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KEY CONSIDERATIONS IN DESIGNING A SOMATOSENSORY NEUROPROSTHESIS

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ABSTRACT

In recent years, a consensus has emerged that somatosensory feedback needs to be provided for upper limb neuroprostheses to be useful. An increasingly promising approach to sensory restoration is to electrically stimulate neurons along the somatosensory neuraxis to convey information about the state of the prosthetic limb and about contact with objects. To date, efforts towards artificial sensory feedback have consisted mainly of demonstrating that some sensory information could be conveyed using a small number of stimulation patterns, generally delivered through single electrodes. However impressive these achievements are, results from different studies are hard to compare, as each research team implements different stimulation patterns and tests the elicited sensations differently. A critical question is whether different stimulation strategies will generalize from contrived laboratory settings to activities of daily living. Here, we lay out some key specifications that an artificial somatosensory channel should meet, discuss how different approaches should be evaluated, and caution about looming challenges that the field of sensory restoration will face.

INTRODUCTION

The manipulation of objects relies critically on somatosensory signals from the hand (Johansson and Flanagan, 2009). Indeed, cutaneous and proprioceptive signals carry information about the shape, weight, size, and texture of objects grasped in the hand, about their motion relative to the skin, and about the forces we exert on them. Without these signals, our ability to grasp or manipulate objects would be severely impaired and, in fact, nearly abolished (Witney et al., 2004). Therefore, in order to be useful for patients (amputees or patients with tetraplegia), i.e. to restore manual dexterity, a neuroprosthesis must not only be able to generate accurate movements but also to provide online feedback about the consequences of these movements and about contact with objects. The recent development of anthropomorphic robotic arms and of algorithms to decode intended movements from muscle activation or directly from neuronal signals has opened the possibility that amputees or tetraplegic patients might achieve dexterous control of prostheses that rivals that of their able bodied counterparts (Collinger et al., 2013; Hochberg et al., 2012; Wodlinger et al., 2015). However, dexterous use of robotic hands will also necessitate sensory restoration. In light of this, efforts have been underway to develop approaches to convey somatosensory feedback (Bensmaia, 2015; Bensmaia and Miller, 2014; Flesher et al., 2016; Graczyk et al., 2016; Saal and Bensmaia, 2015). One family of approaches – sensory substitution – consists of applying mechanical stimuli, typically skin vibrations, to an intact and sensate patch of skin somewhere on the body and modulate the activation of these tactors according to the movements of the prosthesis and/or its contact with objects (Antfolk et al., 2013). While this approach achieves some success in laboratory settings with contrived experimental tests, it fails catastrophically as soon as subjects/patients divide their attention between hand use and other tasks, a common requirement during activities of daily living. The other family of approaches consists of activating, using electrical stimulation, the neuronal populations that would be activated if the limb and nervous system were intact. For amputees, somatosensory restoration involves interfacing with the nerve using chronically implanted multi-electrode arrays (Clark et al., 2014; Dhillon and Horch, 2005; Raspopovic et al., 2014; Tan et al., 2014). For tetraplegic patients, somatosensory feedback is conveyed by directly stimulating the brain, somewhere along the neuraxis from the brain stem through the somatosensory cortex (Bensmaia and Miller, 2014; Cushing, 1909; Dadarlat et al., 2015; Davis et al., 1998; Fitzsimmons et al., 2007; Kim et al., 2015; O'Doherty et al., 2009; O'Doherty et al., 2011; O'Doherty et al., 2012; Penfield and Boldrey, 1937; Richardson et al., 2016; Romo et al., 1998; Tabot et al., 2013). Besides restoring touch, this approach was also shown to be effective in decreasing or eliminating phantom limb pain (Horch et al., 2011; Rossini et al., 2010; Tan et al., 2014). Here, we examine some of the key considerations in designing approaches to conveying sensory feedback in upper-limb neuroprostheses.

