via ICMS on the surface of the postcentral gyrus, a promising step toward providing functional tactile feedback during object manipulation with prosthetic hands.

## Methods

# Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted under Investigational Device Exemption (IDE G170010) by the FDA for the purpose of

evaluating bilateral sensory and motor capabilities of microelectrode array implants. The study protocol was approved by the FDA, the Johns Hopkins Medicine Institutional Review Board 2 (JHM IRB-2; study IRB00106844 approved in July 2017), and the Naval Information Warfare Center Atlantic Human Research Protection Office and is a registered clinical trial (Investigation on the Bidirectional Cortical Neuroprosthetic System [BiCNS], NCT03161067). Recruitment targeted individuals with complete or incomplete quadriplegia resulting from SCI. The participant provided informed consent for the research detailed below in accordance with our approved study protocol.

### **Clinical Study Design**

This is a report of intermediate results of the BiCNS trial from the first participant given the potential impact of disseminating this information and anticipated long time period before the remaining participants are enrolled and subsequent full completion of the trial.

The participant in this study was a 48-year-old man affected by a C5 (sensory)/C6 (motor) American Spinal Injury Association B SCI 31 years before the study. He retained some movement with weakness in the upper arms and wrist, with near-total paralysis in the fingers bilaterally. Peripheral somatosensation was reported as intact by the participant, with some deficits noted in pinprick examination preoperatively. The participant engages in many daily activities that use his residual upper arm motor and sensory capabilities (e.g., pushing his wheelchair).

### **Implantation Planning**

Our team used an implantation targeting approach leveraging both preoperative functional imaging and intraoperative functional mapping. This approach has been reported previously<sup>23</sup> and is summarized in brief here. Before surgery, the participant was anatomically and functionally mapped in a high-resolution 7T MRI scanner. fMRI was captured during sensory and motor tasks in a block-based design.<sup>24</sup> Sensory mapping via mechanical stimulation of individual fingers confirmed sensory representations lateral to the hand knob, consistent with prior reports.<sup>25</sup> MRI and fMRI maps of sensorimotor function were used to target the placement of high-density ECoG grids (1-mm contacts, 3-mm spacing) intraoperatively. During an awake portion of the surgery, real-time mapping of high gamma (70–110 Hz) modulation during vibratory stimulation of the fingertips was performed with custom software for online signal processing and visualization.<sup>26</sup> These maps were used to inform the placement of the stimulating microelectrode arrays within specific finger representations in somatosensory cortex (Figure 1B).

### **Neural Stimulation and Recording**

Six microelectrode arrays were implanted as 3 pairs, each consisting of a 96-channel recording ( $4 \times 4$  mm, platinum tips) and a 32-channel stimulating array ( $4 \times 2.4$  mm, 400-µm pitch, custom population within  $6 \times 10$  configuration, with sputtered iridium oxide film tips). Two pairs were implanted in the left hemisphere, and one was implanted in the right hemisphere (Figure 1B). Each array pair was wired to a skull-fixed transcutaneous metal pedestal to enable wired interface to the recording and stimulating hardware. In this clinical trial, platinum arrays were approved for recording only, while sputtered iridium oxide film arrays were approved for recording or simulation. The number of electrodes in each array was derived from a preceding clinical trial (NCT01894802) of a recording and stimulating neuroprosthetic system.<sup>18</sup>

Neurostimulation was delivered via the Cerestim R96 (Blackrock Neurotech, Salt Lake City, UT), controlled by either the manufacturer-provided software or MATLAB (MathWorks, Inc, Natick, MA) scripts messaging a custom interface software module. The custom interface module was written to reject stimulation parameters outside the safety parameters of the study, governed by prior work with NHPs.<sup>27</sup> Neural recording and impedance measurements were performed with the NeuroPort system (Blackrock Neurotech). During the experiments described in this report, recording was used solely for verification of proper connection and safety monitoring via visual inspection of the local field potential signal for unexpected artifacts that could pose risk.

Stimulation for this study was provided in 100-Hz pulse trains, with symmetric, charge-balanced, cathodic-first pulses. The cathodic and anodic phases of each pulse were 200 microseconds in duration, with 100-microsecond interphase between. Pulse train durations were typically either 500 millisecond or 1 second, with only minor differences in perceived intensity reported between these 2 conditions. These parameters were informed by prior NHP<sup>11</sup> and human studies<sup>18,19</sup> to maximize response likelihood without the need to perform parameter sweeps.

