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Intracortical microstimulation of human somatosensory cortex

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Intracortical microstimulation of the somatosensory cortex offers the potential for creating a sensory neuroprosthesis to restore tactile sensation. Whereas animal studies have suggested that both cutaneous and proprioceptive percepts can be evoked using this approach, the perceptual quality of the stimuli cannot be measured in these experiments. We show that microstimulation within the hand area of the somatosensory cortex of a person with long-term spinal cord injury evokes tactile sensations perceived as originating from locations on the hand and that cortical stimulation sites are organized according to expected somatotopic principles. Many of these percepts exhibit naturalistic characteristics (including feelings of pressure), can be evoked at low stimulation amplitudes, and remain stable for months. Further, modulating the stimulus amplitude grades the perceptual intensity of the stimuli, suggesting that intracortical microstimulation could be used to convey information about the contact location and pressure necessary to perform dexterous hand movements associated with object manipulation.

INTRODUCTION

The loss of somatosensation causes severe deficits in motor control (*1*–*6*) and abolishes the ability to dexterously manipulate objects (*7*). A major goal in neurorehabilitation is to restore motor function, and significant progress has recently been made toward this goal. For example, we demonstrated that a person with tetraplegia could simultaneously control up to 10 degrees of freedom of an anthropomorphic robotic limb using a cortical neural interface (*8*, *9*). Although promising, prosthetic limb movements were often slower than able-bodied movements, and interacting with objects was challenging, as might be expected when somatosensation is absent and vision is the sole source of sensory feedback. For prosthetic limbs to achieve the full functionality of a native limb, then, somatosensory feedback must be restored. Electrically stimulating peripheral nerves in amputees can elicit conscious percepts that enable improvements in prosthetic control (*10*–*13*) and discrimination of surface coarseness (*14*). However, in individuals who cannot benefit from an interface with the peripheral nervous system, such as people with spinal cord injury, intracortical microstimulation of the primary somatosensory cortex (S1) is a promising approach to artificially evoke tactile percepts. This method not only is liable to restore aspects of the conscious experience of touch but also may lead to improvements in the performance of cortically controlled limb prostheses (*15*–*20*).

Intracortical microstimulation of S1, specifically area 3b (*19*, *21*) and area 1 (*18*, *19*), has been shown to enable animals to perform sensory discrimination tasks with performance similar to mechanical stimulation of the hand. In addition, stimulation of area 1 has been used to instruct target selection in a brain-computer interface control task (*22*). However, although animals can learn to use intracortical microstimulation to classify different stimuli after many months of training, experiments with animals provide little insight into how stimulation is perceived or whether artificial sensations are natural or intuitive. In humans, stimulation of the surface of the somatosensory cortex through large electrodes (*23*–*25*) evokes sensations reported to originate from the hand but tends to be diffuse and poorly localized. Whereas the intensity of the elicited percepts can be modulated by pulse amplitude and frequency (*25*), the sensations are often nondescript, or described as paresthesias or buzzing. In the visual cortex, intracortical microstimulation in nonhuman primates can elicit detectable phosphenes at different locations and with different sizes and colors (*26*–*28*). Intracortical microstimulation of human visual cortex has also been shown to elicit phosphenes and, occasionally, more complex percepts (*29*, *30*).

To assess the viability of intracortical microstimulation as a means to restore cutaneous feedback in view of improving prosthetic control, we must first establish the perceptual properties of the evoked artificial sensations. To this end, we sought to investigate the nature of the sensations evoked through microstimulation of S1 in a 28-year-old male participant with tetraplegia, incurred as the result of a spinal cord injury sustained 10 years before beginning this study. Electrode arrays were implanted chronically, and we tracked, over a 6-month period after implantation, the quality of the evoked artificial sensations, the projected locations of these sensations, and the participant's sensitivity to intracortical microstimulation, measured using classical psychophysical methods. Our results can be used as the basis for the implementation of artificial somatosensory feedback in upper-limb neuroprostheses.

RESULTS

Electrode targeting and surgical implantation

This study was conducted under an Investigational Device Exemption from the U.S. Food and Drug Administration, approved by the Institutional Review Boards at the University of Pittsburgh (Pittsburgh, PA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA), and registered at ClinicalTrials.gov (NCT01894802). Informed consent was obtained before any study procedures were conducted. Two microelectrode arrays were implanted in area 1 of S1, each with 32

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functional electrodes arranged on a 6 × 10 grid, and coated with a sputtered iridium oxide film. Two microelectrode arrays were also implanted in the motor cortex as part of a larger investigation of sensorimotor brain-computer interfaces. Preoperative imaging, consisting of structural magnetic resonance imaging (MRI) and magnetoencephalography (MEG), was used to guide the placement of the S1 electrode arrays on the postcentral gyrus. The peak areas of MEG activity on the postcentral gyrus (Fig. 1C) that were related to the imagined and/or actual cutaneous stimulation of the thumb, index finger, little finger, and palm followed the expected somatotopic organization (*31*). The edges of the hand-related area in the somatosensory cortex (from thumb to palm) spanned about 4 cm, which is considerably larger than the size of the electrode arrays (2 × 4 mm). Therefore, the arrays were implanted in locations that were surgically accessible and centered over areas associated with the index and little fingers. The array locations (Fig. 1C) were documented with intraoperative photos and a postoperative computed tomography (CT) scan, which confirmed that the arrays were placed in area 1 through co-registration with Brodmann's area atlas (*32*).

Spontaneous sensations and first detection

Testing began 1 week after surgery and was performed two or three times per week for up to 4 hours per session. During the initial weeks after implant, the participant reported spontaneous sensations in the absence of electrical stimulation, often described as tingling, occurring throughout his right hand and arm, which were of moderate intensity and frequency but not bothersome. These spontaneously occurring sensations were temporally linked to increases in the spontaneous firing rate of recorded S1 neurons (fig. S1A). Three weeks after implant, the spontaneous sensations began to subside, became restricted to the hand, and, at 4 weeks after implant, were usually imperceptible. Two months after implant, all spontaneous sensations had ceased, as had the spontaneous bursts of neural activity in S1 (fig. S1B).

