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Title

Prosthesis with neuromorphic multilayered e-dermis perceives touch and pain

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Abstract

The human body is a template for many state-of-the-art prosthetic devices and sensors. Perception of touch and pain are fundamental components of our daily lives that convey valuable information about our environment while also providing an element of protection from damage to our bodies. Advances in prosthesis designs and control mechanisms can aid an amputee's ability to regain lost function but often lack meaningful tactile feedback or perception. Through transcutaneous electrical nerve stimulation (TENS) with an amputee subject, we discovered and quantified stimulation parameters to elicit innocuous (non-painful) and noxious (painful) tactile perceptions in the phantom hand. Electroencephalography (EEG) activity in somatosensory regions confirms phantom hand activation during stimulation. We invented a multilayered electronic dermis (e-dermis) with properties based on the behavior of mechanoreceptors and nociceptors to provide neuromorphic tactile information to an amputee. Our biologically inspired e-dermis enables a prosthesis and its user to perceive a continuous spectrum from innocuous to noxious touch through a neuromorphic interface that produces receptor-like spiking neural activity. In a Pain Detection Task (PDT), we show the ability of the prosthesis and amputee to differentiate non-painful or painful tactile stimuli ~~and the ability to mitigate potential damage~~ using a pain reflex feedback control system. ~~For the first time,~~ an amputee subject can discriminate object curvature, including sharpness, based on perceptions of touch and pain. This work demonstrates novel possibilities for creating a more natural sensation spanning a range of tactile stimuli for prosthetic hands.

Summary

A multilayered e-dermis allows for a prosthesis and an amputee to perceive a range of tactile and noxious stimuli.

MAIN TEXT

Introduction

One of the primary functions of the somatosensory system is to provide exteroceptive sensations to help us perceive and react to stimuli from outside of our body *(1)*. Our sense of touch is a crucial aspect of the somatosensory system and provides valuable information that enables us to interact with our surrounding environment. Tactile feedback, in conjunction with proprioception, allows us to perform many of our daily tasks that rely on the dexterous manipulation of our hands *(2)*. Mechanoreceptors and free nerve endings in our skin give us the means to perceive tactile sensation *(2)*. The primary mechanoreceptors in the glabrous skin that convey tactile information are Meissner corpuscles, Merkel cells, Ruffini endings, and Pacinian corpuscles. The Merkel cells and Ruffini endings are classified as slowly adapting (SA) and respond to sustained tactile loads while the Meissner and Pacinian corpuscles as rapidly adapting (RA), which respond to the onset and offset of tactile stimulation *(1, 3)*. More recently, research has shown the role of fingertips in coding tactile information *(4)* and extracting tactile features *(5)*.

A vital component of our tactile perception is the sense of pain. Our perception of pain provides a protection mechanism for a body part or region that experiences a potentially damaging stimulus. In the event of an injury, increased sensitivity can even render innocuous stimuli as painful *(6)*. Pain is often an undesired experience but is essential for protecting both our exterior and internal organs. Nociceptors are dedicated sensory afferents in both glabrous and non-glabrous skin responsible for conducting tactile stimuli that we perceive as painful *(6)*. Free nerve endings in the epidermal layer of the skin act as high threshold mechanoreceptors (HTMRs) and respond to noxious stimuli through Aβ, Aδ, and C nerve fibers *(1)*, which enables our perception of tactile pain. It was discovered that Aδ fiber HTMRs respond to both innocuous and noxious mechanical stimuli with an increase in impulse frequency while experiencing the noxious stimuli *(7)* and the presence of C fibers were found intertwined in Meissner corpuscles, indicating the role of low threshold mechanoreceptors (LTMRs) in nociception *(8, 9)*. It is also known that mechanoreceptor activation along with nociceptor activation helps inhibit our perception of pain and our discomfort increases when only nociceptors are active *(10)*, which helps explain our ability to perceive a range of innocuous and noxious sensations. At the same time, such a wide variety and range of perceptions are not available in today's prosthetic hands.

The undoubted importance of our sense of touch, and lack of sensory capabilities in today's prostheses, has spurred research on artificial tactile sensors and restoring sensory feedback to those with upper limb loss. Novel sensor developments utilize flexible electronics *(11-13)*, self-healing *(14, 15)* and recyclable materials *(16)*, mechanoreceptor-inspired elements *(17, 18)*, and even optoelectronic strain sensors *(19)*, which will likely impact the future of prosthetic limbs. Local force feedback to a prosthesis is known to improve grasping *(20)*, but in recent years there has been a major push towards providing sensory feedback to the prosthesis and the amputee. Groundbreaking results show that implanted peripheral nerve electrodes *(21-24)* as well as noninvasive electrical nerve stimulation methods *(25)* can successfully elicit sensations of touch in the phantom hand of amputees.

Recent approaches aim to mimic biological behavior of tactile receptors using advanced skin dynamics *(26)* and what are known as neuromorphic *(27)* models of tactile receptors for sensory feedback. A neuromorphic system aims to implement components of a neural system, for example the representation of touch through spiking activity based on biologically driven models. Several reasons for utilizing a neuromorphic approach is to create a biologically relevant representation of tactile information using actual mechanoreceptor characteristics, which could create a more natural perception of touch during nerve stimulation. Neuromorphic techniques have been used to convey tactile sensations for differentiating textures using SA-like dynamics for the stimulation paradigm to an amputee subject *(27)* and for feedback to a prosthesis to enhance grip functionality *(28)*. While important, methods of sensory feedback have been limited to sensations of pressure *(22)*, proprioception *(24)*, and texture *(27)* even though our perception of tactile information culminates in a sophisticated, multifaceted sensation that also includes pain, temperature, and stretch.

Current forms of tactile feedback fail to address the potentially harmful mechanical stimulations that could result in damage to cutaneous tissue, or, in this context, the prosthesis itself. We investigate the idea that a sensation of pain could benefit a prosthesis by introducing a sense of self-preservation and the ability to automatically release an object when pain is detected, similar to the functionality of a healthy reflex system. Pain serves multiple purposes in that it allows us to convey useful information about the environment to the amputee user while also preventing damage to the fingertips or cosmesis, a skin-like covering, of a prosthetic hand.

We postulate that the presence of both innocuous and noxious tactile information will help in creating more advanced and realistic prosthetic limbs. We developed a multilayered electronic dermis (e-dermis) and neuromorphic interface to provide, for the first time, tactile information to enable the perception of touch and pain in an upper limb amputee and prosthesis. Closed-loop feedback to the user through transcutaneous electrical nerve stimulation (TENS) elicits either an innocuous or painful sensation in the phantom hand based on the area of activation on the prosthesis. We show the use of TENS for producing sensations of comfortable and painful activation in regions of a transhumeral amputee's phantom hand (Fig. 1). Furthermore, we identify unique features of peripheral nerve stimulation, specifically pulse width and frequency, that play key roles in providing both innocuous and noxious tactile feedback. Quantifying the differences in perception of sensory feedback, specifically innocuous and noxious sensations, adds dimensionality and breadth to the type and amount of information that can be transmitted to an upper limb amputee. Finally, we demonstrate the ability of the prosthesis and the user to differentiate between safe (innocuous) and painful (noxious) mechanical tactile sensations during grasping and appropriately react using a prosthesis reflex, modeled as a polysynaptic withdrawal reflex, to prevent damage and further pain.