For a 4-month period (months 3–7 after surgery), we switched the cable interfacing with the right hemispherestimulating array. The difference in cables was the current return path: the new cable had a current return path through the implanted reference wire as opposed to ground (i.e., the patient pedestal). It became clear that the evoked percepts while the new cable was used were much more variable than the evoked percepts while the original ground return path cable was used, and we switched the cable back to the ground return path cable. This determination was made qualitatively after observation of low-intensity percepts that were not selfconsistent in location. Qualitative surveys using this data were discarded from analysis in this study.

#### **Finger Discrimination Task**

The participant performed a blinded finger discrimination task to quantify stimulation percept accuracy. The participant was asked to determine the finger percept stimulated by ICMS of randomly selected, finger-associated electrode sets, ranging from 1 to 3 electrodes. Trials were pseudorandomly ordered in software across all conditions, with 10 trials per condition, including a no-stimulation condition. Stimulation was performed with 1-second trains with the standard waveform parameters described above. Stimulation amplitudes for this task were 80  $\mu$ A, with some sessions using 90  $\mu$ A in the right hemisphere for increased reliability. Stimuli were presented with a corresponding auditory cue, identical across all conditions.

The participant was briefly trained with the set of electrodes by being introduced to the elicited sensation of the electrode and confirming its location on the desired finger. The task then proceeded as a fixed-choice reporting task in which the participant was instructed to name 1 of the mapped fingers or





(A) Portions of the hand that were reported as part of a percept for any single electrode on multiple days. Hue denotes finger; saturation denotes finger segment; and hatching denotes a dorsal hand percept. (B) Microelectrode array implantation locations, as localized via intraoperative photos, shown as gray boxes. Colored circles denote intraoperative electrocorticographic high gamma responses, manually filtered for most salient results. (C) Colored array maps refer to their reconstructed positions and orientations on the MRI in panel B. For each electrode on the array, the set of colors present within the square corresponds to a finger segment in panel A that was reported for that electrode. Gray squares are electrodes not wired for stimulation, and white squares did not elicit any single percept multiple times. C.S. = central sulcus.

#### Neurology.org/N

Neurology | Volume 98, Number 7 | February 15, 2022 **e681** 

say that no finger was stimulated. The participant was blinded to results during the testing.

On subsequent testing days, if the prior electrode set associated with a particular finger did not re-elicit the expected finger percept, several new electrodes were selected and evaluated as replacements. For all blocks, the 4 right fingers and left thumb were used. The penultimate session assessed the 4 right fingers, left thumb, and left index finger. The final session in addition incorporated the left middle finger, including all 7 stimulated fingers, because the middle finger percept had recently been reported.

#### **Projected Field Location Surveys**

Qualitative report of ICMS projected field location was collected in 1 of 2 ways. For most of the study, projected field size and location were approximated from a verbal report of a provided map with region codes corresponding to experimenterdefined subportions of the hand and fingers. Stimulation during the verbal report surveys followed standard stimulation parameters described above and were designed to be suprathreshold, with amplitudes of 60 or 80 µA. The maps included 4 quadrants in each of the distal finger segments and vertically divided halves on the intermediate and proximal finger segments. The palm and dorsum were each divided into 10 segments, as used in a previous study.<sup>18</sup> Projected field spatial information was collected along with intensity and character or qualitative aspect of the percept. To calculate the size of manually marked projected fields for each stimulation event, segments of the hand were combined in the following manner: (1)the 4 fingertip regions were combined into 1 fingertip segment; (2) the halved intermediate segments were combined into 1 intermediate segment per finger; and (3) the halved proximal segments were combined into 1 proximal segment per finger.

For the fingertip projected field size study, the participant was asked to mark his projected field on a laptop using a custom drawing application. Manual marking was used to avoid overestimation of the projected field size estimates. In all projected field estimation experiments, delivery of stimulation was handled by the experimenter but managed by the participant in that he frequently requested repeat delivery of stimulation (e.g., 2–3 times) to better report the locations and intensities. Stimuli during both verbally and manually reported surveys were presented with a corresponding auditory cue, identical across all conditions.

In analyzing the projected field size, a 3-way analysis of variance model was used with factors: (1) electrode identity, (2) stimulation intensity, and (3) inclusion of a fingertip in the drawn percept. Inputs to this model were logarithmically transformed pixel counts of projected fields with several inclusion and exclusion criteria: (1) we considered only contralateral projected fields; (2) null responses were not considered; (3) outlier projected fields were discarded if their area was greater than the 75th percentile plus 1.5 interquartile ranges (IQRs); and (4) projected fields with no pixel overlap between any of the 4 stimulated intensities were discarded.