SOMATOSENSATION IS FOR MANIPULATION, NOT EXPLORATION

Haptic exploration is commonly used to illustrate the importance of touch: we reach into our pockets where there are sundry items and, by touch, identify our keys, which we are then able to extract (Lederman and Klatzky, 1993). While this paradigmatic example highlights the ability of the somatic senses to convey information about object identity, this is not the most critical function of these senses; we typically rely on vision for exploration. Rather, as alluded to above, the key role of somatosensation is to guide our interactions with objects. When we reach for and grasp an object, we need precise information about the timing of contact with the object, information about what parts of the hand are touching it, how much pressure we are exerting on it (Figure 1) (Johansson and Flanagan, 2009). Somatosensory signals from the hand also indicate when the object is slipping from our grasp (Johansson and Westling, 1987; Srinivasan et al., 1990). Crucially, in the case of object manipulation, vision is a poor substitute for touch and our proficiency at object manipulation and grasping declines markedly in the absence of somatosensory feedback (Augurelle et al., 2003).

The sensory information required for object manipulation is different from, though overlapping with, that involved in object recognition. For example, tactile shape perception is relatively independent of stimulus amplitude. That is, we can perceive by touch the two-dimensional structure of a pattern – an edge or combination of edges – as long as it is not too faint (peri-threshold)(Bensmaia et al., 2006). In contrast, information about contact pressure is critical for object manipulation (Johansson and Westling, 1984).

Given the primary role of touch in object manipulation, assays of artificial touch must involve object manipulation. Indeed, a sensory encoding algorithm might fruitfully support texture recognition or navigation but might be completely ineffective for object manipulation because it fails to convey information about the forces exerted on or by the object, about its frictional properties, or about slip.

CORTICAL VERSUS PERIPHERAL INTERFACES

The somatosensory system involves multiple pathways, which play overlapping but complementary functional roles. The medial lemniscal pathway, which has received the most experimental attention, is the pathway that is most strongly implicated in conscious touch and proprioception. As discussed above, however, the main rationale for restoring somatosensation in neuroprostheses is to improve their dexterity. Restoration through cortical interfaces bypasses many pathways that are thought to play a key role in supporting motor behavior, for example spinal circuits (Schouenborg, 2008) or the cerebellum (Kawato et al., 2003; Nowak et al., 2007). In contrast, peripheral nerve interfaces allow for the engagement of all the somatosensory pathways, and may thus restore dexterity more effectively.

Even in the worst case scenario, cortical interfaces will relieve some of the burden that would otherwise be placed on the visual system to monitor the behavior of the limb. For example, patients will not have to watch their hands continuously while holding an object to ensure that it remains firmly in their grasp. To compensate for the bypassed circuits in cortical interfaces, the function of circuits that are bypassed may be implemented in the robotics of the limb (for example, by building in stretch reflexes and reflexive grip adjustments). Finally, plastic structural changes can occur at different levels along the neuraxis (see below). While stimulation at the level of the cortex might benefit (or suffer) from local plasticity, peripheral approaches will involve participation of all circuits along the neuraxis to the cortex and therefore provide room for plasticity at each level.

STIMULATION APPROACH MUST BE SCALABLE

The hand is a remarkably complex and sophisticated organ that can move in many different ways, comprising about 27 degrees of freedom. The human hand is innervated by tens of thousands of mechanoreceptive afferents, each of which conveys different (albeit overlapping) information about grasped objects. To convey proprioceptive information about the state of the hand would require about 27 different channels of information, each tracking one degree of freedom of joint movement. To completely restore touch would require thousands, or at least hundreds, of channels (Saal and Bensmaia, 2015). When designing a sensory encoding algorithm for use in a hand prosthesis, then, it is important to consider whether it will scale to accommodate the complexity of the hand.

