STABILITY OF SENSORY TOPOGRAPHIES IN ADULT SOMATOSENSORY CORTEX

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ABSTRACT

Textbooks teach us that the removal of sensory input to sensory cortex, e.g. following arm amputation, results in massive reorganisation in the adult brain. Here, we critically examine evidence for functional reorganisation of sensory cortical representations, focusing on the sequelae of arm amputation on somatosensory topographies. Based on literature from human and non-human primates, we conclude that the cortical representation of the limb remains remarkably stable despite the loss of its main peripheral input. Furthermore, the purportedly massive reorganisation results primarily from potentiation of new pathways in subcortical structures and does not produce novel functional sensory representations. We discuss the implications of the stability of sensory representations on the development of upper-limb neuroprostheses.

PLASTICITY IN SENSORY CORTICAL TOPOGRAPHIES

One of the key concepts in contemporary neuroscience is that experience shapes the central nervous system throughout life. The ability of the brain to adaptively change how it processes inputs based on new experience is termed "plasticity" and underlies our ability to mature, learn new skills, and recover from injury. Our current understanding of neuroplasticity has been moulded by the work of Hubel and Wiesel in the 1960's, who studied the visual cortex of cats following temporary occlusion of visual input from one eye [1-3]. They found that input loss to one eye in early development drives profound physiological and behavioural changes: Neurons in visual cortex normally devoted to the occluded eye respond to input from the non-occluded eye. Accordingly, when forced to rely on the previously occluded eye, the kittens showed profound visual impairments. This line of research demonstrated the brain's extraordinary capacity for change: Loss of primary input to a brain area does not lead to the abolishment of processing but rather to a reassignment of processing, resulting in increased functional representation of an alternative input. This process, termed cortical reorganisation, is perhaps the most extreme form of brain plasticity. According to these early studies, however, reorganisation is much more restricted in the adult brain: adult cats subjected to visual occlusion did not exhibit the same deficits and cortical changes as did kittens [3] (see refs. [4] and [5] for related evidence in monkeys and humans, see [6] for current debate on the adult's visual cortex capacity for reorganisation).

Perhaps the most striking example of the adult brain's capacity to reorganise comes from electrophysiological studies of primary somatosensory cortex (SI) after the loss of peripheral input (as a result of limb amputation, e.g.). A well-known characteristic of SI in intact individuals is the well-defined topographic map of the body – so-called somatotopic organisation – with neighbouring neurons responding to adjacent and overlapping regions of the body *[7]* (Figure 1A). Removal of input from a body part (due to amputation *[8]* or nerve transection *[9]*) results in changes in the somatotopic organisation, such that the representation of cortically adjacent body parts takes over the "freed up" brain territory (see *[10]* for a review of similar results from the barrel cortex of rodents). When input is lost from the entire hand and arm, for example, the

representation of the lower part of the face invades the cortical territory of the missing hand, resulting in massive reorganisation, sometimes spanning half of the sensory homunculus *[11,12]* (see *[13]* for review)(Figure 1B).

These observations have led to the conclusion that even the adult brain has the potential to reorganise under the right circumstances. Here, we examine the nature of this apparent reorganisation. Do the invading body representations benefit from this additional neuronal territory? What are the perceptual consequences of this reorganisation? What is its neural basis? We bring together behavioural, imaging, and neurophysiological studies investigating the consequences of limb amputation. We highlight evidence showing that the previously observed reorganization reflects the potentiation of new pathways but that the original pathways are to a large extent spared. We reach the conclusion that the reorganisation in SI does not result in novel functional sensory representations and that the original somatotopic organisation persists despite drastic sensory input loss in adulthood. The stability of sensory topographies has important implications for ongoing efforts to restore somatosensation in upper limb neuroprostheses.

FUNCTIONAL BENEFITS OF REORGANISATION?