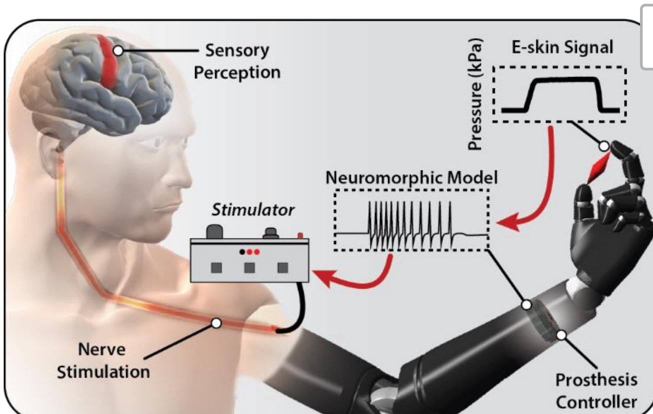

Fig. 1. Prosthesis system diagram. Tactile information from object grasping is transformed into a neuromorphic signal through the prosthesis controller. The neuromorphic signal is used to stimulate the peripheral nerves of an amputee subject to elicit sensory perception of touch and pain.

Results

Biologically inspired electronic dermis (e-dermis)

Mechanoreceptors in the human body are uniquely structured within the dermis and, in the case of Meissner corpuscles (RA1) and Merkel cells (SA1), lie close to the epidermis boundary *(1)*. RA1 receptors are often found in the dermal papillae, which lend to the Meissner corpuscles' ability to detect movement across the skin, and SA1 receptors tend to organize at the base of the epidermis. However, in glabrous skin the HTMR free nerve endings extend into the epidermis (i.e. the outermost layer of skin) *(1)*. We used this natural layering of tactile receptors to guide the multilayered approach of our e-dermis (Fig. 2A) to create sensing elements to capture signals analogous to those detected by mechanoreceptors (dermal) and nociceptors (epidermal) in healthy glabrous skin (Fig. 2B). The sensor was designed using a piezoresistive (Eeonyx, Pinole, USA) and conductive fabrics (LessEMF,

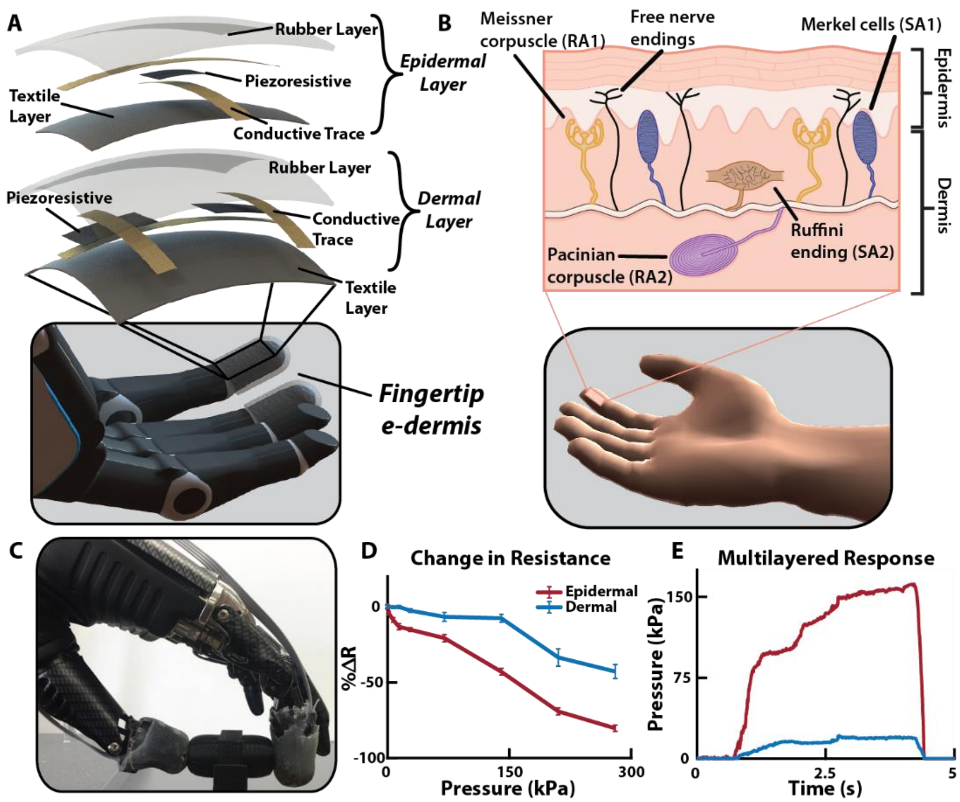

Fig. 2. Multilayered e-dermis design and characterization. (**A**) The multilayered e-dermis is made up of conductive and piezoresistive textiles encased in rubber. A dermal layer of two piezoresistive sensing elements are separated from the epidermal layer, which has one piezoresistive sensing element, with a 1 mm layer of silicone rubber. The e-dermis was fabricated to fit over the fingertip of a prosthetic hand. (**B**) The natural layering of mechanorecptors in healthy glabrous skin makes use of both rapidly adapting (RA) and slowly adapting (SA) recpetors to encode the complex properties of touch. Also present in the skin are free nerve endings (nociceptors) that are primarily responsible for conveying the sensation of pain in the fingertips. (**C**) The prosthesis with e-dermis fingertip sensors grasps an object. (**D**) The multilayered design of the e-dermis allows for a top sensing layer that is more sensitive compared to the bottom layer. The top sensing layer has a larger change in resistance compared to the bottom layer. Error bars are present but are so small that they are not visible. (**E**) Differences in sensing layer outputs are captured during object grasping and can be used for adding dimensionality to the tactile signal.

Latham, USA) to measure applied pressure on the surface of the e-dermis. A 1 mm rubber layer (Dragon Skin 10, Smooth-On, Easton, USA) between the artificial epidermal (top) and dermal (bottom) sensing elements provides skin-like compliance and distributes loads during grasping. There are 3 tactile pixels, or taxels, with a combined sensing area of approximately 1.5 cm^2 in each fingertip sensor. The sensor layering resulted in variation of the e-dermis output during loading (Fig. 2C). The change in resistance in the tactile sensor was greater for the epidermal layer, enabling higher sensitivity. During grasping of an object, the e-dermis exhibited differences between the sensing layers behavior, which can be used for extracting additional tactile information such as pressure distribution and object curvature (Fig. 2D-E).

Touch and pain perception

To provide sensory feedback, we used targeted TENS to extensively map and understand the perception of a transhumeral amputee's phantom limb during sensory feedback, a method we previously demonstrated in multiple subjects *(25)*. Although the subject did not undergo any targeted muscle or sensory reinnervation during surgery, there was a natural regrowth of peripheral nerves into the remaining muscles, soft tissue, and skin around the amputation. The median and ulnar nerves were identified on the amputee's left residual limb and targeted for noninvasive electrical stimulation because these nerves innervated relevant areas of the phantom hand. The subject received more than 25 hours of sensory mapping in addition to over 150 trials of sensory stimulation experiments to quantify the perceptual qualities of the stimulation. Extensive mapping of the residual limb showed localized activation of the amputee's phantom hand (Fig. 3A).

The subject identified multiple unique regions of activation in his phantom hand from the electrical stimulation. The subject did not report any sensory activation of his residual limb at the stimulation sites, indicating that all perceived sensation occurred in his phantom hand. Psychophysical experiments showed the subject's perception of changes in stimulation pulse width and frequency on his median and ulnar nerves (Fig. 3B-C). In general, the stimulation was perceived primarily as a pressure with some sensations of electrical tingling (paresthesia) (Fig. 3D). Stability of the subject's sensory activation (fig. S1) and stimulation perceptual thresholds (fig. S2) were tracked over several months in his thumb and index fingers (median nerve) as well as his pinky finger (ulnar nerve).