In initial stimulation sessions, train duration, then frequency, and finally amplitude were increased gradually, and the participant was asked to self-report any elicited sensations. He did not report any sensation for the first 3 weeks. During the 4th week, the participant verbally reported the first sensation evoked by intracortical microstimulation using simultaneous stimulation on multiple channels (three channels

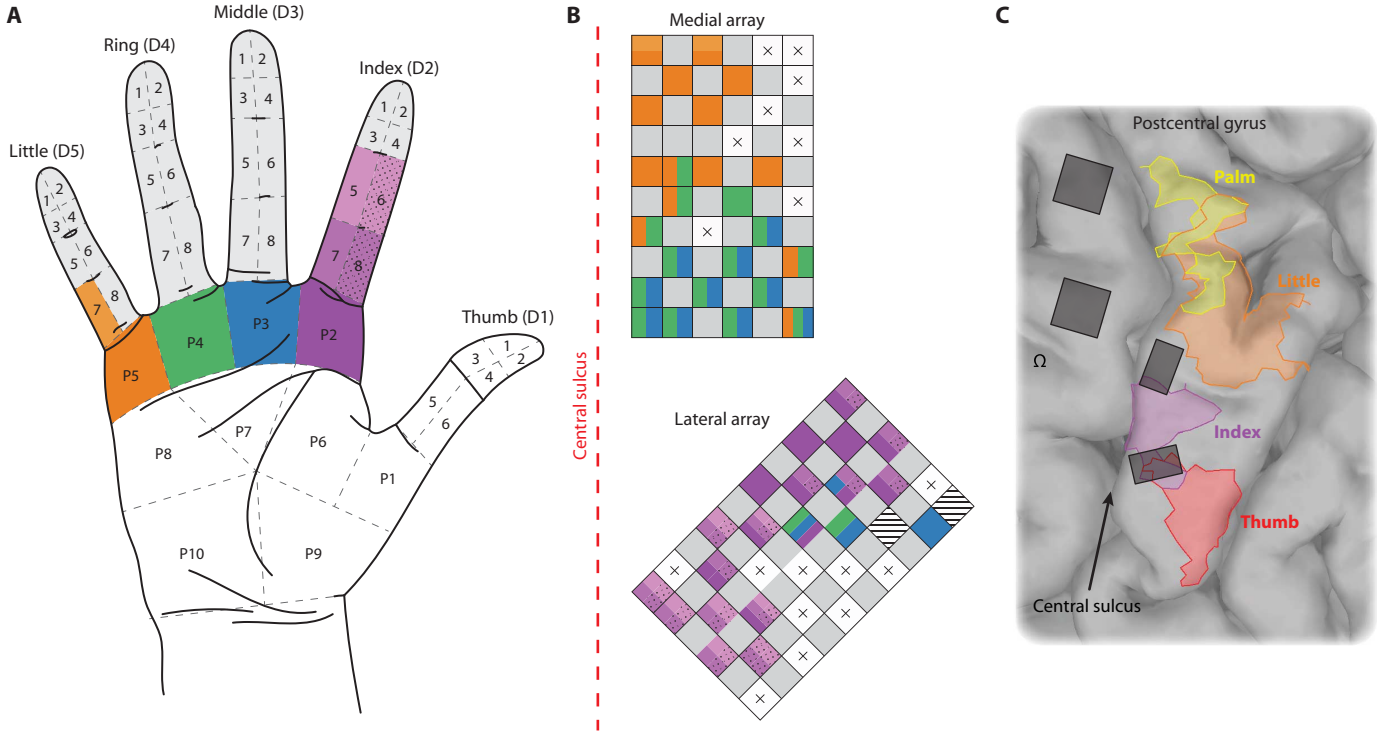

Fig. 1. Projected field maps for the hand in response to intracortical microstimulation of S1. (**A**) This diagram of the palmar side of the hand was shown to the participant during test sessions and he reported which regions of the hand sensations were felt to originate from during stimulation (for example, P2 and index 7/8). Colored areas indicate all the projected fields that were reported more than once and that were not part of diffuse sensations without a focal projected field. Gray regions of the hand indicate the maximum extent of the projected fields and include regions that were reported only once or were reported more frequently as part of diffuse percepts. (**B**) The two electrode arrays implanted in S1 are represented by the 6 × 10 grids and are shown in their approximate orientation with respect to the central sulcus (red dashed line). Colored boxes indicate the cumulative projected fields for each electrode and correspond to the colors and patterns in (A). Multiple colors and patterns in a single box indicate an electrode with a projected field that spanned more than a single area and include all locations reported for that electrode. These electrodes may have elicited more focal percepts on individual test days (see fig. S2C). Electrodes that did not elicit a sensation on more than one occasion are indicated by the x symbol. On the lateral array, two electrodes (indicated by hatched boxes) had complex projected fields that covered components of all four fingers. Gray boxes indicate electrodes that were not physically wired to the stimulator. (**C**) MEG mapping was used to identify regions in the somatosensory cortex that were responsive to imagined and/or actual somatosensory input originating from the palm (yellow), little finger (orange), index finger (purple), and thumb (red). The cortical surface map was generated using a subject-specific structural MRI. The colored areas indicate the extent of the regions (rather than the centroid of activity) with increased activity for each of the various inputs. Gray boxes represent the actual implanted locations of the arrays based on intraoperative photos and a postsurgical CT scan. The anterior direction is to the left, and the motor hand knob is indicated by Ω.

at 40 μA), and within 1 week, single-channel stimulation began to elicit percepts. Before the first detected sensations, those same electrodes had been stimulated at up to 80 μA individually. The ability to both detect and describe single-channel microstimulation approximately coincided with the reduction in spontaneous sensations after implant, a phenomenon that has been previously described to follow a similar time course (*30*).

Projected fields and somatotopic organization

Intracortical microstimulation through the implanted electrodes evoked sensations with projected fields at the base of the four fingers (D2 to D5) on the palmar side of the hand, extending to the proximal portion of the fingers and as far as the distal interphalangeal joint of D2 (Fig. 1A). The projected fields of some electrodes extended to the sides of the second and fifth digits. The participant verbally reported the location of detected sensations using a map of the hand (Fig. 1A) shown on a screen. The locations of the projected fields elicited by intracortical microstimulation coincided well with the preoperative mapping (Fig. 1C) and followed the expected medial (D5) to lateral (D1) organization of S1 (*31*, *33*, *34*). The electrodes did not elicit sensations that projected to the thumb or to the tips of any digits. In area 1 of S1, proximal regions of the digits are represented near the central sulcus, whereas distal regions of the digits are represented more posteriorly (*34*, *35*). Individual stimulation electrodes located more posteriorly in the cortex should have elicited sensations closer to the tips of the finger; however, no such progression was observed with these small arrays.