If deafferented cortex begins to process a new patch of the sensory sheet (on the retina or the skin), one would expect that the additional cortical volume would lead to perceptual gains for this "invading" region (i.e. adaptive plasticity, [14,15]). For example, SI remapping following digit amputation results in increased representation of the neighbouring digits, which in turn should lead to increased acuity for these digits [8]. Such perceptual gains would imply that signals arising to the re-assigned area (e.g. missing digit territory) are processed normally in their new cortical home. To the best of our knowledge, however, direct perceptual gains due to input loss have not been conclusively established. For example, finger amputation in humans does not result in lower detection thresholds or improved spatial acuity on the remaining fingers [16]. Earlier reports for increased tactile acuity on the stump of amputees (see refs. [17,18]) have been subsequently challenged (see [16] for details). Other studies showing perceptual gains following temporary experimentally-induced input loss

emphasise the role of concurrent sensory input from non-affected body parts (e.g. [19,20]). In other words, previously recorded perceptual gains might be caused by behavioural adaptations, and not by deprivation-triggered reorganisation. Similarly, the popular notion that cross-modal reorganisation in the visual cortex of the blind contributes to heightened tactile abilities has been recently challenged (see [21] for review). Indeed, enhanced tactile perception in blind individuals can be explained by greater experience with or dependence on touch to guide interactions with objects [22]. Thus, reorganisation in adult SI does not seem to lead to any direct benefits in processing the invading sensory input. To establish such benefits would require causal evidence, for example by demonstrating perceptual consequences of disrupting local processing in deprived cortex [23] or inducing a novel sensory experience referred to the invading body region by artificially activating deprived cortex [24].

PHANTOM AND REFERRED SENSATIONS

If remapping in SI does not result in direct perceptual gains, are there any other functional consequences to SI remapping? In other words, are these invading signals behaviourally relevant? The most extensively documented and captivating consequence relates to distorted phantom sensations following amputation. Even decades after injury, amputees report a continued sensation of the limb that is no longer there. These phantom sensations can be as vivid and as natural as the perception of one's own body and span a range of qualities, including pressure, temperature, tingling, itch, and pain [25]. Phantom sensations can be commonly triggered through stimulation of the stump, which may simply reflect peripheral reinnervation (see below). However, a more striking phenomenon that implies SI reorganisation is when phantom sensations are evoked through stimulation of the face.

In a famous series of studies [26,27], three amputees reported experiencing precise and stable point-to-point correspondence between touch applied on their face and referred sensation perceived on the phantom hand (see [28,29] for similar reports). Importantly, the reported referred sensations from the face to the hand were topographically organised, such that neighbouring sites on the face elicited sensations

on neighbouring fingers (Figure 2A). These findings were interpreted as perceptual correlates of the face-driven activity in the limb representation that had been previously observed in monkeys [11]: If hand neurons in SI now respond to the face (Figure 1B), brain regions receiving input from the SI hand representation will interpret activation in this region as arising from the missing hand, resulting in dual sensations on the face and the phantom hand. Furthermore, the mismatch between the invading facial inputs and residual representation of the missing hand is thought to result in an "error" signal, interpreted by the brain as pain arising from the missing hand (phantom limb pain, [30,31]; see [32] for a critical review). Importantly, this phenomenology is consistent with the interpretation that reorganisation is taking place in cortex, since the cortical topography is predictive of the perceptual remapping. The hypothesis is that, following elimination of input from the limb, lateral projections from face to limb representations either sprout or become unmasked, leading to the observed reorganisation [33] (see [34] for the roles of the thalamus and brainstem in driving reorganisation).

Referred sensations following amputations received tremendous attention both in the scientific community and in the popular media [35] but some of the key findings should be interpreted with caution. Indeed, subsequent studies that used more objective approaches to characterize referred sensations found that these could be triggered by touch applied on multiple body parts (e.g. feet, chest and neck; [36,37]) whose representations are not cortical neighbours of the hand area (Figure 2B). Referred sensation were even reported when touch was applied to body parts contralateral to the missing hand. Moreover, the mapping from trigger region to referred region was typically not consistent across amputees. These findings thus generally weakened the hypothesis that referred sensations result from SI reorganisation since referred sensations do not respect cortical topographies.

REORGANISATION IN HUMANS

Results from neuroimaging studies in human amputees further challenge the view that neighbouring cortical representations invade the deafferented ones. While the lip representation encroaches somewhat on the limb representation following

amputation, it does not invade it altogether [38-40] in contrast to what is observed in monkeys [11,12]. Rather, the deafferented territory begins to respond to body regions that the amputees overuse to supplement lost hand function (mainly the intact hand), resulting in a highly idiosyncratic remapping [41,42] which, again, does not necessarily involve adjacent representations in SI. A possible explanation for the difference in reorganisation observed in humans and monkeys is that disabled monkeys (following long-term deafferentation) may use their mouths to compensate for the lost limb function more than humans do. In any case, the evidence suggests that, while cortical neighbours sometimes invade deafferented cortex, this is far from the rule. The most straightforward prediction of the cortical reorganisation hypothesis – that it will be dictated by cortical topographies – is thus violated.