For the first time, sensory feedback of noxious tactile stimuli was delivered using TENS to an amputee and the perception quantified. Our psychophysical experiments show that changes in both stimulation frequency and pulse width influences the perception of painful tactile sensations in the phantom hand (Fig. 3E). The relative discomfort of the tactile sensation was reported by the user on a modified comfort scale ranging from -1 (pleasant) to 10 (very intense, disabling pain that dominates the senses) (table S1). In this experiment, the highest perceived pain was rated as a 3, which corresponded to uncomfortable but tolerable pain. The most painful sensations were perceived at relatively low frequencies between 10 and 20 Hz and at higher amplitudes. Higher frequency stimulation tends towards more pleasant tactile sensations, which is contrary to what might be expected *(29)*. In addition, very low frequencies generally resulted in innocuous activation of the phantom hand whereas frequency patterns that are closer to the discrete detection boundary (15 – 30 Hz) resulted in more noxious sensations in the activated region. We used electroencephalography (EEG) signals to localize and obtain an affirmation of the stimulus associated pain perception. The stimulation caused activation in contralateral somatosensory regions of the amputee's brain, which corresponded to his left hand (Fig.

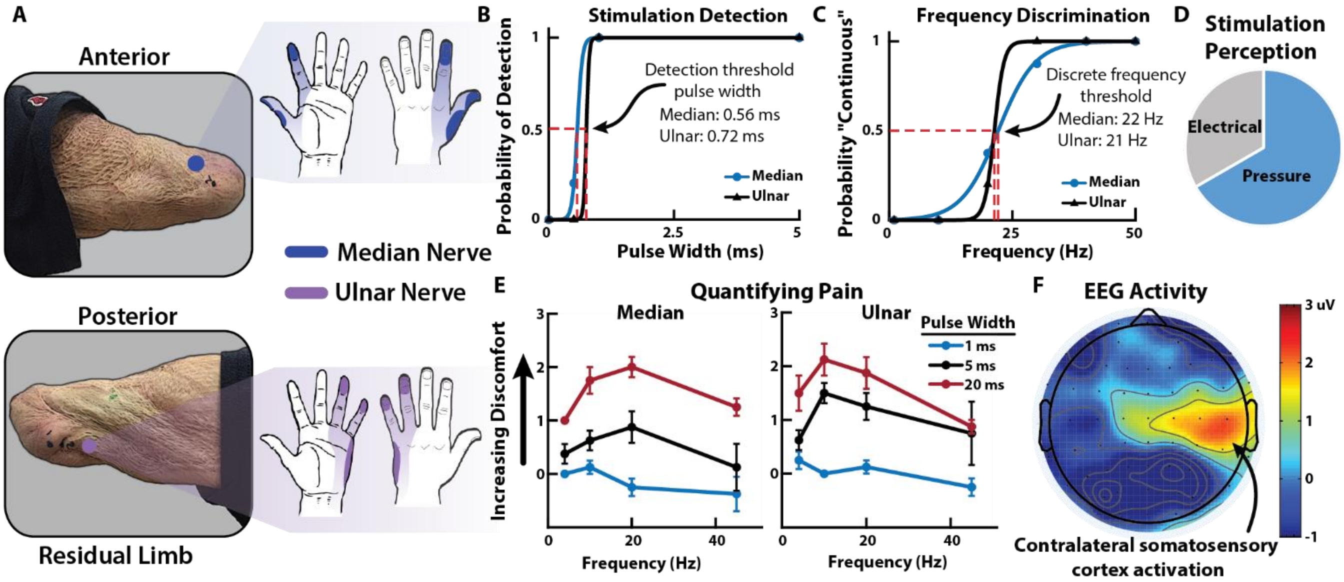

Fig. 3. Sensory feedback and perception. (**A**) Median and ulnar nerve sites on the residual limb of the amputee subject and the corresponding regions of activation in the left phantom hand due to TENS. (**B**) Psychophysical experiments quantify the perception of the nerve stimulation including detection and (**C**) discrete frequency discrimination thresholds. In both cases the stimulation amplitude was held at 1.4 mA. (**D**) The perception of the nerve stimulation was largely a tactile pressure on the activated sites of the phantom hand although sensations of electrical tingling also occured. (**E**) The quantification of pain from nerve stimulation shows that the most noxious sensation is percevied at higher stimulation pulse widths but also in the 10 – 20 Hz stimulation range. (**F**) Contralateral somatosensory cortex activation during nerve stimulation shows relevant cortical representation of sensory perception in the amputee subject (movie S1).

3F) *(30)*. EEG activation during stimulation is significantly higher ($p < 0.05$) than baseline activity, confirming the perceived phantom hand activation experienced by the user (fig. S3, movie S1).

Neuromorphic transduction

As mentioned previously, a neuromorphic system attempts to mimic behavior found in the nervous system. Based on the results from the sensory mapping of an amputee subject, the neuromorphic representation of the tactile signal was developed to enable the sensation of both touch and pain. To enable direct sensory feedback to an amputee through peripheral nerve stimulation, the e-dermis signal was transformed from a pressure signal into a biologically relevant signal using a neuromorphic model. The aim for the neuromorphic model was to capture elements of our actual neural system, in this case to represent the neural equivalent of a tactile signal for feedback to an amputee. To implement the biological activity from tactile receptors, namely the spiking response in the peripheral nerves due to a tactile event, we utilized the Izhikevich model of spiking neurons *(31)*, which provides a neuron modeling framework based on known neural dynamics while maintaining computational efficiency and easily allowing for different neuron behaviors from parameter adjustments. The Izhikevich model has been used in previous work for providing tactile feedback to amputees through nerve stimulation *(27)*. Mechanoreceptor and nociceptor models produced receptor-specific outputs, in terms of neuron voltage, based on the measured pressure signal on the prosthesis fingertips. The mechanoreceptor model combined characteristics of SA and RA receptors through the regular and fast spiking Izhikevich neurons, respectively, to convey more pleasant tactile feedback to the amputee. The nociceptor model utilized fast spiking Izhikevich neuron dynamics to mimic behavior of the free nerve endings.

When an object was grasped by the prosthesis, a higher number of active taxels indicated a larger distribution of the pressure on the fingertip, which was conveyed in the neuromorphic transduction as an innocuous (i.e. non-painful) tactile sensation. Changes in the tactile signal were captured in the neuromorphic transduction by changes in stimulation frequency and pulse width to correspond to the appropriate perceived levels of touch or pain during sensory feedback. Based on the results from the psychophysical experiments and the quantification of pain, the perception of noxious tactile feedback was achieved through the nociceptor model (see Materials and Methods).