Approaches might be limited in their scalability because of technical restrictions on the number of possible independent channels of information. For example, electrical interfaces with the brain may be limited by the fact that physiologically relevant stimulation currents spread and activate large pools of neurons (see below). Increasing the number of stimulation channels will not be useful beyond the point at which current delivered through one electrode spreads beyond the adjacent ones (unless approaches to steer current come to fruition) (Histed et al., 2009; Joucla et al., 2012).

Another more pernicious way in which approaches might not scale is if the resulting artificial sensory space cannot be learned (Sadtler et al., 2014). For example, suppose that stimulation of the nerve produces poorly localized paresthesias (a common occurrence). One might propose to signal movement of the fingers with stimulation through electrodes 1 through 5 and contact with the fingertips with stimulation through electrodes 6 through 10. One might further demonstrate that a subject can easily distinguish the sensations evoked by stimulation through each of the 10 electrodes. However, an adult patient may not be able to learn to associate each essentially meaningless tingling continuum with their corresponding meanings about the state of the hand and use this information fruitfully in guiding the manipulation of objects. If the resulting sensations are natural rather than paresthetic, trying to unlearn their original meanings to associate them with their new meaning might be even harder. One might make the case that the brain is a learning engine and any arbitrary space can be learned, no matter how complex. But there is no evidence that this is true beyond about 2 dimensions, and this case needs to be made *empirically*. Indeed, there is evidence to the contrary: In patients with peripheral nerve damage reconstructive surgery allows peripheral nerve fibers to reinnervate the hand and restore sensibility, but individual fibers will generally not reinnervate their original targets; while young patients are generally able to relearn the new innervation pattern and regain full tactile function, older patients are unable to, probably due to limited plasticity of the nervous system (Lundborg and Rosen, 2001).

One way to mitigate the problem of scalability when it comes to the learnability of the space is to exploit, to the extent possible, existing perceptual representations (Bensmaia, 2015; Saal and Bensmaia, 2015). Indeed, to the extent that we can reproduce the patterns of neuronal activation that would be produced with an intact limb and nervous system, the resulting percepts will be natural and the patient will not have to learn anything. Of course, given the current state of technology and of our understanding of the nervous system, we cannot reproduce completely natural patterns of neuronal activation. However, we might be able to leverage certain key principles of sensory representations in the development of our algorithms. For example, the systematic somatotopic organization of somatosensory cortex might be used to convey information about contact location, both in cortex (Tabot et al., 2013) and in the sensory nerves (Stewart, 2003). We might be able to reproduce the coarse dynamics of neuronal activation evoked during object manipulation by modulating the dynamics of stimulation (Saal and Bensmaia, 2015), in the hopes of evoking more natural percepts during grasping and restoring crucial cues about contact events (Cipriani et al., 2014). Finally, we might even be able to exploit the built in topographies of feature-selective representations to produce sensory experiences with specific qualities. For example, a subpopulation of neurons in S1 is strongly selective for the direction in which objects move across the skin (Pei et al., 2011). If stimulation of these neurons evokes percepts of tactile motion, perhaps this phenomenon can be exploited to convey information about objects moving across the prosthetic hand (Bensmaia, 2015; Bensmaia and Miller, 2014).

THE PROBLEM OF CORTICAL PLASTICITY

When a region of S1 loses its sensory input, for example through amputation of a limb, the deafferented neurons begin to respond to other parts of the body (Pons et al., 1991). Typically, the invading signals stem from body regions with adjacent S1 representations (in the case of limb amputation, the face or the trunk), or from body sites that are overused to compensate for the missing limb (Makin et al., 2013a; Philip and Frey, 2014). If the brain is so malleable, and the underlying neuronal representations change so dramatically, how important is it to understand the pre-injury representations? Does it make sense to try to exploit them in designing feedback algorithms?