Up to the maximum stimulus amplitude of 100 μA, 59 of the 64 stimulation electrodes generated detectable sensations, with 54 electrodes having projected fields located just below the palmar digital creases (P2 to P5 regions; Fig. 1A). Of these, the projected fields for 15 electrodes also extended up into the proximal phalanx of D5 and a further 17 extended into the proximal and intermediate phalanges of D2. Five electrodes had projected fields that were restricted to D2. Similar proportions were also seen in the subset of data collected during surveys of all the electrodes at 60 μA (100 pulses per second for 1 s), in which projected fields for 46 electrodes were reported (Fig. 1B). No sensations were projected to other regions of the hand or any other part of the body. In the 60-μA surveys, we found that the projected fields were typically focal, with the percepts from 23 individual electrodes projecting to a single identified region of skin. For the 18 electrodes that elicited sensations on larger regions of the hand, the projected fields covered at most eight defined regions (based on the segmentation in Fig. 1A). Only one electrode elicited sensations that projected to disconnected projected fields over repeated testing. Frequently, sensations were felt to originate from the center of a joint and below the skin rather than solely on the surface of the skin. This was particularly true for the D2 proximal interphalangeal joint, with 10 electrodes eliciting sensations projected to this location.

Perceptual quality

A key issue with intracortical microstimulation, and one that is only directly measureable in humans, surrounds the question of what stimulation feels like. To address this, the participant was routinely asked to describe the quality of the evoked sensations according to a range of specified metrics (see Materials and Methods and Table 1) during the 60-μA surveys, which were conducted nine times in the first 6 months. Most commonly, stimulus trains were described as feeling possibly natural, were felt to originate both from the skin surface and below the skin, and were usually described as feeling like pressure coming from a specific location on the hand (Table 1). These pressure sensations were occasionally elaborated on voluntarily by the participant and included descriptions such as "it's almost like if you pushed there, but I didn't quite feel…the touch." In certain cases, stimulation-evoked sensations were described as light touch, although these reports were infrequent. During these surveys, the number of electrodes that elicited sensations on a given day ranged from 7 to 26 (median, 13). No pain or discomfort of any kind was ever reported even up to the maximum stimulus amplitude (100 μA). Sensations of tingle or electrical current were reported on some electrodes; however, the participant reported that these sensations did not feel like electrical stimulation of the skin in regions with normal sensation, a procedure that he had experienced as part of this study. Rather, these sensations were described as being nearly vibratory in nature and were similar to the sensations elicited when a mechanical vibrator was briefly touched to the skin. Paresthesias, specifically sensations of "pins and needles," were never experienced during stimulation. Table 1 summarizes the perceptual qualities for every case when a sensation was reported.

The participant reported 93% of the stimulus trains as being "possibly natural" (Table 1), reflecting the difficulties in assessing the naturalness of stimulation-evoked sensations. This is perhaps, in part, because he experienced abnormal sensation on the radial side of his hand as a result of his spinal cord injury. To provide context for the interpretation of the naturalness scale, the participant reported on the same set of perceptual dimensions during both electrical and mechanical stimulation of the skin of the hand and arm. Electrical stimulation of the volar surface of the arm at 0.5 mA and 100 Hz, in a region where the residual

Table 1. Percept qualities evoked by intracortical microstimulation. The number of trials evoking each response type is shown. The totals in each category (naturalness, depth, etc.) differ because the participant did not always provide a complete response for every case where he could detect a stimulus. In 79 cases, a sensation of "tingle" was described without being further described by one of the subcategories.

Naturalness (250)		Depth (247)		Pain (280)		Somatosensory quality (190)	
Totally natural	0	Skin surface	9	0 (no pain)	280	Mechanical	Touch (2), pressure (128), sharp (0)
Almost natural	12	Below skin	5	1, 2, 3	0	Movement	Vibration (1), movement (0)
Possibly natural	233	Both	233	4, 5, 6	0	Temperature	Warm (30), cool (0)
Rather unnatural	5			7, 8, 9	0	Tingle (79)	Electrical (29), tickle (0), itch (0)
Totally unnatural	0			10 (most pain)	0		

sensation was normal, was described as being "almost natural" because the percept matched the stimulus being applied. However, he further stated that electrical stimulation on the surface of the arm elicited pain [5 on a scale of 0 (no pain) to 10 (extremely painful)] and felt "extremely different" than microstimulation of S1. Comparatively, mechanical indentation of the skin on the forearm with the blunt end of a cotton swab felt "totally natural," was not associated with any pain, and evoked sensations with qualities of "pressure," "sharp," and "touch." This same indentation at the base of the index finger, a place with altered sensation due to spinal cord injury, was described as feeling "pretty much the same" as microstimulation through an electrode with a coincident projected field.

Stimulus detection thresholds, perceived intensity, and just-noticeable differences

We measured the detection threshold for intracortical microstimulation using a two-alternative forced-choice (2AFC) paradigm, where the participant reported which of the two intervals contained a stimulus train (Fig. 2A). Mean detection thresholds, measured for 59 electrodes, ranged from 15 to 88 μA (Fig. 2B), with a median of 34.9 μA and lower and upper quartiles of 24.8 and 60.0 μA, respectively (Fig. 2B). Near the detection threshold, the participant typically could not describe the qualities of the stimulus, including the projected field, as is typically the case for perithreshold natural stimuli. Figure 2C shows the spatial layout of the mean detection threshold for every electrode across the two implanted arrays. A general pattern emerged where the anterior edge of the arrays yielded the lowest detection thresholds and the posterior edge yielded the highest ones. The depth of electrodes within the cortex is known to affect detection thresholds (*36*–*38*), so cortical curvature or mechanical effects of the wire bundles, which exited the arrays at their posterior edges, may have resulted in different electrode depths and, consequently, the observed gradient of stimulus thresholds.