PERSISTENT REPRESENTATION DESPITE INPUT LOSS

A further challenge to the notion that reorganisation causes functional consequences is provided by the perceptual correlates of nerve stimulation. Numerous studies have shown that, when the residual (injured) nerve is electrically stimulated, either directly [43,44] or transcutaneously [45,46], individuals experience the evoked somatosensory percepts as vividly and clearly arising from their phantom hand (Figure 2C), and not from other body parts such as the face. In fact, stimulation of the nerve can be used to evoke quasi-naturalistic percepts that are highly localised to spatially restricted regions of the distal limb [44], as one would expect in the absence of any reorganisation. These results suggest that the pathway from somatosensory nerves to their cortical targets seems to be preserved, even years after amputation (cf. [8]). Perhaps the most striking evidence for the immutability of SI topographies despite input loss comes from cortical microstimulation studies in humans. Flesher and colleagues [47] investigated the sensory consequences of intracortical microstimulation of SI in a human tetraplegic patient. Despite the fact that the somatosensory input from the hand had been massively reduced for a decade, induced activity in the hand area resulted in vivid localised sensations on the patient's insensate hand and never elsewhere. Thus, sensory input loss did not result in replacement of the original representation.

NEURAL BASIS OF REORGANISATION

The persistence of sensory experience despite peripheral input loss can be explained in part by local reorganisation in the peripheral nervous system. A severed sensory axon typically regenerates and reinnervates intact tissue, for example on the residual arm (see [48] for physiological review). As a result, touch applied to the reinnervated tissue will produce signals that are mislabelled by the central nervous system as arising from the missing hand. This phenomenon has been elegantly exploited to redirect cutaneous sensations from the hand to the chest skin of amputees to create an intuitive interface for controlling an artificial limb (targeted reinnervation, [49]). Peripheral nerve regeneration can thus lead to the resumption of somatosensory input to the deafferented cortical region, potentially giving rise to phantom sensations following peripheral injury (see [50] for related results).

The massive functional cortical reorganisation observed in the animal's SI was originally also thought to result from widespread sprouting of intracortical connections [11,33]. However, recent evidence in monkeys suggests that the bulk of reorganisation following nerve injury takes place in the brain stem. Indeed, the activation of the deafferented limb representation in SI through face stimulation is abolished when the cuneate nucleus is inactivated. This suggests that projections from the trigeminal nucleus – which receives signals from the face – to the cuneate nucleus – which receives signals from the limb – become potentiated after the cuneate nucleus is deafferented [51](Figure 1A; see [52] for alternative somatosensory pathways mediating this process). In fact, there is little anatomical evidence of reorganisation in SI: Very few axons project across the face-hand boundary in SI of intact animals (see [53] for similar evidence in humans) and deafferentation of the hand region does not result in any measurable increase in these boundary-crossing projections [54]. In other words, almost none of the previously documented reorganisation seems to actually occur in cortex. These new findings resolve the potential discrepancy between the classical evidence, showing face-related activity in the missing hand cortex of monkeys, and recent evidence in humans showing little structural and functional change following amputation.

STABILITY OF SENSORY TOPOGRAPHIES IN ADULT CORTEX

In summary, loss of input from a body region in adulthood leads to the formation or potentiation of lateral connections in the brainstem, which gives rise to a new pathway from periphery to cortex, with little evidence of remapping in the cortex itself. The original pathway seems to be relatively spared as evidenced by the elicitation of sensations evoked on the amputated or insensate limb through stimulation of the peripheral nerve or somatosensory cortex. Furthermore, fMRI studies show that the representation of the missing limb is maintained in human amputees decades after amputation [38,55], such that the canonical functional hand layout [7] persists in the missing hand SI area despite several decades of amputation [56] (Figure 3). Interestingly, hand topography is also preserved in individuals that have suffered brachial plexus injuries – which result in the avulsion of the nerves – suggesting that the persistence does not depend on peripheral inputs (see [56] for suggested contributions from the motor system). Finally, there is no evidence that the new pathway afforded by brainstem is in any way functional: the increased cortical volume has never been conclusively shown to result in functional benefits. In other words, the remapped activity described in previous studies does not result in a functional sensory representation of the remapped body part. These new pathways can thus lead to activation of deafferented cortex, but do not seem to do so in the way the original pathways did.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES FOR BRAIN MACHINE INTERFACES