The evidence suggests that the reorganization of S1 after deafferentation is not as dramatic as it might seem. First, invading signals from other body regions reflect the unmasking of lateral connections at the level of the cuneate nucleus (Kambi et al., 2014), rather than major structural and functional changes in deafferented cortex. Second, neural activity is evoked in the deafferented cortex during phantom hand "movements" (Makin et al., 2013b; Raffin et al., 2012). Third, electrical stimulation of deafferented limb regions of S1 in human amputees evokes sensations on the phantom limb rather than on the invading body regions (Ojemann and Silbergeld, 1995; Woolsey et al., 1979). Thus, while deafferented cortex can be excited by other body parts, downstream cortical regions still interpret this activation as originating from the missing or deafferented limb.

The question remains whether the functional properties of these neurons, whose somatotopic organization seems to be rather stable, change after deafferentation. For example, does tuning for tactile motion direction disappear a year post-injury? If so, feature-specific representations cannot be exploited to expand the repertoire of tactile sensations, as sketched out in the previous section. While refined through sensory experience, feature selectivity is driven in part by endogenous mechanisms of development (White et al., 2001), so it likely reflects structural properties of cortex that are not so easily undone.

In summary, then, sensory representations in S1 seem to be highly stable, even after chronic deafferentation. Thus, while exploiting native representations might not be necessary, the evidence suggests that it may be possible.

ADAPTATION

A universal property of sensory neurons is that their responses change during sustained stimulation. The most rudimentary form of adaptation is the progressive desensitization during prolonged activation. Adaptation plays an important role in adjusting the sensitivity of the sensory system to ambient stimulation levels, so that it can better respond to *changes* in stimulation (Wark et al., 2007). Without adaptation, sensory systems would be saturated in environments dominated by high-intensity stimuli and completely quiescent in environments consisting entirely of low-intensity stimuli. This form of adaptation plays a key role in our ability, for example, to see in ambient light that can span 8 orders of magnitude from starlight to sunlight. In touch, neuronal adaptation has been observed at all stages of the somatosensory hierarchy, from peripheral afferents (Bensmaia et al., 2005; Leung et al., 2005) to cortical neurons (Maravall et al., 2007) and is also reflected in tactile perception (Hollins et al., 1990; Ollerenshaw et al., 2014). Similarly, sustained electrical stimulation of neuronal tissue results in a desensitization of neurons to electrical stimulation (McCreery et al., 1997). In addition, direct stimulation of cortical neurons (Logothetis et al., 2010; Masse and Cook, 2010) activates both excitatory and inhibitory circuits and can lead to long-lasting depression. As a result, a perceptible stimulus can rapidly become indiscernible as a result of adaptation and the perceived magnitude of a constant electrical stimulus decreases over time.

In developing sensory encoding algorithms, then, it is important to (1) understand how the electrical stimulation applied to the neuronal tissue will desensitize it and (2) estimate the degree to which an intact nervous system would adapt given the level of stimulation experienced by the prosthesis (Figure 2). Indeed, if electrical stimulation adapts very rapidly, then it may be necessary to progressively increase the stimulation intensity to compensate for the adaptation. If electrical stimulation did not adapt, it would be desirable to decrease the gain of the stimulation in the presence of strong, sustained stimulation, to mimic the natural adaptation. To the degree that electrical adaptation does not match its mechanical counterpart, these two aspects of adaptation need to be reconciled. A biomimetic algorithm (Saal and Bensmaia, 2015) may lead to neuronal activation patterns that are sufficiently similar to their natural counterparts that the electrically induced adaptation matches its naturally induced counterpart, in both extent and time course, but this is very unlikely, given the very different modes of neuronal activation involved in natural and electrical stimulation (Bensmaia et al., 2005).