In another set of experiments, we measured the perceived intensity of stimulation-evoked sensations using a free magnitude estimation paradigm. In this task, different stimulus amplitudes were presented in a random order, and the participant rated the perceived intensity on a numerical scale. As might be expected, increases in stimulation amplitude led to increases in the perceived intensity of the sensation (Fig. 3, A and B). All five electrodes tested using this paradigm yielded a significant linear relationship between stimulus amplitude and perceived intensity ($P < 0.001$ for all electrodes), with a mean coefficient of determination of 0.62 (range, 0.35 to 0.91). The best-performing electrode is shown in Fig. 3A, whereas the intensity ratings averaged across electrodes (after normalizing to the mean within an electrode) are shown in Fig. 3B.

We also measured the participant's ability to discriminate changes in intracortical microstimulation amplitude to estimate the number of distinguishable increments one might be able to evoke through a given stimulating electrode. To this end, we measured the just-noticeable difference using a 2AFC task, where the participant was presented with a pair of microstimulation trains and reported which was more intense. In these experiments, one of the stimuli, the reference stimulus, was set to a low (20 μA) or high (70 μA) amplitude. The just-noticeable difference was defined as the minimum change in stimulation amplitude that the participant could correctly identify 75% of the time. Across the seven electrodes tested, just-noticeable differences were found to be 15.4 ± 3.9 μA (Fig. 3C); that is, 35 μA was discriminable from 20 μA and 55 μA was discriminable from 70 μA with 75% accuracy. The just-noticeable difference was independent of the amplitude of the reference stimulus ($P = 0.86$, Wilcoxon signed-rank test), consistent with findings in nonhuman primates (*19*).

Response stability

An important consideration for the use of intracortical microstimulation in a neuroprosthesis is the stability of the evoked responses over time. Mapping projected field locations and detection thresholds is a time-consuming and tedious process. If these maps required frequent revision, as is typically the case with algorithms to decode intended movements from the responses of neurons in motor cortex (*8*, *9*, *39*–*41*), this approach to restoring somatosensation might not be viable. Detection thresholds were measured three or more times on 19 electrodes. Of these, six electrodes had thresholds that changed significantly over

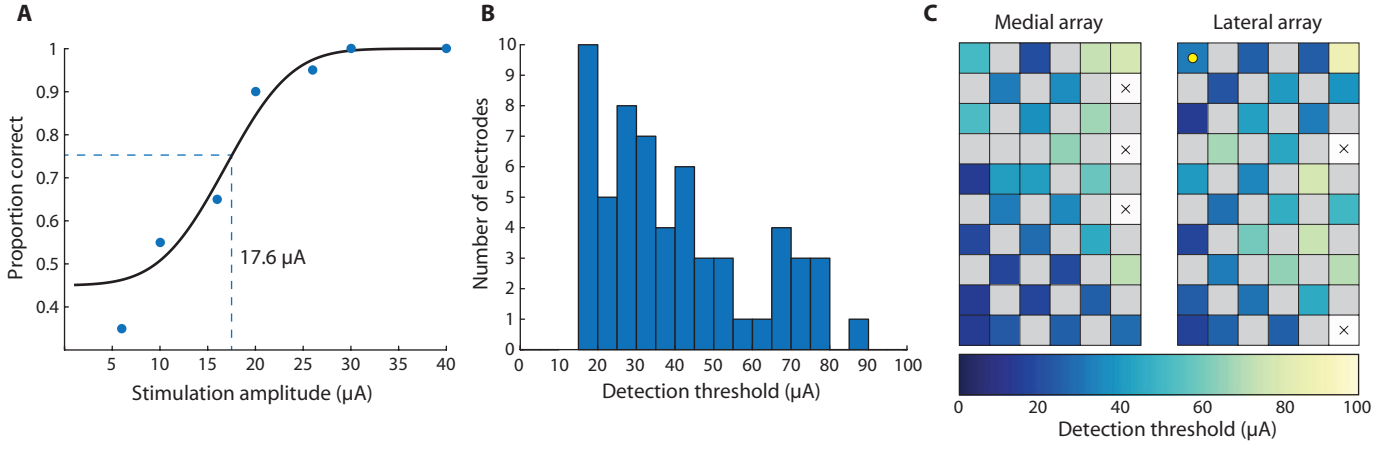

Fig. 2. Intracortical microstimulation detection thresholds. (**A**) Example of the data from a detection task for a single electrode [electrode highlighted with yellow dot in (C)]. The measured detection threshold was 17.6 μA. Twenty responses were collected at each stimulus amplitude, and a psychometric function was fit to the data. (**B**) Histogram of the mean detection threshold for each electrode ($n = 59$). Twenty-three electrodes had a mean detection threshold less than 30 μA. (**C**) Mean detection thresholds arranged spatially on the two arrays. Gray boxes indicate electrodes that were not physically wired to the stimulator, and the x symbol indicates electrodes where a stimulation threshold could not be measured below the maximum stimulus amplitude of 100 μA. Electrodes located anteriorly (left) had lower detection thresholds than those located posteriorly (right).