The above reinterpretation of the behavioural, imaging, and neurophysiological results imply a more nuanced view of cortical plasticity: while sensory cortices of adults are endowed with plasticity, this plasticity cannot result in the formation of completely novel representations, even under the extreme circumstance of deafferentation. Contrary to the prominent view of input loss triggering massive cortical reorganisation, we suggest that use-dependent plasticity may be a more important driver of reshaping properties of somatotopic maps, one that operates on a finer scale.

The development of chronically implanted electrodes arrays has opened up the possibility that intracortical microstimulation (ICMS) could be used as a means to restore sensation to patients who have lost it (e.g. due to deafferentation) and for whom more peripheral neural interfaces are not an option. Early work demonstrated that stimulation of primary visual cortex evoked phosphenes, the location of which depended systematically on the location of the electrodes on the retinotopic map [57]; stimulation of SI evoked tactile percepts that followed from the homunculus [58]; electrically stimulating primary auditory cortex elicits an auditory percept the frequency of which is determined by the location of the electrode on the tonotopic map [59].

The evidence reviewed above for preserved functional layout of somatosensory cortical processing opens up exciting opportunities for restoring tactile feedback following peripheral or spinal cord injury. The most straightforward strategy to restore sensation through ICMS is to mimic natural patterns of cortical activation [60]. The idea is that the more the electrically induced neuronal activation resembles its natural counterpart, the more naturalistic the evoked sensations will be. The obvious way to attempt to produce naturalistic patterns of activation is to respect and exploit the native topographies. For example, to signal contact at some location on the body, one would stimulate neurons that responded to that part of the body before the injury. However, if those topographies are completely remapped after injury, as the classical theory of cortical reorganization suggests, the biomimetic approach would no longer be tenable. From the standpoint of neuroprosthetics, then, the stability of cortical representations implies that exploiting native topographies in sensory cortex is an option.