#### **ICMS Detection Thresholds**

ICMS detection thresholds were estimated with a 2-alternative forced-choice (2AFC) paradigm on a subset of electrodes with reliable percepts and projected fields that spanned the different regions of the hands. In the 2AFC detection test, the participant verbally reported which of two 1-second intervals contained a 500-millisecond, 100-Hz stimulus. Intervals were marked with an auditory cue, with different tone frequencies for each interval. Detection thresholds were estimated with the method of constant stimuli on 3 electrodes. Each ICMS, amplitude was presented 10 to 20 times. For the method of constant stimuli, the psychometric curve was fit to the data using a logistic function:

$$Pcorrect(x) = 0.5 + \{/1 + \exp[-\beta(x - \alpha)]\},\$$

where x is the stimulation amplitude,  $P_{correct}(x)$  is the probability of correctly identifying the phase containing the stimulation for a given amplitude, L determines the ceiling performance,  $\beta$  is the steepness of the curve, and  $\alpha$  is the midpoint of the psychometric function.<sup>28</sup> The detection threshold was defined as the ICMS amplitude needed to elicit a sensation with probability of detection of 75% in the resulting psychometric fit. A rapid 3 down-1 up (3D-1U) adaptive staircase procedure<sup>29</sup> was also used to estimate 29 additional detection thresholds across various electrode sites. The adaptive staircase method was implemented by decreasing the stimulus amplitude until there was no discernible percept, at which point a reversal occurred and the stimulation amplitude increased again. The stimulus amplitude increased with every incorrect response from the participant. To use the 3D-1U paradigm, 3 correct responses in a row at a given stimulus amplitude led to a decrease in the stimulus amplitude, with a step size of 5 µA. A reversal occurred whenever the slope of the staircase changed, and the detection threshold was calculated by averaging the stimulus amplitude at all reversals. It should be noted that the 2AFC 3D-1U adaptive staircase procedure estimates the amplitude for 79.4% detection probability.<sup>29</sup> For the detection threshold, each stimulation site (n = 29) was tested until 4 (n = 2) or 6 (n = 27) reversals occurred. Stimulation sites used to measure the detection threshold contained either 1 (n = 10) or 2 (n = 22) electrodes. Statistical comparison between these 2 groups, which were not normally distributed (Shapiro-Wilk test, p = 0.025 and p < 0.001, respectively), was done with a Wilcoxon rank-sum test.

#### **Data Availability**

Anonymized data not published within this article will be made available by request from any qualified investigator.

## Results

# Location and Quality of ICMS-Evoked Sensations

Beginning 25 days after implantation, all 96 stimulating electrodes (i.e., 32 on each array) were stimulated individually, and the participant was asked to report the projected field

location(s) using a segmented image of the hand. Projected fields were obtained across multiple sessions spanning the first 2 years after implantation; individual electrodes were surveyed between 6 and 31 times over 50 survey sessions during that period. Projected fields that were observed on  $\geq$ 2 separate days for a given electrode over the course of the study are shown in Figure 1. The participant reported sensations projected to the first through fourth digits on both hands, including percepts localized to the fingertips, fingers, and hands. Dorsal hand and finger percepts were concentrated in the posterior aspects of the left-hemisphere arrays (Figure 1C).

Stimulation early after implantation led primarily to sensations that were described by the subject as being "electric." Later in the study (>14 weeks after implantation), percepts consisted of pressure sensations, either similar to an externally applied pressure or described as a pressure originating from within (i.e., the participant likened this to a throb, Video 1). A minority of stimulated sensations were described as pins and needles, with only rare reports of any other type of sensation.

Percepts on the fingers and hand exhibited a somatotopic gradient from the ring finger to thumb as they progressed mediolaterally along the array, as expected. On the left-hemisphere arrays, fingertip sensations were concentrated posteriorly, near the crown of the postcentral gyrus (Figure 1B). All reported percepts elicited from the right hemisphere array were located on the fingertips.

#### **Consistency of Projected Fields**

To assess within-session consistency of the projected fields, we performed blinded assessments during which the subject received stimulation to 1 of several digit-associated electrode sets and reported the specific digit on which the sensation was experienced; the subject also had the option to report that no sensation was experienced. An increasing number of electrodes were included in the test set, ranging from 5 to 7 (plus a null condition) across 6 sessions spanning 25 weeks of testing. The subject was highly consistent in his identification of the projected field, with a mean accuracy of 99.0% (i.e., 386 of390 trials correct, including 78 of 80 in a block with 7-digit conditions and a no-stimulation condition).