To demonstrate the neuromorphic representation of a tactile signal, three different objects were used, each of equal width but varying curvature, to elicit different types of tactile perception in the prosthesis during grasping (Fig. 4A). The objects follow a power law shape where the radius of curvature (R_c) was modified using the power law exponent n, which ranges between 0 and 1 and effectively defines the sharpness of the objects (see Materials and Methods). The power law exponents used were ¼, ½, and 1 and correspond to Object 1, Object 2, and Object 3, respectively. The response of the fingertip taxels during object loading captured differences in object curvature based on the relative activation of all sensing elements (Fig. 4B-C, movie S2). As expected, the epidermal layer was the most activated taxel during loading and absorbed the largest pressure. The sharp curvature of

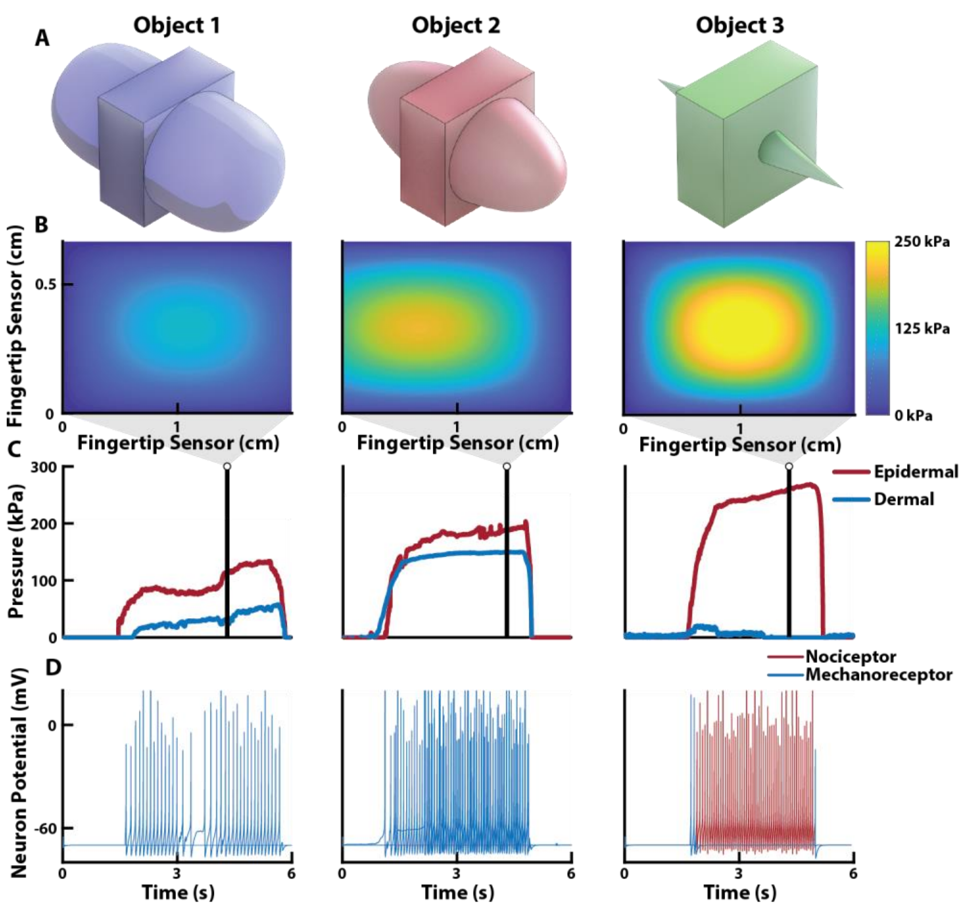

Fig. 4. E-dermis and neuromorphic tactile response from different objects. (**A**) Three different objects, with equal width but varying curvature, are used to elicit tactile responses from the multilayered e-dermis. (**B**) The pressure heatmap from the fingertip sensor on a prosthetic hand during grasping of each object and (**C**) the corresponding pressure profile for each of the sensing layers. (**D**) The pressure profiles are converted directly to the input current, *I*, for the Izhikevich neuron model for sensory feedback to the amputee user. Note the highly localized pressure during the grasping of Object 3 and the resulting nociceptor neuromorphic stimulation pattern, which is realized through changes in both stimulation pulse width and the neuromorphic model parameters.

Object 3 produced a highly localized pressure source on the epidermal layer of the e-dermis, which elicited a more painful sensation in the phantom hand of the amputee through the nociceptor neuromorphic stimulation model (Fig. 4D).

Prosthesis tactile perception and pain reflex

As an extension of the body, a prosthetic hand should exhibit similar behavior and functionality of a healthy hand. The perception of both innocuous touch and pain are valuable at both the local (i.e. the prosthetic hand) and the global (i.e. the user) levels. At the local level, a reflex behavior from the prosthesis to open when pain is detected can help prevent unintended damage to the hand or cosmesis. To demonstrate a local closed-loop pain reflex, a prosthetic hand, with a multilayered e-dermis on the thumb and index finger, grasped, held, and released one of the previously described objects (Fig. 5A-5C). The sensor signals were used as feedback to the embedded prosthesis controller to enable differentiation of the various objects and determine pain. We used pressure distribution (Fig. 6A), contact rate (Fig. 6B), and the number of activated sensing elements per finger (Fig. 6C) as input features in a linear discriminant analysis (LDA) algorithm for object detection.

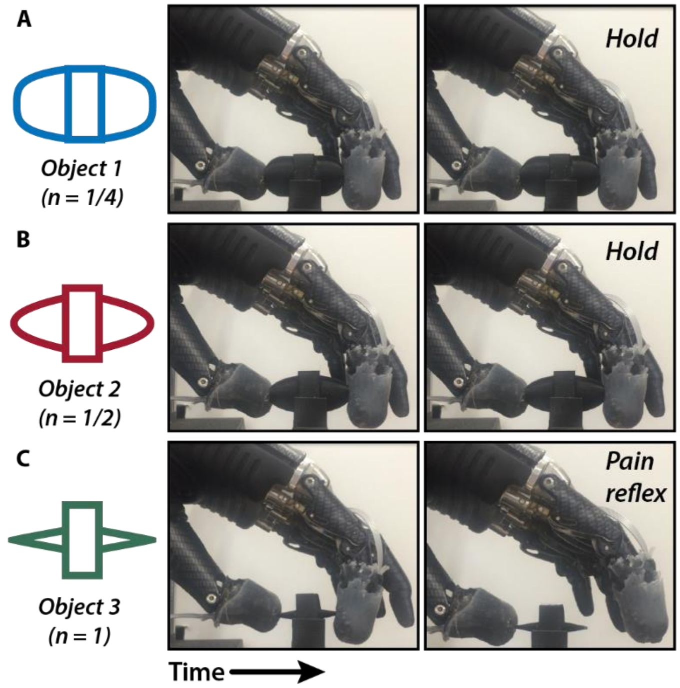

Fig. 5. Prosthesis grasping and control. To demonstrate the ability of the prosthesis to determine safe (innocuous) or unsafe (painful) objects, we performed the pain detection task (PDT). The objects are (**A**) Object 1, (**B**) Object 2, and (**C**) Object 3, each of which are defined by their curvature. In the case of a painful object (Object 3), the prosthesis detects the sharp pressure and releases its grip through its pain reflex (movie S3).