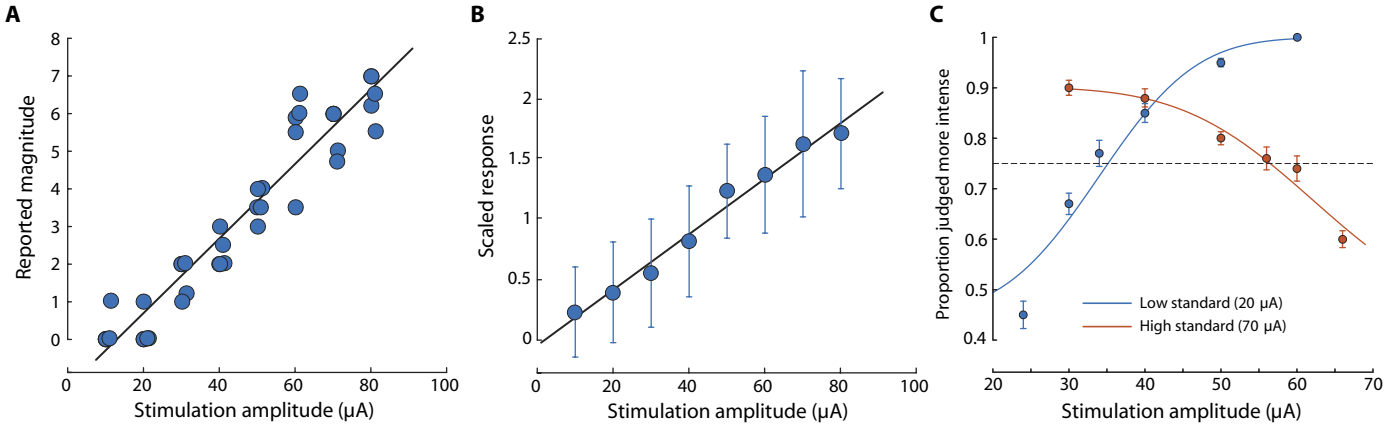

Fig. 3. Increasing stimulus amplitude increases perceived intensity. (**A**) The relationship between the perceived intensity and stimulation amplitude is shown for an example electrode. There was a highly significant linear relationship between the perceived intensity and stimulus amplitude (R^2 = 0.91, P < 0.001). The y axis uses arbitrary units selected by the participant. (**B**) This significant relationship was found for all tested electrodes (n = 5) after normalizing each electrode to its mean response (R^2 = 0.98, P < 0.001). Each data point represents the mean of 40 individual data points, and error bars represent ±1 SD from the mean. (**C**) Just-noticeable differences from five electrodes using identical test parameters with a low (20 μA) and high (70 μA) standard amplitude. Data points are the mean and SE from 100 repetitions at each amplitude. The just-noticeable difference was 15.2 ± 5.1 μA at the low standard and 14.6 ± 4.3 μA at the high standard. There was no difference between the just-noticeable differences at the two standard amplitudes (P = 1.0, Wilcoxon signed-rank test).

the testing period: thresholds for five electrodes significantly increased by an average of 0.35 ± 0.16 μA per day, and the threshold for one electrode significantly decreased by 1.65 μA per day (P < 0.05, linear regression). Figure S2A shows a distribution of the regression slopes for the 60 electrodes with multiple threshold measurements, whereas fig. S2B shows a summary of all the detection threshold measurement data highlighting the electrodes with significant regression slopes. During the 60-μA survey trials, the number of electrodes with reported sensations increased over time (fig. S2C). We also found that the projected field locations were generally consistent over a period of 6 months (fig. S2C), as has been found with intracortical microstimulation in the visual cortex (*26*). Thirty-three electrodes elicited sensations during more than one of the 60-μA survey sessions, and 9 of these had identical projected fields every time they were reported. Twenty-one electrodes had projected fields that overlapped across surveys, but never shifted by more than one adjacent region, whereas the remaining electrodes had projected fields that were always constrained to the same digit. In summary, the overall somatotopic organization of the projected fields remained consistent over a period of 5 months.

Location discrimination using a prosthetic hand

To test the ability of the participant to discriminate the location of presented stimuli, we mapped the output from the torque sensors in the D2 to D5 finger motors of the Modular Prosthetic Limb (Johns Hopkins University Applied Physics Lab) (*42*) to groups of electrodes that had been identified to elicit percepts on the corresponding finger. When the prosthetic fingers were touched, the resulting increase in motor torque (from 0.05 to 0.4 Nm) was linearly converted to stimulation amplitude over a range of 20 to 80 μA. An experimenter touched individual prosthetic fingers, as well as pairs of fingers simultaneously, and the blindfolded participant was asked to identify the location of the stimulus (movie S1). Across the 13 sessions involving a total of 62 to 65 repetitions on each finger, the overall success rate for finger identification was 84.3%. The index and little fingers were usually identified correctly, whereas the middle and ring fingers were less accurately identified. Errors typically consisted of attributing the sensation to the adjacent finger (Table 2). The participant performed at a high accuracy on the very first session (>85% correct), even though feedback about performance was not provided to the participant other than the total number of correct trials at the end of a block. In two additional sessions with a combined 26 trials, the participant was told that more than one finger might be touched. He correctly identified at least one of the fingers in every trial and correctly identified both fingers being touched 53% of the time.

Table 2. Accuracy of prosthetic finger discrimination. The percentage of times that sensations were reported to originate from a specific finger (columns) when each prosthetic finger was touched (rows).

	Reported D2	Reported D3	Reported D4	Reported D5
Actual D2	96.9 ± 7.2%	1.5 ± 5.3%	1.5 ± 5.3%	0%
Actual D3	0%	73.5 ± 18.1%	21.9 ± 18.4%	0%
Actual D4	0%	18.5 ± 22.8%	73.1 ± 24.6%	6.5 ± 16.8%
Actual D5	0%	3.1 ± 7.2%	3.1 ± 10.7%	93.9 ± 12.1%

Stimulus safety considerations

Over the period of time reported, 52 stimulation sessions were performed that each included hundreds of individual stimulus trains. After three of these stimulus trains, the evoked sensation lasted longer than the stimulus itself, as has been reported for stimulation in the visual cortex (*30*). In one instance, the sensation persisted for just under 1 min, whereas in the other cases sensations subsided within a few seconds.

Intracortical microstimulation has the potential to damage the electrode (*43*), surrounding tissue (*44*), or both, depending on the injected charge and charge density. However, the maximum stimulation amplitude (see Materials and Methods) used in this study has been shown to affect tissue to no greater extent than that which may occur due to the

insertion of the microelectrode arrays themselves (*45*, *46*). As a result of his injury, our study participant could not move his digits and was insensate on the ulnar side of the arm including the third through fifth digits. However, some sensation remained on the radial side of the arm, including the first two digits and thenar eminence. To document changes in residual sensation that might occur as a result of implantation and stimulation through the electrode arrays, we measured the detection thresholds for electrical stimulation of the skin surface at several locations on the hand and arm before and after implantation. Detection thresholds on sensate regions of the skin did not change after implantation of the electrode arrays (fig. S3), nor did the participant report changes in the sensory capacity of the sensate regions of his hand.

As a further test of the changes that could occur in the cortex as a result of intracortical microstimulation, neural activity was recorded from the electrodes in S1 at the beginning of every session. The signal-to-noise ratio (SNR) did not change over time (fig. S4A), the most highly stimulated electrodes continued to record well-isolated action potentials months after implant (fig. S4B), and single-unit activity was recorded across the arrays throughout the study (fig. S4C). These findings suggest that implantation of the microelectrode arrays and stimulation over a period of 6 months did not compromise spared sensory capabilities of the hand, nor did it impair the function of neurons in close proximity to the electrodes, as it has been shown that recording single-unit action potentials requires that the electrode be within 140 μm of a neuron (*47*).