#### **Spatial Extent of Projected Fields**

To estimate the size of the projected fields, the participant marked the projected fields on an image of the hand using a computer track pad. Projected fields from all electrodes were queried at intensities of 20, 40, 60, and 80  $\mu$ A. The experiment was conducted over 4 experimental sessions, with each session including all intensities at every fourth electrode (e.g., the first session included electrodes A1, A5, A9, etc). The participant was blinded to both the intensity and stimulated electrode, with conditions ordered pseudorandomly (i.e., random trial ordering across all intensities on 25% of the electrodes). Example projected fields are shown in Figure 2, A and B. Projected field size was quantified by counting the pixels encompassed in the projected field marking, normalized to

the fingertip size for interpretability. The median size of all projected fields (across all electrodes and stimulation intensities) was 33% larger than the distal finger pad area (Figure 2C). The median (IQR) of percept size at each stimulation amplitude, normalized to index finger pad size, was 0.91 (IQR 0.89) at 20  $\mu$ A, 1.24 (IQR 0.97) at 40  $\mu$ A, 1.41 (IQR 1.16) at 60  $\mu$ A, and 1.45 (IQR 1.65) at 80  $\mu$ A.

The vast majority of percepts were reported as contralateral to the stimulating electrode, with a few percepts experienced on the ipsilateral hand or on both hands; 7.7% of percepts had at least some ipsilateral component. However, any ipsilateral components of projected fields were highly unstable and observed only at a single intensity level on each electrode. Projected fields that included finger areas were largely confined to 1 or 2 digits, with the proportion of individual finger percepts ranging from 16 of 18 (88.9%) at 20 µA to 28 of 42 (66.7%) at 80  $\mu$ A (Figure 2D). The projected field size increased modestly as the stimulation current amplitude increased (Figure 2E), confirmed via 3-way analysis of variance across electrode (p = 1.4e-09), stimulation intensity (p =0.0068), and inclusion of a fingertip in the percept (p = 0.15). Despite a 4-fold increase in current (from 20 to 80  $\mu$ A), presumably resulting in a considerable increase in the activated neuronal population, projected field sizes increased only by 21% over this range. In addition, the size of projected fields including fingertip(s) was statistically indistinguishable from that of projected fields elsewhere on the hand.

# Psychophysical Quantification of ICMS Detection

ICMS detection thresholds were collected on a variety of stimulation sites (n = 32) over the study period. In some cases, an entire psychometric function was obtained; in others, threshold was estimated with a more efficient but somewhat less precise tracking approach. When possible, a logistic function was fit to the subject's detection performance as a function of amplitude for an electrode. An example site with a projected field on the right ring finger and a detection threshold of 15.2 µA is shown in Figure 3A. Across both methods, thresholds ranged from 9.2 to 35  $\mu$ A, with a median value of 16.7  $\mu$ A (mean 18.6 μA, SD 6.3 μA, Figure 3, A and B). Some stimulation sites contained 1 electrode, and others contained 2 electrodes with overlapping projected fields (Figure 3C). Single electrode detection thresholds (9.4-29.2 µA) had a range similar to that of multielectrode thresholds (9.2–35  $\mu$ A), and the 2 distributions were not significantly different (p = 0.072), although thresholds for single electrodes appear to have more variance across the sites test (Figure 3C).

## Discussion

To achieve a dexterous neuroprosthesis requires the restoration of reliable and interpretable tactile feedback. Recent studies provide evidence of the benefits of artificial somatosensory feedback. Feedback delivered to human participants via

Neurology | Volume 98, Number 7 | February 15, 2022 e683

#### Figure 2 Drawn Projected Fields



(A) Example projected fields (elicited at 80  $\mu$ A) drawn by the participant. Drawn percepts on each hand were elicited through a different single electrode in each drawing. Top right example (showing perception on the right thumb) elicited sensation on both palmar and dorsal sides of the finger. In the leftmost hand on the bottom row, small dots within the projected field indicate "dull pencil point" sensations at those specific points. (B) Projected fields for 4 stimulation intensities through 2 distinct electrodes. Electrode numbers are included below each hand drawing in panels A and B for reference against eFigure 1 (Supplement http://links. lww.com/WNL/B694). (C) Distributions of projected field sizes, log-normalized to the size of the index fingertip. (D) Number of electrodes (of the full 96 tested) for normalized to the within-electrode mean. Error bars denote the SEM. Outlying projected field sizes, determined from the log-normal distribution, were omitted from this plot. Hand images used for recording and reporting subject responses in panels A and B adapted from a publication by Lameira et al.<sup>30</sup>