In the online Pain Detection Task (PDT), the prosthesis grabs, holds, and releases an object (movie S3). In this work, the curvature of Object 3 was assumed to be considered painful during grasping. When pain was detected, a prosthesis pain reflex caused the hand to open, releasing the object. Results showed the prosthesis' ability to reliably detect which object is

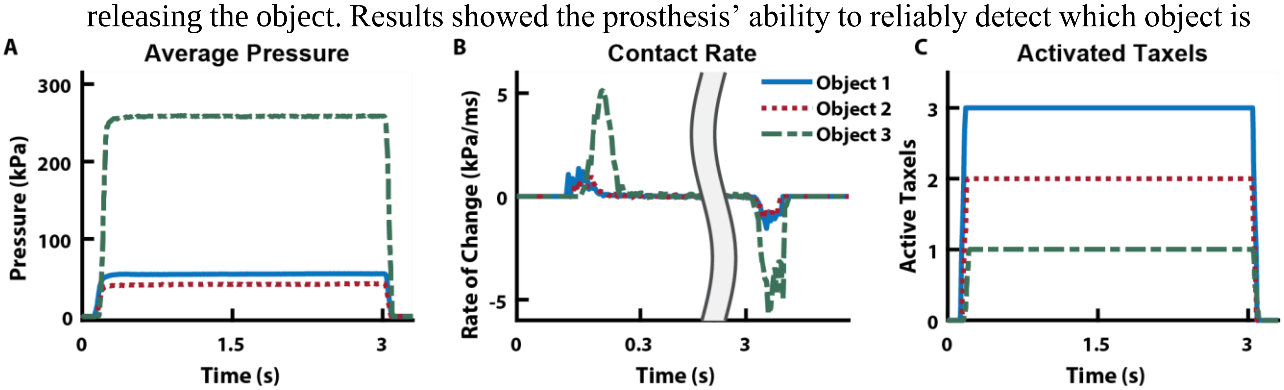

Fig. 6. Tactile features for prosthesis perception. To determine which object is being touched during grasping, we implemented LDA to discriminate between the independent classes. As input features into the algorithm, we used (**A**) sensor pressure values, (**B**) the rate of change of the pressure signal, and (**C**) the number of active sensing elements during loading.

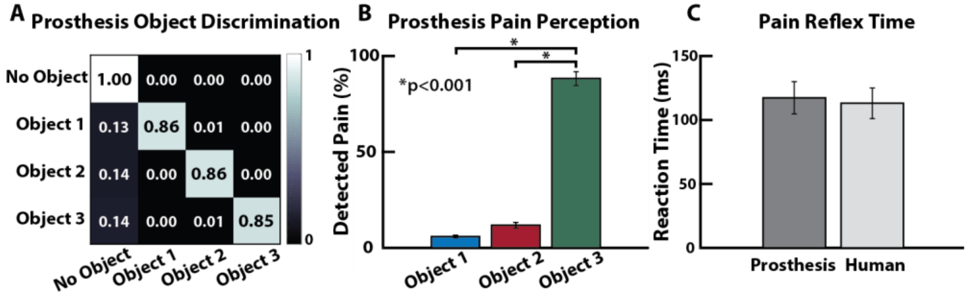

Fig. 7. Real-time prosthesis pain perception. We implemented this linear classification method in the online PDT. (**A**) shows the classifier's accuracy across the various conditions and (**B**) shows the percentage of trials where the prosthesis perceived pain during grasping. Note that the high percentage of detected pain during the PDT for Object 3. (**C**) We also used the rate of change of the pressure signal to precisely determine object contact and release. Using previously published data from pain reflex time in healthy adults *(32)*, we show the similarity between a prosthesis and human reflex to pain.

being grasped, as well as the absence of an object during grasping (Fig. 7A). The prosthesis had a high likelihood of perceiving pain while grasping Object 3 and a significantly less likelihood of perceiving pain for Objects 2 and 1 ($p < 0.001$) (Fig. 7B). The reaction time for the prosthesis to complete a reflex after perceiving pain was recorded and was similar to reaction times in healthy humans from previously published data *(32)* (Fig. 7C).

User tactile perception

With the added ability to perceive both innocuous and noxious tactile sensations in a single stimulation modality, an amputee user can, for the first time, utilize more realistic tactile sensations to discriminate between objects with a large or small (sharp) radius of curvature. The subject demonstrated his ability to perceive both innocuous and noxious tactile sensations by performing several discrimination tasks with a prosthetic hand. The neuromorphic tactile signal was passed from the prosthesis controller directly to the stimulator to provide sensory feedback to the amputee. The subject could reliably detect, with perfect accuracy, which of the fingers of the prosthesis were being loaded (Fig. 8A). The subject also received sensory feedback from varying levels of pressure applied to the prosthetic fingers. A light (< 100 kPa), medium (< 200 kPa), or hard (> 200 kPa) touch presented to the prosthesis was translated to the peripheral nerves of the subject using the neuromorphic representation of touch (figs. S4-S5). To demonstrate the ability of the prosthesis and user to perceive differences in object shape through variation in the comfort levels of sensory feedback, each of the three objects were presented to the prosthesis. Sensory feedback to the thumb and index finger regions of the phantom hand enabled the subject to perceive variations in the object curvatures, which was realized through changes in perceived comfort of the sensation. The results show an inversely proportional relationship between the radius of curvature of an object and the perceived discomfort of the tactile feedback (Fig. 8B). In addition to being able to perceive variation in sharpness of the objects as conveyed by the discomfort in the neuromorphic tactile feedback, the subject was able to reliably differentiate between the three objects with high accuracy (Fig. 8C). Finally, the subject performed an object grasping task with his prosthesis where he picked up and moved one of the three objects (movie S4). The prosthesis pain reflex control was implemented during the grasping task, which resulted in the prosthesis automatically releasing an object when pain was detected. During actual amputee use, the prosthesis pain reflex registered over half of the Object 3 movements as painful, significantly more than for the other objects ($p < 0.05$) (Fig. 8D).

Responses from subjective surveys of the perception of the sensory stimulation show that the subject felt as if the tactile sensations were coming directly from his phantom hand. In addition, the subject stated that he could clearly feel the touch of objects on the prosthetic hand and that it seemed that the objects themselves were the cause of the touch sensations that he was experiencing during the experiments (table S2).

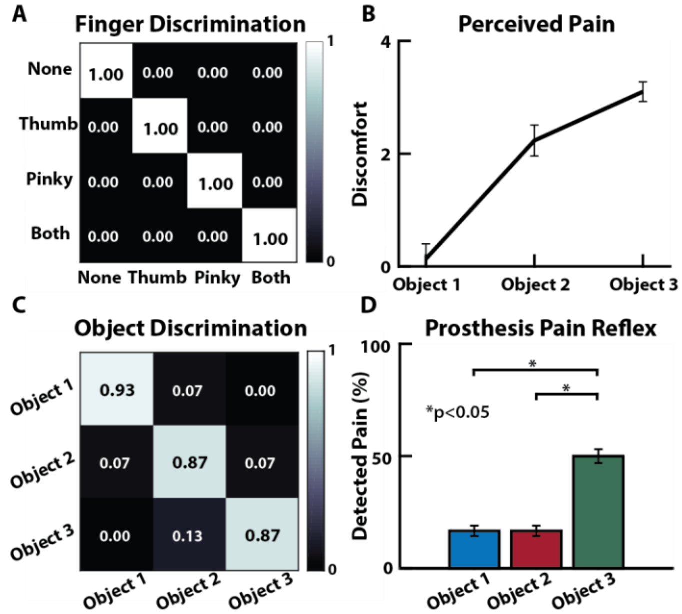

Fig. 8. Innocuous (mechanoreception) and noxious (nociception) prosthesis sensing and discrimination in an amputee. (**A**) The amputee subject could discriminate which region of his phantom hand was activated, if at all. (**B**) Perception of pain increases with decreasing radius of curvature (i.e. increase in sharpness) for the objects presented to the prosthetic hand. (**C**) Discrimination accuracy shows the subject's ability to reliably identify each object presented to the prosthesis based purely on the sensory feedback from the neuromorphic stimulation. (**D**) Results from the PDT during user controlled movements, with pain reflex enabled.