MOTOR DECODERS AND SENSORY FEEDBACK

One of the key milestones in the field of neuroprosthetics was the demonstration that intended movements could be decoded from the recorded responses of neurons in motor cortex (Bensmaia and Miller, 2014). Motor decoding has recently culminated in many degree-of-freedom control of an anthropomorphic robotic limb by a tetraplegic patient (Collinger et al., 2013). Most decoders are trained to infer the desired kinematics from recorded neuronal activity, a fruitful approach for controlling limb movements, and so placing the hand somewhere in three-dimensional space. Kinematic decoding has not achieved nearly the same success with individual finger movements, in part because of their much greater dimensionality. Another potentially serious problem, however, arises when we interact with an object, and after we have established contact with it: we do not “move” our fingers into it; rather, we exert forces onto it. In line with this, tactile signals (or their artificial counterparts in a neuroprosthesis) primarily convey information about the forces exerted on objects; it is not clear, therefore, how this force-related information could be used to guide kinematics-based control of the hand. This disconnect between the frame of reference of the control signal – kinematics – and that of the feedback signal –

dynamics – may require a significant rethinking of motor decoders. Attempts to build hybrid kinematic/dynamic decoders has been fraught with challenges (Bensmaia and Miller, 2014).

NEUROPROSTHETICS RESEARCH NEEDS TO GENERALIZE

Neuroprosthetics research often consists of demonstrating that a given neural interface can in principle convey useful information for hand control or object recognition. The research team shows that artificial percepts are evoked and that these percepts can be used to perform more or less artificial tasks designed by the investigative team. Because each team uses a different behavioral assay, comparing one approach to another is difficult or impossible. One might ask: How does the sensory information conveyed through electrical stimulation of the brain compare to that conveyed through electrical stimulation of the nerve? This comparison is not possible based on existing work.

For comparison to be possible, standard psychophysical paradigms must be applied to probe artificial sensation. Psychophysical paradigms have been honed over two centuries – from Weber and Fechner to Green and Swets to Stevens – to develop measures of the sensitivity, discriminability, and reliability of sensory percepts (Gescheider, 1997). Quantities like absolute thresholds, just noticeable differences, or power function exponents for magnitude functions can be compared across studies, subjects, and approaches (Kim et al., 2015). They can also be used to assess the quality of sensory restoration relative to the intact somatosensory system. Finally, these basic perceptual quantities can then be used to interpret the performance of the sensory encoding algorithms in more functional assays. For example, the inability to perform a given task may be a straightforward consequence of low acuity, which can be quantified using standard measures of acuity.

However, it is not sufficient to assess sensitivity and reliability of artificial percepts using classical psychophysical technique. One must also demonstrate that these percepts can be useful in functional tasks. While most studies do include a functional task or two, these tasks are often not of the right sort (exploration rather than object manipulation, e.g.), and they differ from study to study so the usefulness of the sensory percepts is difficult or impossible to compare across studies. As important as it is to assay the perceptual properties of artificial sensations using classical psychophysical measures, it is as important to assay their functional utility using standardized tests. Many behavioral tests are designed to provide a quantitative evaluation of sensory motor performance to assess the consequences of injury or disease (Jebsen et al., 1969; Penta et al., 1998). Again, standardized functional tests can draw on decades of data from healthy subjects to provide a baseline index of performance.

HARDWARE CONSIDERATIONS

As mentioned above, electrical interfaces can be applied anywhere along the neuraxis, from periphery to cortex, but most existing interfaces are with the nerve or with cortex.

Interfaces with the nerve either penetrate it (intra-fascicular) or stimulate it from the outside (Saal and Bensmaia, 2015). Critically, peripheral nerve interfaces confront a trade-off between selectivity and stability. On the one hand, to achieve high selectivity – that is, the capability to stimulate one or a few neurons at a time –, is important because each fiber conveys different and complementary information about contact events and grasped objects. Thus, the more fibers you can stimulate independently, the more closely natural patterns of neuronal activation can be approximated. Penetrating electrode arrays can in principle allow for the independent stimulation of individual afferents while stimulation through an extra-fascicular electrode activates a population of afferents. Computational models of tactile afferents can now achieve real time simulation of populations of afferents with millisecond precision (Saal et al., in revision), so the more stable, independent stimulation channels are available, the more natural the resulting artificial touch will be. On the other hand, implant stability is also critical for providing long-term sensory feedback. While much higher selectivity can be obtained through intra-fascicular implants (Davis et al., 2016; Dhillon and Horch, 2005; Raspopovic et al., 2014; Rossini et al., 2010), only extra-fascicular implants have exhibited stability for long periods of time (Tan et al., 2015; Tan et al., 2014).