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FIGURES

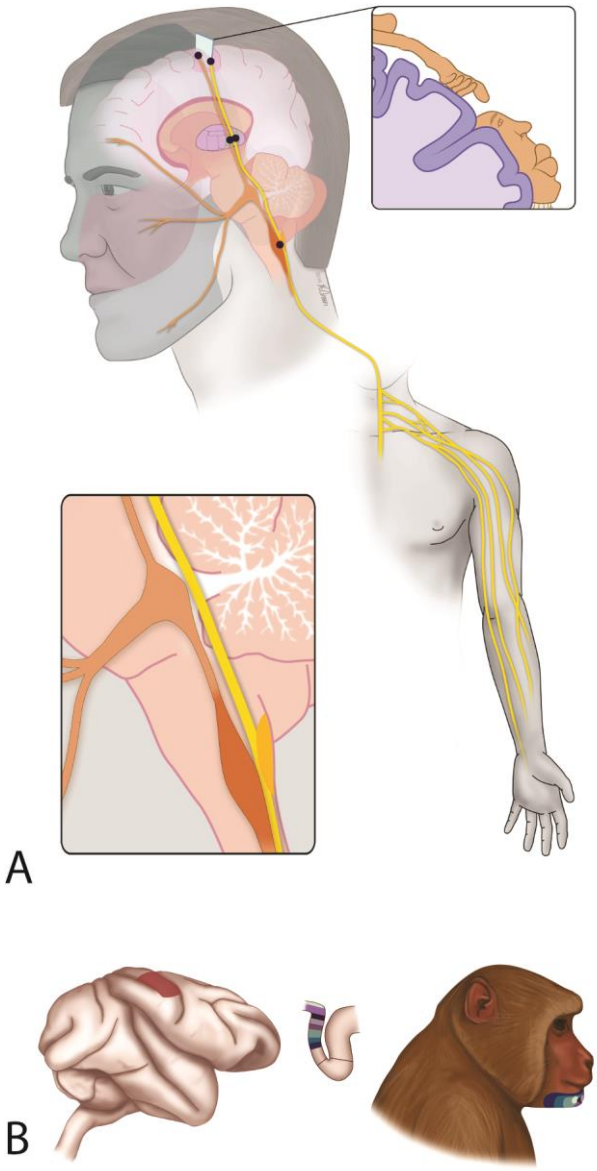

Figure 1. A| Diagram of the somatosensory pathways from the limb (yellow) and face (orange) to primary somatosensory cortex. The somatosensory nerves from the limb synapse onto the cuneate nucleus, located in the brainstem, which then sends projections to the the ventroposterior lateral nucleus of the thalamus, which in turn projects to primary somatosensory cortex. The somatosensory nerves from the face project to the trigeminal nucleus, also in the brainstem, which then projects to the ventroposterior medial nucleus of the thalamus, then to cortex. The primary somatosensory cortex comprises a complete map of the body, where adjacent body parts are represented in adjacent patches of cortex (with some necessary discontinuities, see cartoon in top right inset). (Note that, in S1 of macaques, the hand representation borders the lower part of the face.) B| Following arm deafferentation, the cortical territory of the (deafferented) limb becomes responsive to stimulation of the lower face. Adapted from *[11]*.