DISCUSSION

Intracortical microstimulation has been suggested as a way to restore somatosensation (*16*, *17*, *48*–*50*) in cases where it has been degraded or lost due to injury or disease. Given the importance of somatosensory feedback in motor control, the restoration of this sensory modality is likely critical to enable manipulative actions in future upper-limb neuroprostheses. Here, we show that (i) tactile percepts at somatotopically appropriate locations can be evoked through microstimulation of S1 in humans, (ii) the perceptual quality of intracortical microstimulation is often naturalistic, (iii) perceptual intensity is modulated by stimulation amplitude, (iv) the evoked percepts are stable over time, and (v) microstimulation over several months has no discernible detrimental consequences on the participant. Further, from the measured detection thresholds (typically 20 to 50 μA) and just-noticeable differences (~15 μA), we estimate that many electrodes can elicit four to six distinct intensity gradations up to the maximum stimulus amplitude of 100 μA. Together, these results suggest that intracortical microstimulation is a promising approach to establish artificial somatosensation.

In motor brain-computer interfaces, performance is immediately evident, whereas it is not directly observable in sensory brain-computer interfaces. Indeed, the artificial sensations evoked in animal studies can only be inferred from a surrogate behavior. These same animal studies have suggested that microstimulation in S1 is capable of eliciting behavior at a performance level similar to that which is possible with natural cutaneous input (*18*, *21*). However, these behavioral studies require substantial training, leaving questions about how analogous naturally and electrically evoked percepts really are, and raises the possibility that observed performance could be due to classical conditioning. In the experiments reported here, intracortical microstimulation elicited intuitive percepts that were easily understood to originate from the participant's own paralyzed limb with sufficient quality to report locations and graded intensities without any training. Furthermore, more complex inputs, such as simultaneous microstimulation at multiple regions of the hand, were immediately reported with limited instruction about the changed paradigm. These observations demonstrate that intracortical microstimulation evokes sufficiently natural sensations to support performance on stimulation-based tasks without additional training.

Microstimulation in S1 can also elicit sensations that have perceptual qualities similar to those that occur as a result of mechanical stimulation of the hand. In previous cortical experiments performed in humans, Penfield (*24*, *51*) reported that stimulating the surface of S1 evoked paresthetic percepts—consisting of "tingling," "pins and needles," and "numbness"—that were occasionally reported to originate from a single finger but more frequently were very diffuse in nature. Such paresthesias were also the most common percepts evoked with thalamic microstimulation, although mechanical and movement sensations also occurred (*52*, *53*).

A limitation of this study is that this approach was tested with just one subject. It is therefore difficult to generalize these findings to other cases of spinal cord injury or to other injuries such as amputation. It could be the case that the specific mechanism of peripheral sensory deafferentation has an impact on the organization of S1 that underlies the capacity of intracortical microstimulation to elicit consciously detectable percepts. As a result, it is unclear to what extent our participant's residual sensation on the radial side of his hand may have contributed to the maintenance of somatotopic organization in S1 or the ability to detect microstimulation pulses. However, in complete spinal cord injury, there is evidence that hand regions of the sensory cortex remain relatively unchanged (*54*), and experiments with long-term amputees suggest that somatotopic structure in S1 is retained (*55*), enabling peripheral electrical stimulation to elicit detectable sensations (*56*). Thus, deafferentation does not seem to lead to a loss of sensibility in the cortex. Consistent with this hypothesis, microstimulation of the spared and deafferented regions of the hand representation in S1 seemed to evoke similar percepts, suggesting that spared sensory input does not have any measurable effects on the sensory consequences of microstimulation.

Percepts evoked by intracortical microstimulation are highly spatially localized, so information about contact location can be conveyed intuitively by stimulating somatotopically appropriate electrodes. The magnitude of microstimulation-evoked percepts increases smoothly with increases in stimulation amplitude, so information about contact pressure can be conveyed by modulating stimulation amplitude according to the output of pressure sensors on the prosthesis. The restoration of these two streams of somatosensory information is likely to have a major impact on the dexterity of prosthetic hands and may enable greater embodiment of the prosthesis (*57*). Implantation of more electrodes would likely allow participants to experience sensations covering more of the hand (*58*–*60*), ideally including the distal digits (*34*, *61*). Future work will also seek to improve the realism of evoked sensations through modulated (*13*) or biomimetically inspired patterning of stimulus trains and to expand the repertoire of artificial sensations to include proprioception as well as other dimensions of touch including shape, motion, and texture.

MATERIALS AND METHODS

Study design

The purpose of this study was to investigate the conscious sensations elicited by intracortical microstimulation in the somatosensory cortex of a human participant and to quantify how these sensations changed

over time using classical psychophysical methods. Somatosensation is a critical component of motor control, and the ultimate aim of this work is to reestablish tactile percepts from prosthetic limbs so that people with injury or disease can recover arm and hand function. A male participant with tetraplegia enrolled in this study and, upon partial examination, presented with a C5 motor/C6 sensory ASIA B spinal cord injury. The injury was sustained about 10 years before the implantation of microelectrode arrays in the left somatosensory and motor cortices when he was 28 years old. Stimulation was performed over a period of 6 months. The participant typically came to the laboratory three times a week for sessions that lasted up to 4 hours.

Array implantation

Two microelectrode arrays were implanted in S1 and were each 2.4 mm × 4 mm in size, with 60 electrode shanks arranged in a 6 × 10 grid pattern. Electrodes were 1.5 mm long, and the tips were coated with sputtered iridium oxide film to improve their charge injection capacity (*62*). The two microelectrode arrays implanted in the motor cortex were each 4 mm × 4 mm in size, with 100 electrode shanks arranged in a 10 × 10 grid pattern. Electrodes were 1.5 mm long, and the tips were coated with platinum. Thirty-two of the 60 electrode shanks on the S1 arrays and 88 of the 100 electrode shanks on the motor cortex arrays were wired to an external connector that was attached to the skull. Two connectors were placed on the skull with each connector wired to one S1 array and one motor cortex array. Electrode array assemblies were manufactured by Blackrock Microsystems. During surgery, electrode placement was guided by functional neuroimaging data using image guidance (Brainlab), as well as anatomical constraints to optimize outcomes such as avoiding blood vessels and placing the arrays on a flat area of cortex.