Cortical interfaces face the same two challenges of selectivity and longevity but in different ways. Indeed, while stimulation of individual afferents can lead to a perceptual experience, stimulation of individual cortical neurons tends not to (although see (Houweling and Brecht, 2008)). Efforts to stimulate cortex thus typically involve the activation of hundreds or thousands of neurons through individual electrodes. As mentioned above, the bottleneck for selectivity is not simply determined by the density of stimulating electrodes, but also by the degree to which current spreads during stimulation. Indeed, to reliably evoke a percept requires stimulating currents that spread hundreds of microns across the neuronal tissue, so the spatial resolution of intracortical microstimulation is limited by this current spread more than by the spatial proximity of electrodes. A serious bottleneck for cortical interfaces is longevity (Bensmaia and Miller, 2014). The electrodes, the neuronal tissue around the electrodes, and the electrode/tissue interface degrade over time (Chen et al., 2014; Kane et al., 2013; McCreery et al., 2010; Prasad et al., 2012) and these changes have devastating effects on the ability to record neuronal activation to decode intended movements (Perge et al., 2013). However, sensitivity to microstimulation seems to be stable, at least under some circumstances (Callier et al., 2015; Parker et al., 2011), so the array technology is less of a limiting factor for the sensory component of cortical interfaces than it is the motor one.

Two other structures between the nerve and cortex – the cuneate nucleus and thalamus – could in principle be implanted with stimulating electrode arrays to restore touch. The types of arrays that are used for cortical interfaces can also be used for the cuneate nucleus (Richardson et al., 2016), but would face somewhat different challenges in terms of stability given differences in the biomechanics of the brainstem compared to cortex. For thalamus, deep brain stimulation (DBS) electrodes offer the benefit of years of experience in thousands of patients. Indeed, thalamic DBS is commonly used to treat multiple diseases involving movement disorders and/or chronic pain. DBS electrodes have been shown to be safe and stable (Haberler et al., 2000; Voges et al., 2007). Finally, thalamic stimulation has been shown to evoke localized tactile sensations (Heming et al., 2010; Weiss et al., 2009). However, they offer very limited selectivity given the low number of contacts and the relatively large contact area of the electrodes. Optimization of electrode design and stimulation parameters can improve selectivity (Howell et al., 2015), but current DBS technology is probably not well suited for prosthetics.

CONCLUSIONS

While upper limb neuroprosthetic devices have made impressive gains in functionality, both on the motor and sensory sides, the state-of-the-art is still far from achieving the dexterity of native human limbs, in part because the incorporation of sensory feedback is still in its infancy. To progress beyond proofs of principle and develop clinically viable upper-limb neuroprostheses will necessitate taking into consideration the neural basis and ecological functions of somatosensation and gauge the sensory and functional consequences of artificial somatosensation using time-tested and systematic approaches. The next decade is sure to bring remarkable advances in this exciting field and we may be on the brink of a new era in which nervous systems communicate directly and fluidly with machines.