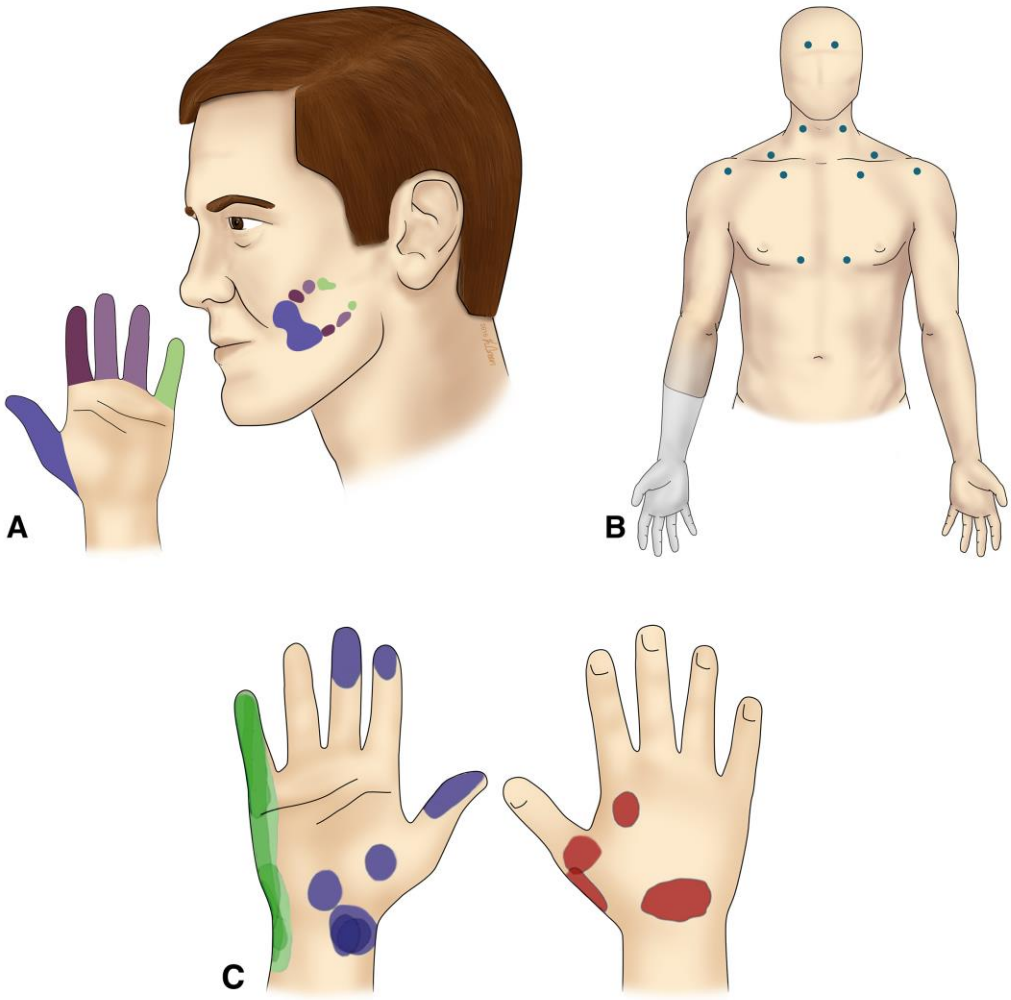

Figure 2. A| In a case-study with human amputees, a systematic mapping was observed between the location of the trigger region on the face and the location of the referred sensation on the left phantom hand. Adapted from *[31]*. B| In other studies, however, touches on many different parts of the body, many of which were not cortical neighbours of the deafferented limb, were found to evoke referred sensations on the missing limb. The blue dots denote cutaneous trigger points evoking referred sensation on the phantom (right) hand in one example participant. Adapted from *[36]*. C| In an amputee with a missing right hand, electrical stimulation of the peripheral somatosensory nerve of the residual arm evokes well-localized and stable percepts on the missing hand. The coloured patches indicate locations of consistent perceived sensations on the phantom hand over the course of two months, during stimulation through different electrodes located on the median (blue) ulnar (green) and radial (red) nerves. Adapted from *[44]*.

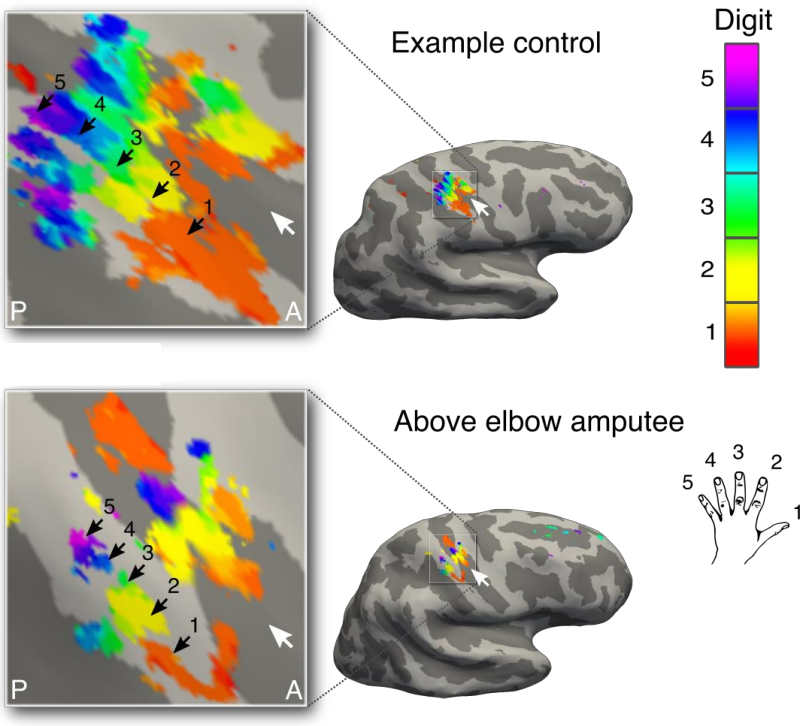

Figure 3. Top: Canonical hand representation in SI of a control subject with an intact hand, showing the distinct, somatotopically organized representation of the five digits. Bottom: Missing hand representation in an amputee 31 years after amputation, mapped during phantom finger movements. Although reduced, digit selectivity, order and extent of the missing hand maps were similar to those observed in controls. White arrows indicate the central sulcus. A = anterior; P = posterior. Adapted from *[56]*.

TRENDS BOX

The reorganisation of primary somatosensory cortex (SI) following arm amputation is considered a prime example of neural plasticity in the adult brain and of its consequences on altered perception

Recent evidence from human and non-human primates shows that the reorganization in SI does not result in novel functional sensory representations and that the original somatotopic organization persists despite drastic loss of sensory input.

Perceptual evidence from humans shows that the loss of sensory input does not result in a replacement of the original representation: Activation of the missing hand area evokes in sensations referred to the missing (phantom) hand and not to the “invading” body regions (e.g., the face).

The evidence for preserved somatotopy following long-term deafferentation has important implications for providing tetraplegic patients with artificial touch through electrical interfaces with the brain.

OUTSTANDING QUESTIONS

Low labile are sensory representations in adulthood?

What is the role of the motor system in restricting reorganisation in SI?

How stable is somatotopic organization if deafferentation occurs in childhood, during the critical period?

What are the functional consequences of the increased baseline activity observed in deprived cortex following input loss during the critical period?

In the intact organism, what is the function of the lateral connections in the brainstem that are potentiated following deafferentation?