Presurgical imaging

Before the implantation surgery, functional imaging was performed using MEG (Elekta Neuromag) to identify cortical areas related to cutaneous sensations from the hand. MEG data were recorded while an experimenter stroked the participant's thumb, index finger, little finger, and palm with a cotton swab. Because of the participant's impaired sensation, he simultaneously watched a video of another person being touched with a cotton swab and imagined the sensation that he would expect to experience. Source localization of the MEG data was performed using Brainstorm software (*63*) to map cutaneous-related activity on the participant's cortical surface, which was reconstructed from a structural MRI of the brain. Co-registration with Brodmann's area atlas was performed using the FreeSurfer (*32*) image analysis suite (http://surfer.nmr.mgh.harvard.edu/).

Neural recording and stimulation

Stimulation and recording sessions were performed two to three times a week for up to 4 hours per session. Neural signals were recorded using the NeuroPort data acquisition system (Blackrock Microsystems), and stimulation was delivered using a CereStim C96 multichannel microstimulation system (Blackrock Microsystems). Setup time, including cable connections, unit sorting, and electrode characterization, took about 45 min per session.

Stimulation pulse trains consisted of cathodal phase first, current-controlled, charge-balanced pulses delivered at frequencies ranging from 25 to 300 Hz. The cathodal phase was 200 μs long, the anodal phase was 400 μs long, and the amplitude of the anodal phase was set to half the amplitude of the cathodal phase. The phases were separated by a 100-μs interphase period. Both symmetric and asymmetric pulses are similarly effective in cortex (*64*). All reported stimulus amplitudes refer to the amplitude of the cathodal phase. The stimulus amplitude on each individual electrode was limited to a maximum of 100 μA per channel. Up to 12 channels could be simultaneously stimulated, but the total instantaneous charge across all electrodes was further limited to 144 nC per phase. These stimulation limits were derived from a series of recent studies (*45*, *46*). Stimulation pulses were delivered exclusively to electrodes implanted in S1.

The voltage delivered to all electrodes was sampled at 100 kHz using a custom National Instruments data acquisition system. This allowed continuous, real-time monitoring and assessment of the voltage transients, and most importantly the interphase voltage, during stimulation. Interphase voltage provides an estimate of the electrode polarization and thus electrochemical safety (*65*). No strict limits on interphase voltage were enforced; however, at the beginning of each session, every electrode was stimulated with 0.5-s, 100-Hz pulse trains at amplitudes of 10 and 20 μA to assess the interphase voltage at low stimulus amplitudes. Typically, the interphase voltage was between −0.40 and −0.75 V at these stimulus amplitudes. Electrodes that exceeded −1.5 V were excluded from testing for the day. The interphase voltage rarely exceeded 1 V during normal testing.

Survey trials and perceptual responses

Survey trials were routinely conducted and consisted of sequentially stimulating individual electrodes on the arrays using 1-s, 100-Hz pulse trains at 60 μA. This amplitude was selected because it was found to be supraliminal for many channels but stayed well below the maximum stimulus amplitude. These survey trials were used to quantify projected field locations and the perceptual quality of elicited sensations in a structured manner over time. No visual or auditory cue was provided to the participant to indicate when stimulation was occurring. The participant was instructed to indicate when a sensation was detected, at which point progression through the trial was paused. The participant verbally reported when he detected a sensation, and the pulse train was repeated as many times as necessary for the participant to be able to accurately describe the location and quality of the sensation. The location of the projected field for each electrode was reported using the partitions of the hand shown in Fig. 1A. These partitions were devised as a compromise between achieving high-resolution projected field maps and doing so in a relatively short period of time. Once the participant reported a sensation, the hand map was shown on a screen in front of the participant, and the projected fields were marked by an experimenter as the participant reported them.

After the location of the percept was established, the participant reported the quality of the sensation using the descriptors in Table 1. The participant's response was documented by the experimenter using a computer interface, and video recordings were also made during all responses. If the participant felt that the sensation was not accurately described by the provided descriptors, his response was recorded, and the best approximation using the descriptors was used. The descriptors included a five-point scale for naturalness ranging from totally unnatural to totally natural, a metric of the location of the sensation on or below the skin surface, and an assessment of pain ranging from 0 to 10. The quality of the sensation was further assessed using the following descriptors: mechanical (touch, pressure, or sharp), movement (vibration or movement across the skin), temperature (warm or cool), and tingle (electrical, tickle, or itch). These descriptors were based on a previously used questionnaire (*52*). Responses were not always provided for each category because percepts at perithreshold levels were

difficult to accurately describe. Further, the participant could report multiple somatosensory qualities for a single stimulus, and in some cases, the subcategories (for example, electrical, tickle, or itch) could not be described.

Detection thresholds

Detection thresholds were determined using 2AFC tasks. In this task, the participant was instructed to focus on a fixation cross on a screen located in front of him. Two 1-s-long windows, separated by a variable delay period, were presented and indicated by a change in the color of the fixation cross. Stimulation was randomly assigned to one of the two windows. After the last window, the fixation cross disappeared, and the participant was asked to report which window contained the stimulus.

Before each block of detection trials, a 1-s, 100-Hz pulse train at a supraliminal amplitude (up to 100 μA) was presented to the participant so that he could focus on the projected field location during the detection task. The stimulus would then be repeated enough times that the participant could describe the location and quality of the projected field. These responses were used to characterize the percepts elicited by electrodes that did not respond during the 60-μA surveys.

Two methods were used to determine the stimulation amplitudes during the detection threshold task: threshold tracking and the method of constant stimuli. For the tracking method, a one-up three-down method was used so that if the participant correctly identified the window containing the stimulus in three consecutive trials, the amplitude was decreased for the next trial. If the participant incorrectly identified the window containing the stimulus, the amplitude was increased for the next trial. Values were increased or decreased by a factor of 2 dB. This method reduced the time spent testing uninformative values but does not guarantee that amplitudes will be tested the same number of times. After five changes in the direction of the stimulus amplitude (increasing to decreasing, or decreasing to increasing), the trial was stopped. The detection threshold was calculated as the average of the last 10 values tested before the fifth direction change, which should correspond to about 75% correct detection. For the method of constant stimuli, a predetermined set of stimulation amplitudes was presented to the participant in a random order a set number of times. The proportion of times the participant correctly identified the window that contained the stimulation train was calculated for each test value, and psychometric curves were generated using a cumulative normal distribution. The threshold was then estimated from the curve as the stimulus amplitude, where the probability of detection was 75%.