FIGURES

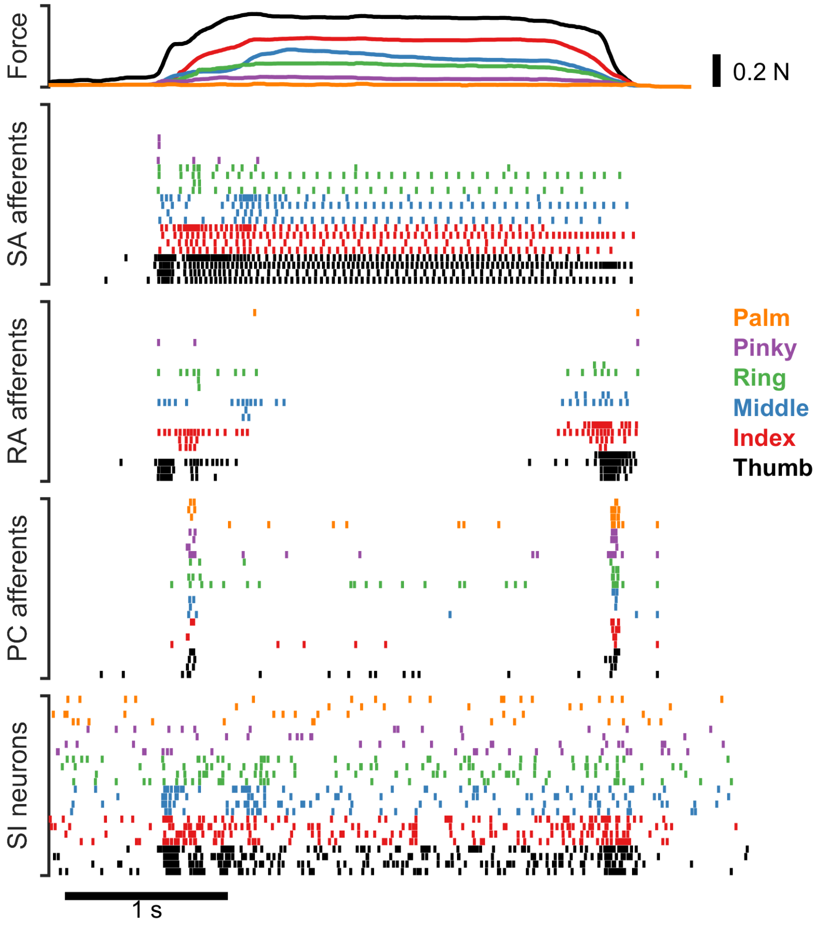

Figure 1. Simulated time course of forces and responses of peripheral and cortical neurons with receptive fields on the hand during object grasp and lift. When we grasp and lift an object, the hand experiences spatiotemporal deformations that lead to patterns of activation in the three populations of mechanoreceptive afferents. These patterns of activation convey information about contact with objects that is critical to our ability to grasp and manipulate them. Similarly, cortical neurons convey information about contact that contributes to our perception of objects grasped in the hand and supports our ability to interact with them.

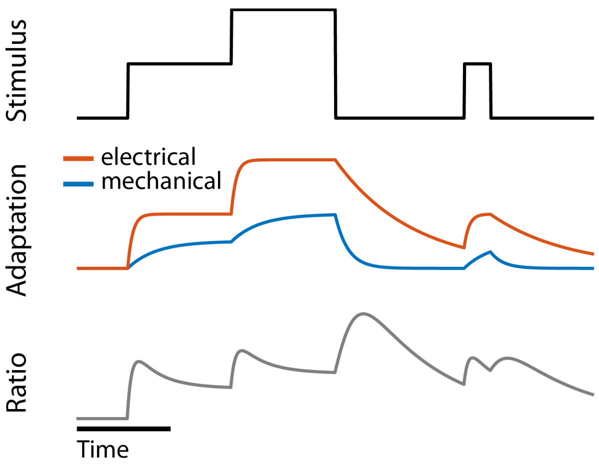

Figure 2. Illustration of the hypothetical time courses of sensory adaptation induced through electrical stimulation of neurons or through mechanical stimulation of the skin. A prolonged tactile or electrical stimulus (black trace) leads to neural adaptation, for example changes in threshold (colored traces). However, both the overall magnitude and the time course of mechanically (blue) and electrically (orange) induced adaptation are likely different. To reproduce natural patterns of adaptation will require that the stimulation gain be modulated according to the ratio between the expected levels of electrical and mechanical adaptation.

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