Discussion

Perceiving touch and pain

Being able to quantify the perception of innocuous and noxious stimuli for tactile feedback in amputees is valuable in that it enables the replacement of a key and extremely valuable piece of sensory information: pain. Not only does pain play a role in providing tactile context about the type of object being manipulated, but it also acts as a mechanism for protecting healthy tissue and receptors in the body. One could argue that this protective mechanism is not necessary in a prosthesis because it is merely an external tool or piece of hardware to an amputee user. We postulate to the contrary in that being able to capture noxious stimuli is more valuable to a prosthesis because it does not possess the same self-healing characteristics found in healthy human skin, although recent research has shown self-healing materials that could be used for future prosthetic limbs *(14, 33)*. To enable an artificial sense of self-preservation, a noxious tactile signal is useful for the prosthesis to ensure it does not exceed the limits of a cosmetic covering or the hand itself. As prosthetic limbs become more sophisticated and sensory feedback becomes more ubiquitous, there will be a need to increase not just the resolution of tactile information but also the amount of useful information being passed to the user. We have identified how changing stimulation pulse width and frequencies enables a spectrum of tactile sensation that captures both innocuous and noxious perceptions in a single stimulation modality.

The results from the PDT showed the ability of the prosthesis to detect pain and reflex to release the object. Object 3 was overwhelmingly detected as painful, due to its sharp curvature (Fig. 7B). The high success rate for detecting and preventing pain for the benchtop PDT is likely due to the controlled nature of the prosthesis grip. The likelihood of detecting Object 3 as painful decreased and the chances of pain being detected for the other objects increased during the PDT with a user controlled prosthesis (Fig. 8D); however, pain detection and reflex were still significantly more likely for Object 3 ($p < 0.05$). This shift in pain detection is likely due to the amputee subject's freedom to pick up the objects with his prosthesis in any way he chose. The variability in grasping orientation and approach for each trial resulted in more instances where Object 3 was not perceived as painful by the prosthesis. The ability to handle objects in different positions and orientations raises an interesting point in that the amount of pain produced is not an inherent property of an object, rather it is dependent on the way in which it is grasped. A sharp edge may still be safely manipulated without pain if the pressure on the skin does not exceed the threshold for pain. To reliably encode both touch and pain for prostheses, tactile signals should be analyzed in terms of pressure as opposed to grip force.

Another major implication of this work is in the discovery of the perceived noxious and innocuous tactile sensations during transcutaneous electrical nerve stimulation of peripheral afferents. One might assume that an increase in discomfort would be associated with an increase in delivered charge; however, we found that the most painful sensations during tactile feedback to an amputee delivered through TENS were primarily dictated by an increase in stimulation pulse width as well as stimulation frequency. Specifically, frequencies that were near the discrete vs continuous detection boundary (15 – 30 Hz) were perceived as more painful than higher frequencies. At the time of writing, this is the first time that perceived discomfort of noxious stimuli from peripheral nerve stimulation is formally quantified. Furthermore, this is the first demonstration of real-time discrimination between object curvature based purely on perceived discomfort in tactile feedback, which was associated with sharpness of the objects by the amputee subject.

Neuromorphic touch

The ability of an amputee to discriminate objects, specifically those that cause pain, is rooted in the neuromorphic tactile transduction and corresponding nerve stimulation. The psychophysical results illuminate the unique stimulation paradigms necessary to elicit tactile sensations that correspond to both mechanoreceptors and nociceptors in the phantom hand of an amputee.

More sophisticated neuron models exist and could be used to capture behavior of individual receptors and transduction *(26)*; however, the limitation of hardware prevents the stimulation of individual afferent nerve fibers. The Izhikevich model is simplistic in its dynamics but still follows basic qualities of integrate-and-fire models with voltage non-linearity for spike generation and extremely low computational requirements, which allow for the creation of a wide variety of neuron behaviors *(31)*. The advantage of the neuromorphic representation of touch in our work is that we can transform signals from the multilayered e-dermis directly into the appropriate stimulation paradigm needed to elicit the desired sensory percepts in the amputee subject. Specifically, the combination of mechanoreceptor and nociceptor outputs enables the additional sensory dimensionality of touch while maintaining a single modality of feedback, both in physical location and stimulation type.

The limitation of this work is the small study sample. Although this work is a case study of a single amputee user, prev~~ious research has shown the viability of TENS as a usable form of sensory feedback for prosthetic limb users *(25)*; furthermore,~~ the extensive psychophysical experiments and stability of the results for this subject show promise that other amputees will experience a similar type of perception from TENS, albeit the psychophysics will likely have slight differences based on age and condition of the amputation. A major implication of this work is the idea that both innocuous and noxious stimuli touch can be conveyed using the same stimulation modality. In addition, we showed that it is not necessarily a large amount of injected charge into the peripheral nerves that elicits a painful sensation. Rather, a unique combination of stimulation pulse width and frequency at the discrete – continuous perception boundary appears to create the most noxious sensations. Further work would include additional amputee subjects who are willing to undergo nerve stimulation, sensory mapping, and psychophysical experiments to the quantify their perceived pain. Our findings have applications not only in prosthetic limb technology but in the field of robotic devices in general, especially devices that rely on tactile information or interactions with external objects. The overarching idea of capturing meaningful tactile information continues to become a reality as we can now incorporate both innocuous and noxious information in a single channel of stimulation. Whether it is used for sensory feedback or internal processing in a robot, the sense of touch and pain together enable a more complete perception of the workspace.

This study illustrates through demonstration in a prosthesis and amputee subject the ability to quantify and utilize tactile information that is represented by a neuromorphic interface as both mechanoreceptor and nociceptor signals. Through our demonstration of capturing and conveying a range of tactile signals, prostheses and robots can incorporate more complex components of touch, namely differentiating innocuous and noxious stimuli, to behave in a more realistic fashion. The sense of touch provides added benefit during manipulation in prostheses and robots, but the sense of pain enhances their capabilities by introducing a novel sense of self preservation and protection.

Materials and Methods

Objectives and study design

Our objectives were 1) to show that a prosthetic hand is capable of perceiving both the sense of touch and pain through innocuous and noxious tactile stimuli, respectively, and 2) to show that an amputee subject was capable of perceiving both the sense of touch and pain through targeted peripheral nerve stimulation using a neuromorphic model.

Subject recruitment

All experiments with human subjects were approved by the Johns Hopkins Medicine Institutional Review Board. The amputee subject was recruited from a previous study at Johns Hopkins University in Baltimore, MD. At the time of the experiments, the subject was a 29-year-old male with a bilateral amputation 5 years prior, due to tissue necrosis from septicemia. The subject has a transradial amputation of the right arm and a transhumeral amputation of the left arm. The left arm was used for all sensory feedback and controlling the prosthesis in this work. The subject consented to participate in all the experiments and to have images and recordings taken during the experiments used for publication and presentations. The experiments were performed on average of once every 2 weeks over a period of 3 months with follow up sessions after 5 and 12 months ~~when the subject visited the Neuroengineering & Biomedical Instrumentation Lab at Johns Hopkins University~~. EEG data was collected in one session over a period of 2 hours.