ICMS<sup>31</sup> or noninvasive stimulation in the periphery<sup>32</sup> was found to reduce completion times for activities of daily living. However, previous attempts to restore touch via ICMS failed to elicit fingertip sensations. Here, we demonstrate that sensations

could be elicited on 8 digits, including fingertips, across both hands from 3 microelectrode arrays implanted bilaterally and that projected field sizes were relatively focal, on average just larger than a finger pad. Somatosensory feedback experienced



(A) Example psychometric function of intracortical microstimulation (ICMS) amplitude detection delivered to a single electrode with a projected field on the right ring finger. (B) ICMS detection thresholds were estimated for 32 stimulation sites and ranged from 9.2 to  $35 \,\mu$ A, with a median value of 18.6  $\mu$ A. (C) Detection thresholds were estimated at sites using either 1 or 2 (i.e., multi) electrodes. Thresholds at stimulation sites with 2 electrodes appear to be more clustered with less variance. Thresholds estimated with the method of constant stimuli are marked with an x. It should be noted that each threshold data point is color coded according to the finger region that encompasses the projected field of that site.

on the fingertips is liable to further improve the outcomes of ICMS-based artificial touch given the key role of fingertips in object manipulation.<sup>6</sup>

To achieve fingertip sensations, we implemented an intraoperative method to target individual fingers, the representations of which were organized somatotopically across 2 hemispheres.<sup>23</sup> We observed a posterior concentration of fingertip sensations in the left-hemisphere arrays, consistent with results from a recent cortical stimulation study.<sup>33</sup> Percepts were extremely stable within each testing session; the subject was able to discriminate up to 7 stimulation sites against each other and a no-stimulation condition with 99% performance on blinded assessments. It is worth noting that the initial percepts elicited in the early part of the study (<14 weeks) were described as electric in nature and then transitioned to pressure percepts. It is not clear what led to this change other than possibly the previously characterized settling period of the electrode-tissue interface, corresponding to a reduction in impedances in the first 10 to 12 weeks after implantation.<sup>27</sup>

Percepts were very focal, with the median projected field size estimated at 133% of a finger pad, similar to those obtained in a recent study with microelectrode arrays that reported percepts of  $\approx$ 115% of a finger pad; the projected fields of ICMS-elicited sensations are smaller than those achieved with micro-ECoG (221%) and standard ECoG (956%).<sup>34</sup> Overall, this study demonstrates the ability to cover a large portion of hand finger sensory area with focal percepts via small (4 × 2.4 mm) microelectrode arrays.

We also demonstrated a small but significant relationship between stimulation intensity and projected field size. Previous work has demonstrated a strong linear relationship between applied stimulation current and perceived intensity.<sup>18</sup> Our work suggests that this relationship also includes a significant but modest change in the size of the perceived projected field (Figure 2D). The modest effect size is surprising given that the size of the recruited cortical population increases systematically with ICMS amplitude.<sup>35</sup> In principle, recruitment of a greater cortical volume should result in a greater swath of the hand representation being activated, resulting in a larger projected field. However, increases in the amplitude of a skin deflection also result in neuron recruitment without a concomitant increase in the perceived area of the stimulus,<sup>36</sup> so the relationship between cortical recruitment and the size of the sensory experience is not straightforward. Regardless, it is potentially useful that intensity of stimulation can be modulated to manipulate perceived magnitude without substantially changing the projected field size, as we observe in this study.

We estimated the ICMS amplitude detection thresholds in a subset of the implanted electrodes (Figure 3). Our observed thresholds ranged from 10 to 35  $\mu$ A, consistent with previous findings in NHPs (20–40  $\mu$ A)<sup>9</sup> and humans (15–88  $\mu$ A, median 35  $\mu$ A).<sup>18</sup> It is notable that we observed some lower thresholds than had been observed in these prior studies, but

the reduced upper bound relative to that of Flesher et al.<sup>18</sup> is likely a result of incomplete electrode sampling in our study. In addition, it is possible that silent electrodes (i.e., electrodes not eliciting a percept in the surveys, see Figure 1C) had a threshold above our survey amplitude of 80  $\mu$ A. That thresholds were comparable for single-electrode and multielectrode ICMS is consistent with previous findings in NHPs<sup>37</sup> (although another study noted increased detectability as the number of stimulating electrodes increased<sup>38</sup>).