To determine whether the detection thresholds changed over time, the channels with multiple measured thresholds were linearly regressed against time. The slope of the regression for each electrode was tested for being statistically different than zero ($P < 0.05$). Electrodes where $P > 0.05$ were considered to have detection thresholds that did not change over time.

Perceived intensities

Stimulation pulse trains were delivered through individual electrodes for 1 s at 100 Hz using amplitudes ranging from 10 to 80 μA in 10-μA increments. Each block of eight stimulus amplitudes was presented six times, and the order of the stimulus presentation was randomized within each block. The participant rated the perceived intensity of each stimulus using a self-selected numerical scale (free magnitude estimation). The participant was instructed to scale the response such that a stimulus that felt twice as strong as a previous stimulus should be reported using a number that was twice as large. Fractional values were allowed, and the participant was also instructed to report zero if the stimulus was not felt. For analysis, responses from the first block were discarded.

Just-noticeable differences

Just-noticeable differences were determined using a 2AFC task, where two stimulus trains (1 s long, 100 Hz) at different amplitudes were presented in two different windows. The participant was asked to respond which of the two intervals contained the most intense stimulus. During a block of tests, one of the stimulus amplitudes remained constant and was set to a low (20 μA) or high (70 μA) reference point. The comparison stimuli for the low reference ranged from 24 to 70 μA, and the comparison stimuli for the high reference ranged from 20 to 66 μA. The threshold for a tested electrode was confirmed to be 20 μA or less before measuring the just-noticeable difference. Psychometric curves were fit to the data using a cumulative normal distribution. The just-noticeable difference was estimated from the curve as the difference between the reference stimulus amplitude and the test stimulus amplitude, where the probability of correctly identifying the interval with the more intense stimulus was 75%.

Location discrimination

As a test of the ability of the participant to correctly identify the perceived location of stimulation, electrodes with projected fields located within a single digit or at the base of a single digit were mapped to torque sensors at the base of the corresponding finger on the Modular Prosthetic Limb. Groups of two to four electrodes were identified for each of the four fingers. The participant was blindfolded, and an experimenter touched individual fingers, which generated a reaction torque in the motor for the associated finger. There was no cue provided about when the fingers were touched. The participant responded verbally with the identity of the finger that was felt to have been touched. Each finger was touched five times in random order during each trial. This task was completed 10 times on four separate days, as well as one additional time where each finger was only tested four times, for a total of 54 presentations of each finger. Finger reaction torques from the prosthetic hand were converted to stimulus trains using a linear mapping between torque and stimulus amplitude. A minimum torque value of about 0.05 Nm was set to a stimulation amplitude of 20 to 40 μA depending on the threshold of the electrode, whereas a maximum torque value of 0.4 Nm was represented as a stimulation amplitude of 80 μA. All stimulus pulses were delivered synchronously at 100 Hz. The duration of the stimulation was dependent on how long the experimenter pressed the finger, but typically ranged from 0.5 to 1 s.

Electrical stimulation of the skin

The participant's ability to perceive peripheral stimulation was evaluated using electrical stimulation of the hand as well as over the median and ulnar nerves at the wrist using a Grass S88X stimulator (Grass Technologies). A ground electrode was placed on the proximal forearm (3M Red Dot), and adhesive bar electrodes (PT30, The Electrode Store) were positioned at each test location. Monophasic, current-controlled pulses, with a pulse width of 200 μs, were delivered at four pulses per second. The electrode at the test location was set as the cathode. Continuous pulse trains were used, and the stimulation amplitude was slowly increased until the participant reported feeling the stimulus. The amplitude was then decreased below the detection threshold, and the process was repeated three times per location. The average of the amplitudes at

which he reported feeling the stimuli was recorded as the threshold. This test was done before implant, periodically in the month after implant (7, 14, and 24 days after implant), and again 140 days after implant. Detection thresholds were regressed against time using linear regression for each location that was tested both before and after implant (tip of the thumb, tip of the index finger, base of little finger, thenar eminence, median nerve, and ulnar nerve) to determine whether the participant's detection of peripheral stimulation had changed over time. If the slope of the regression was significantly different than zero ($P < 0.05$), the threshold for that location was considered to have changed over time.

Signal-to-noise ratio

All SNR calculations were performed on single units that were sorted offline. The spike amplitude for each unit was set to the maximum absolute deviation of its average waveform. The baseline noise was two times the SD of the first five samples from all snippets for the unit. SNR was calculated as the spike amplitude divided by the baseline noise, and the channel SNR was set to the largest SNR of all units recorded on that channel.

Statistical analysis

Statistical analyses were performed in Matlab (The MathWorks). Unless otherwise noted, data are reported as means ± SD. Specific statistical tests are typically noted in the text. To determine which electrodes had detection thresholds that changed significantly over time, linear regression was performed between the detection thresholds and the post-implant day for each electrode. Electrodes where the regression slope was significantly different than zero at the $P < 0.05$ level were considered significant. Threshold values with a residual larger than expected in 95% of the thresholds for an electrode were considered outliers.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/8/361/361ra141/DC1

Fig. S1. Spontaneous neural activity in S1.

Fig. S2. Stability of stimulation responses.

Fig. S3. Surface electrical stimulation detection thresholds over time.

Fig. S4. Changes in S1 signal strength over time.

Movie S1. Example of finger location discrimination using a prosthetic hand.

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Intracortical microstimulation of human somatosensory cortex

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A sense of touch

Touch is essential for hand use. Yet, brain-controlled prosthetic limbs have not been endowed with this critical sense. In a new study by Flesher *et al*., microelectrode arrays were implanted into the primary somatosensory cortex of a person with spinal cord injury and, by delivering current through the electrodes, generated sensations of touch that were perceived as coming from his own paralyzed hand. These sensations often felt like pressure, could be graded in intensity, and were stable for months. The authors suggest that this approach could be used to convey information about contact location and pressure necessary for prosthetic hands to interact with objects.

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