Sensory Feedback

The sensory feedback experiments consisted of TENS of the median, and ulnar nerves using monophasic square wave pulses. We performed mapping of the phantom hand using a 1 mm beryllium copper (BeCu) probe connected to an isolated current stimulator (DS3, Digitimer Ltd., UK). An amplitude of 0.8 mA and frequency of 2 – 4 Hz were used while mapping the phantom hand. Anatomical and ink markers were used, along with photographs of the subject’s limb, to map the areas of the residual limb to the phantom hand. For all other stimulation experiments, we used a 5 mm disposable Ag-Ag/Cl electrode. A 64-channel EEG cap with Ag-Ag/Cl electrodes (impedance < 10 kΩ) was used for the EEG experiment. The subject was seated and stimulation electrodes were placed on his median and ulnar nerves. Each site was stimulated individually for a period of 2 s followed by a 4 s delay with

25% jitter before the next stimulation. There was a total of 60 stimulation presentations with varying pulse width (1-20 ms) and frequencies (4-45 Hz) with an amplitude of 1.6 mA. A time window of 450 ms starting at 400 ms after stimulation was used to average EEG activity across trials and compared to baseline activity using methods similar to those in *(34)*.

Psychophysical Experiments

Psychophysical experiments were performed to quantify the perception of TENS on the median, radial, and ulnar nerves of the amputee subject. Experiments included sensitivity detection (varying pulse width at 20 Hz), detection of discrete versus continuous stimulation (varying frequency with pulse width of 5 ms), and scaled pain discrimination. For the pain discrimination experiment the subject used a discomfort scale that ranged from pleasant or enjoyable (-1) to no pain (0) to very intense pain (10) (table S1). Stimulation current amplitude was held at 2 mA while frequency and pulse width were modulated to quantify the effect of signal modulation on perception in the subject's phantom hand. Every electrical stimulation was presented as a 2 s burst with at least 5 s rest before the next stimulation. Experiments were conducted in blocks up to 5 min with a break up to 10 min between each block. Every stimulation condition was presented up to 10 times and at least 4 times. Psychometric functions were fit using a sigmoid link *(25)*.

E-dermis fabrication

The e-dermis was constructed from piezoresistive transducing fabric (Eeonyx, USA) placed between crossing conductive traces (stretch conductive fabric, LessEMF, USA), similar to the procedure described in previous work *(35)*. The piezoresistive material is pressure sensitive and decreases in resistance with increased loading. The intersection of the conductive traces created a sensing taxel, a tactile element. The top sensing layer was a 1 x 1 sensing array while the bottom sensing array was a 2 x 1 array (Fig. 2A). The piezoresistive and conductive fabrics were held in place by a fusible tricot fabric with heat activated adhesive. A 1 mm layer of silicone rubber (Dragon Skin 10, Smooth-On, USA) was poured between two sensing layers. After the intermediate rubber layer cured, the textile sensors were wrapped into the fingertip shape and a 2 mm layer of silicone rubber (Dragon Skin 10, Smooth-On, USA) was poured as an outer compliance and protection layer. The skin-like compliance of rubber on fingertip sensors is known to benefit prosthesis grasping *(20)*. The e-dermis was placed over the thumb, index, and pinky phalanges of a prosthetic hand (Fig. 1B). Each fingertip cuff contained 3 sensing elements and had a combined sensing area of approximately 1.5 cm^2 on the prosthesis' finger pad.

Prosthesis control

A bebionic™ prosthetic hand (Ottobock, Duderstadt, Germany) was used for the experiments. Prosthesis movement was controlled using a custom control board, with an ARM Cortex-M processor, developed by Infinite Biomedical Technologies (IBT) (Baltimore, USA). The board was used for interfacing with the prosthesis, reading in the sensor signals, controlling the constant current stimulator, and implementing the neuromorphic model. During the user controlled PDT, the amputee used his own prosthesis (fig. S6), a bebionic™ hand with Motion Control wrist and a UtahArm 3+ arm with elbow (Motion Control Inc, Salt Lake City, USA). The amputee controlled his prosthesis using a linear discriminant analysis (LDA) algorithm on an IBT control board for electromyography (EMG) pattern recognition. The electrodes within his socket were bipolar Ag-Ag/Cl EMG electrodes from IBT.

Neuromorphic models

We implemented artificial mechanoreceptor and nociceptor models to emulate natural tactile coding in the peripheral nerve. We tuned the model to match the known characterization of TENS in the amputee subject to elicit the appropriate sensation. Constant current was applied during stimulation and both pulse width and spiking frequency were modulated by the model. Higher grip force was linked to increased stimulation pulse width and frequency, which was perceived as increased intensity in the subject's phantom hand. Innocuous tactile stimuli resulted in shorter pulse widths (1 ms or 5 ms) whereas the noxious stimuli produced a longer pulse width (20 ms), a major contributor to the perception of pain through TENS as shown by the results. To create the sensation of pain, we varied the parameters of the model in real-time based on the output of the e-dermis. We converted the e-dermis output to neural spikes in real-time with a C++ implementation of the Izhikevich neuron framework *(31)* on the prosthesis control board. The neuromorphic mechanoreceptor model was implemented as a combination of SA and RA receptors modelled as regular and fast spiking neurons. The nociceptor model was made up of Aδ neurons, which were modeled as fast spiking neurons to elicit a painful sensation in the phantom hand. It should be noted that the fast spiking neuron model was perceived as noxious with an increase in pulse width, which allows us to use the same Izhikevich neuron for both mechanoreceptors and nociceptors. The e-dermis output was used as the input current, I, to the artificial neuron model. The evolution of the membrane potential v and the refractory variable u are described by Eqs. 1 and 2. When the membrane potential reaches the threshold v_{th} the artificial neuron spikes. The membrane potential was reset to c and the membrane recovery variable u was increased by a predetermined amount d (Eq. 3). The spiking output was used to directly control the TENS unit for sensory feedback.

$$\frac{dv}{dt} = Av^2 + Bv + C - u + \frac{I}{RC_m} \tag{1}$$

$$\frac{du}{dt} = a(bv - u) \tag{2}$$

$$if\ (v \geq v_{th}), then \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} \tag{3}$$

Because we are not directly stimulating individual afferents in the peripheral nerves we tuned the model to represent behavior of a population of neurons. The parameters used for the different receptor types were: $A = 0.04/\text{Vs}$; $B = 5/\text{s}$; $C = 140\ \text{V/s}$; $C_m = 1\ \text{F}$; $R = 1$; $b = 0.2/\text{s}$; $c = -65\ \text{mV}$; $d = 8\ \text{mV/s}$; $v_{th} = 30\ \text{mV}$; and

$$a = \begin{cases} 0.02/s, & Regular\ spiking\ (RS) \\ 0.01/s, & Fast\ spiking\ (FS) \end{cases}$$

It should be noted that R is dimensionless in this model. The fast spiking neurons fire with high frequency with little adaptation, similar to responses from nociceptors during intense, noxious stimuli *(7)*. In the model, fast spiking is represented by a very fast recovery (a). Values for the parameters were taken from *(27)* and *(31)*.