There were several limitations of the current study that point to new research directions. We implanted only 1 participant, albeit eliciting fingertip sensations with arrays in 2 hemispheres, which limits the potential generalizability of the study. More work is therefore needed to understand the degree of individual variability in the location of fingertip representations relative to the central sulcus, which determine their accessibility via electrode technologies approved for use with human subjects. Also of note, the participant in this study had a significant degree of retained sensation, which may have affected the cortical touch representations accessible via ICMS. Partial tetraplegia can be associated with heterogeneous levels of retained sensation, which may in turn lead to differences in the sensory consequences of ICMS.

Fingertip sensory restoration is a critical step in creating dexterous closed-loop brain-machine interfaces for patients with SCI and related disorders. While demonstrated in only 1 subject (although in 2 hemispheres), our results build on prior work in NHPs and humans to demonstrate that sensory percepts can be elicited within fingertip cortical representations, yielding promise for better informing prosthetic finger movements.

#### Acknowledgment

The authors extend thanks to the study participant, whose insights into the subjective experiences of the stimulation were invaluable. They also thank Rob Franklin, Stephen Hou, and the staff at Blackrock Neurotech for their technical support and surgical planning insights; Chad Gordon, Teresa Wojtasiewicz, Adam Schiavi, and the surgical team at Johns Hopkins Hospital for performing the implantation; Christian Cooke, Bryanna Yeh, Zachary Koterba, and Eric Nguyen for contributing to the hardware and software infrastructure used for stimulation testing; Christopher Coogan for software support of WebFM software and processing of preoperative imaging; Leigh Hochberg for guidance on surgical approaches; Jared Wormley, Christopher Dohopolski, John Roycroft, and Matthew Johannes for technical infrastructure design and support; and Joseph O'Doherty, Spencer Kellis, Luke Bashford, Michelle Armenta-Salas, Sharlene Flesher, Robert Gaunt, John Downey, Thierri Callier, Jeff Yau, Adam Cohen, and Mike Wolmetz for helpful discussions about ICMS-induced perception over the course of the project.

#### **Study Funding**

This research was developed with funding from the Defense Advanced Research Projects Agency's (Arlington, VA)

Revolutionizing Prosthetics program (contract N66001-10-C-4056) and Neurally Enhanced Operations program (contract HR001120C0120). Development of experimental setup and support for regulatory submissions associated with this study were provided by a grant from the Alfred E. Mann Foundation. Study software infrastructure and study preparation were developed with internal funding from Johns Hopkins University Applied Physics Laboratory and Johns Hopkins University.

#### Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

#### **Publication History**

This manuscript was prepublished in medRxiv; 10.1101/2020.05.29.20117374 Note: substantial edits exist with this submitted version. Received by Neurology May 24, 2021. Accepted in final form November 19, 2021.

#### Appendix Authors

Name	Location	Contribution
Matthew Stephen Fifer, PhD	Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; statistical analysis; contributed to various components of the intraoperative ECoG mapping; experimental design and stimulation testing with implanted arrays; wrote software for controlling stimulation or collecting responses; led manuscript preparation
David P. McMullen, MD	National Institute of Mental Health, NIH, Bethesda, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; Study concept or design; analysis or interpretation of data; led implantation planning and execution; contributed to various components of the intraoperative ECoG mapping experimental design and stimulation testing with implanted arrays; led manuscript preparation
Luke E. Osborn, PhD	Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; experimental design and stimulation testing with implanted arrays; supported preparation of figures and video

Location	Contribution
Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis o interpretation of data; contributed to various components of the intraoperative ECoG mapping; supported preparation of figures and video
Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Major role in the acquisition of data; analysis or interpretation of data; experimental design and stimulation testing with implanted arrays
Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; preoperative fMRI planning and analysis
Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; contributed to various components of the intraoperative ECoG mapping
Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Study concept or design; analysis or interpretation of data; experimental design and stimulation testing with implanted arrays; wrote software for controlling stimulation or collecting responses
Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Study concept or design; analysis or interpretation of data
Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD	Major role in the acquisition of data; study concept or design
UMC Utrecht Brain Center, Utrecht, Netherlands	Study concept or design; analysis or interpretation of data; preoperative fMRI planning and analysis
UMC Utrecht Brain Center, Utrecht, Netherlands	Study concept or design; analysis or interpretation of data; preoperative fMRI planning and analysis
Department of Organismal Biology and Anatomy, University of Chicago, Chicago, IL	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
	Location  Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD  Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Baltimore, MD  Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD  Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD  Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD  Department of Physical Medicine and Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD  Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD  UMC Utrecht Brain Center, Utrecht, Netherlands  Department of Organismal Biology and Anatomy, University of Chicago, Chicago, IL

Name	Location	Contribution
William S. Anderson, MD, PhD	Department of Neurosurgery, Johns Hopkins University, Baltimore, MD	Major role in the acquisition of data; study concept or design; led implantation planning and execution
Brock A. Wester, PhD	Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; contributed to various components of the intraoperative ECoG mapping; wrote software for controlling stimulation or collecting responses; supported figure and video preparation
Nathan E. Crone, MD	Department of Neurology, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; led implantation planning and execution; contributed to various components of the intraoperative ECoG mapping
Pablo A. Celnik, MD	Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; led the clinical study; preoperative fMRI planning and analysis
Gabriela L. Cantarero, PhD	Department of Physical Medicine and Rehabilitation, Johns Hopkins University, Baltimore, MD	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; preoperative fMRI planning and analysis
Francesco V. Tenore, PhD	Research and Exploratory Development Department, Johns Hopkins University Applied Physics Laboratory, Laurel, MD	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; led the clinical study, experimental design and stimulation testing with implanted arrays, supported video preparation

References

Appendix (continued)

- Ghez C, Gordon J, Ghilardi MF. Impairments of reaching movements in patients without proprioception, II: effects of visual information on accuracy. J Neurophysiol. 1995;73(1):361-372
- Johansson RS, Hger C, Bäckström L. Somatosensory control of precision grip during 2. unpredictable pulling loads, III: impairments during digital anesthesia. Exp Brain Res. 1992;89(1):204-213
- Richardson AG, Attiah MA, Berman JI, et al. The effects of acute cortical somato-3. sensory deafferentation on grip force control. Cortex. 2016;74:1-8.
- Rothwell JC, Traub MM, Day BL, Obeso JA, Thomas PK, Marsden CD. Manual 4 motor performance in a deafferented man. Brain. 1982;105(pt 3):515-542.