We limited the spiking frequency of the neuromorphic model to 40 Hz and 20 Hz for the mechanoreceptor and nociceptor models, respectively. The transition of the neuromorphic model from mechanoreceptors to nociceptors relies on the pressure measured at the fingertips of the prosthesis, the number of active sensing elements, and the standard deviation of the pressure signal across the active taxels. The prosthesis fingertip pressure (P) is used to determine the neuromorphic stimulation model for sensory feedback. Highly localized pressure above a threshold β triggers the FS model whereas the RS model is used in cases of more distributed fingertip pressure. The follow pseudocode explains the stimulation model is chosen, where $\beta = 150\ kPa$, *n* is the number of active taxels, and *pw* is the stimulation pulse width:

$$if\ (P \geq \beta\ \&\ n < 2), then\ \left(nociceptor\ (\mathrm{A}\delta)\ (FS{:}\ pw = 20\ ms)\right)$$

$$else\ if\ (P \geq \beta\ \&\ n = 2), then\ \left(mechanoreceptor\ (SA/RA)\ (FS{:}\ pw = 5\ ms)\right)$$

$$else\ \left(mechanoreceptor\ (SA/RA)\ (RS{:}\ pw = 1\ ms)\right)$$

Prosthesis pain reflex

To mimic biology, we modeled the prosthesis pain withdrawal as a polysynaptic reflex *(36, 37)* in the prosthesis hardware. In our model, the prosthesis controller was treated as the spinal cord for the polysynaptic reflex. The nociceptor signal was the input, *I(t)*, to an integrating interneuron Γ whose output $I_\Gamma(t)$ was the input to an alpha motor neuron, which triggered the withdrawal reflex through a prosthesis hand open command after ~100 ms of pain. Formally, both neurons can be modelled as leaky-integrate-and-fire with a synapse from the alpha motor neuron causing the reflex movement (Eqs. 4-5, fig. S7), similar to the EMG signals generated during a nociceptive reflex *(38)*.

$$Interneuron\ (\Gamma){:}\ \tau_m \frac{dv_\Gamma}{dt} = E + RI(t) - v_\Gamma(t) \qquad (4)$$

$$Alpha\ motor\ neuron\ (\alpha){:}\ \tau_m \frac{dv_\alpha}{dt} = E + RI_\Gamma(t) - v_\alpha(t) \qquad (5)$$

Both neurons had time constant $\tau_m = 10$ ms, resting potential $E = -60$ mV, membrane resistance $R = 20\ \Omega$, and a spiking threshold of $v_{th} = -40$ mV. The time step was 5 ms and the nociceptor signal was normalized, enveloped, and scaled by $\beta = 0.2$ mV. The prosthesis reflex parameters were chosen to trigger hand withdrawal after ~100 ms of pain to mimic the pain reflex in healthy humans *(32)*. Fingertip pressure, the rate of contact, and the number of active sensing elements on each fingertip were used as features for an LDA algorithm to detect the different objects. Object 3 was labeled as a painful object. A taxel was considered active if it measured a pressure greater than 10 kPa. The pattern recognition algorithm was trained using sensor data from 5 trials of prosthesis grasping for each object and validated on 10 different trials.

Object design and fabrication

We created 3 objects of equal size with varying edge curvatures, defined by the edge blend radius, using a Dimension 1200es 3D printer (Stratasys, USA). Each object has a width of 5 cm but differed in curvature. Each object's curvature followed a power law where the leading edge of the protrusions vary in blend radii and range from flat to sharp. The radius of curvature, R_c, of the leading edge can be modified by the body power law exponent, n where

$$R_c = \frac{1}{|nA\,(n-1)|}\left[x^{\frac{2(2-n)}{3}} + (nA)^2 x^{\frac{2(2n-1)}{3}}\right]^{\frac{2}{3}} \qquad (6)$$

A is the power law constant, which is a function of *n*, and *x* is the position along the Cartesian axis in physical space. The objects for this study were designed to maintain a constant width, *w* (fig. S8) to prevent the ability to discriminate between the objects based on overall width. The three objects used had a power law exponent, *n*, of ¼, ½, and 1 and were referred to as Object 1, Object 2, and Object 3, respectively. More details and explanation of power law shaped edges can be found in *(39, 40)*.

Experimental design

Finger discrimination: The multilayered e-dermis was placed over the thumb and pinky finger of the prosthesis. Activation of each fingertip sensor corresponded directly to nerve stimulation of the amputee subject in the corresponding sites of his phantom hand. The amputee subject was seated, and his vision was occluded. The experimenter pressed either the prosthetic thumb, pinky, both, or neither in a random order. Each condition was presented 8 times. The stimulation amplitude was 1.5 mA and 1.45 mA for the thumb and pinky sites on the amputee's residual limb, respectively. Next, the experimenter pressed the prosthetic thumb or pinky with either a light (< 100 kPa), medium (< 200 kPa), or hard (> 200 kPa) pressure (figs. S4-S5). Each force condition was presented 10 times in a random order for each finger. The experimenter practiced pressing the prosthetic fingertips at the different loads for 30 minutes before conducing the experiment with the amputee subject.

Object discrimination: Fingertip sensors were placed on the thumb and index finger of a stationary bebionic™ prosthetic hand. The amputee subject was seated, and his vision of the prosthesis was occluded. A stimulating electrode was placed over the region of his residual limb that corresponded to his thumb and index fingers on his phantom hand. The experimenter presented one of the 3 objects on the index finger of the prosthetic hand for several seconds. The subject responded with the perceived object as well as the perceived discomfort based on the tactile sensation. Each block consisted of up to 15 object presentations. The subject performed 3 blocks of this experiment. Each object was presented randomly within each block, and each object was presented the same number of times as the other objects. The subject visually inspected the individual objects before the experiment took place, but he was not given any sample stimulation of what each object would feel like. This was done to allow the subject to create his own expectation of perception of what each object should feel like if he were to receive sensory feedback on his phantom hand.

Pain Detection Task: In the benchtop PDT, the prosthesis was mounted on a stationary stand with the multilayered sensors on the thumb and index finger. The object was placed on a stand and the prosthesis grabbed the object using a closed precision pinch grip. Each object was presented to the prosthesis at least 15 times in a random order. For the user controlled PDT, the amputee subject used his prosthesis to pick up and move one of the three objects, mounted in a stand. Each object was presented at least 10 times. The instances of prosthesis reflex were recorded. The subject took a subjective survey at the end of the experiments (table S2).

Data collection

Each taxel of the multilayered e-dermis was connected to a voltage divider. Sensor data was collected by the customized prosthesis controller and sent through serial communication with a baud rate of 115,200 bps to MATLAB (MathWorks, USA) on a PC for further post-processing and plotting. Each sensing element in the e-dermis was sampled at 200 Hz. Responses from the psychophysical experiments were recorded using MATLAB and stored for processing and plotting. The prosthesis controller communicated with MATLAB through Bluetooth communication with a baud rate of 468,000 bps. 64 channel EEG data was recorded at 500 Hz by a SynAmp2 system (Neuroscan, UK) and processed in MATLAB using the EEGLab Toolbox (Swartz Center for Computational Neuroscience, UC San Diego, USA). EEG data was downsampled to 256 Hz and band-pass filtered between 0.5 to 40 Hz using a 6th order Chebyshev filter. Muscle artifacts were rejected by the Automatic

Artifact Rejection (AAR) blind source separation algorithm using canonical correlation approach. Independent Component Analysis (ICA) was performed for removal of the eye and remnant muscle artifacts to obtain noise-free EEG data. Results from data collected over multiple trials of the same experiment were averaged together. Statistical *p*-values were calculated using a one-tailed, two-sample t-test. Error bars represent the standard error of the mean, unless otherwise specified.

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Competing interests: L.E.O and N.V.T. are inventors on intellectual property regarding the multilayered e-dermis, which has been disclosed to Johns Hopkins University. N.V.T. is co-founder and R.R.K. is CEO of Infinite Biomedical Technologies. This relationship has been disclosed to and is managed by Johns Hopkins University. The other authors declare that they have no competing interests.

Data and materials availability: Contact L.E.O. or N.V.T for any questions regarding experimental raw data or the software. Data and software code can be made available by materials transfer agreement upon reasonable request.

SUPPLEMENTARY MATERIALS