- Christel MI, Kitzel S, Niemitz C. How precisely do bonobos (Pan paniscus) grasp small objects? Int J Primatol. 1998;19(1):165-194.
- Johansson RS, Flanagan JR. Coding and use of tactile signals from the fingertips in 6. object manipulation tasks. Nat Rev Neurosci. 2009;10(5):345-359.
- Callier T, Brantly NW, Caravelli A, Bensmaia SJ. The frequency of cortical micro-7. stimulation shapes artificial touch. Proc Natl Acad Sci USA. 2020;117(2):1191-1200.
- O'Doherty JE, Lebedev MA, Ifft PJ, et al. Active tactile exploration using a brain-8. machine-brain interface. Nature. 2011;479(7372):228-231.
- Tabot GA, Dammann JF, Berg JA, et al. Restoring the sense of touch with a prosthetic 9. hand through a brain interface. Proc Natl Acad Sci USA. 2013;110(45):18279-18284.
- 10. Hughes CL, Flesher SN, Weiss JM, Boninger M, Collinger JL, Gaunt RA. Perception of microstimulation frequency in human somatosensory cortex. eLife. 2021;10: e65128
- Kim S, Callier T, Tabot GA, Gaunt RA, Tenore FV, Bensmaia SJ. Behavioral as-11. sessment of sensitivity to intracortical microstimulation of primate somatosensory cortex. Proc Natl Acad Sci USA. 2015;112(49):15202-15207.
- Dadarlat MC, O'Doherty JE, Sabes PN. A learning-based approach to artificial sensory 12. feedback leads to optimal integration. Nat Neurosci. 2015;18(1):138-144.
- London BM, Jordan LR, Jackson CR, Miller LE, Electrical stimulation of the pro-13. prioceptive cortex (area 3a) used to instruct a behaving monkey. IEEE Trans Neural Syst Rehabil Eng. 2008;16(1):32-36.
- O'Doherty JE, Lebedev M, Hanson TL, Fitzsimmons N, Nicolelis MAL. A brain-14. machine interface instructed by direct intracortical microstimulationS1. Front Integr Neurosci, 2009;3:20.
- 15. Berg JA, Dammann JF III, Tenore FV, et al. Behavioral demonstration of a somatosensory neuroprosthesis. IEEE Trans Neural Syst Rehabil Eng. 2013;21(3): 500-507.
- 16. Klaes C, Shi Y, Kellis S, Minxha J, Revechkis B, Andersen RA. A cognitive neuroprosthetic that uses cortical stimulation for somatosensory feedback. J Neural Eng. 2014:11(5):056024.
- O'Doherty JE, Shokur S, Medina LE, Lebedev MA, Nicolelis MAL. Creating a neu-17. roprosthesis for active tactile exploration of textures. Proc Natl Acad Sci USA. 2019; 116(43):21821-21827.
- Flesher SN, Collinger JL, Foldes ST, et al. Intracortical microstimulation of human 18. somatosensory cortex. Sci Transl Med. 2016;8(361):361ra141.
- 19. Armenta Salas M, Bashford L, Kellis S, et al. Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. eLife. 2018;7:e32904.
- Hiremath SV, Tyler-Kabara EC, Wheeler JJ, et al. Human perception of electrical 20. stimulation on the surface of somatosensory cortex. PLoS One. 2017;12(5):e0176020.
- 21. Lee B, Kramer D, Armenta Salas M, et al. Engineering artificial somatosensation through cortical stimulation in humans. Front Syst Neurosci. 2018;12:24.
- 22. Kramer DR, Lee MB, Barbaro M, et al. Mapping of primary somatosensory cortex of the hand area using a high-density electrocorticography grid for closed-loop brain computer interface. J Neural Eng. 2021;18(3): 036009.
- McMullen DP, Thomas TM, Fifer MS, et al. Novel intraoperative online functional 23. mapping of somatosensory finger representations for targeted stimulating electrode placement: technical note. J Neurosurg. 2021;1(aop):1-8.
- 24. Vansteensel MJ, Pels EGM, Bleichner MG, et al. Fully implanted brain-computer interface in a locked-in patient with ALS. N Engl J Med. 2016;375(21):2060-2066.
- Schellekens W, Petridou N, Ramsey NF. Detailed somatotopy in primary motor and somatosensory cortex revealed by gaussian population receptive fields. NeuroImage. 2018:179:337-347.
- 26. Milsap G, Collard M, Coogan C, Crone NE. BCI2000Web and WebFM: browserbased tools for brain computer interfaces and functional brain mapping. Front Neurosci, 2019:12:1030.
- 27. Chen KH, Dammann JF, Boback JL, et al. The effect of chronic intracortical microstimulation on the electrode-tissue interface. J Neural Eng. 2014;11(2):026004.
- Kingdom FAA, Prins N. Psychophysics: A Practical Introduction. Academic Press; 2009. 28. Leek MR. Adaptive procedures in psychophysical research. Percept Psychophys. 2001; 29.
- 63(8):1279-1292.
- 30. Lameira AP, Gawryszewski LG, Guimarães-Silva S, et al. Hand posture effects on handedness recognition as revealed by the Simon effect. Front Hum Neurosci. 2009;3:59.
- Flesher SN, Downey JE, Weiss JM, et al. A brain-computer interface that evokes tactile 31. sensations improves robotic arm control. Science. 2021;372(6544):831-836.
- Ganzer PD, Colachis SC, Schwemmer MA, et al. Restoring the sense of touch using a 32. sensorimotor demultiplexing neural interface. Cell. 2020;181(4):763-773.e12.
- 33. Roux FE, Diidieli I, Durand IB, Functional architecture of the somatosensory homunculus detected by electrostimulation. J Physiol. 2018;596(5):941-956.
- Kramer DR, Kellis S, Barbaro M, et al. Technical considerations for generating 34. somatosensation via cortical stimulation in a closed-loop sensory/motor braincomputer interface system in humans. J Clin Neurosci, 2019:63:116-121.
- Tehovnik EJ, Tolias AS, Sultan F, Slocum WM, Logothetis NK. Direct and indirect 35. activation of cortical neurons by electrical microstimulation. J Neurophysiol. 2006; 96(2):512-521.
- Callier T, Suresh AK, Bensmaia SJ. Neural coding of contact events in somatosensory 36. cortex. Cereb Cortex. 2019;29(11):4613-4627.
- Kim S, Callier T, Tabot GA, Tenore FV, Bensmaia SJ. Sensitivity to microstimulation 37. of somatosensory cortex distributed over multiple electrodes. Front Syst Neurosci. 2015;9:47.
- Zaaimi B, Ruiz-Torres R, Solla SA, Miller LE. Multi-electrode stimulation in so-38 matosensory cortex increases probability of detection. J Neural Eng. 2013;10(5): 056013.