Title:
Cortical reorganisation in the primary sensorimotor cortex following hand loss

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Key abbreviations:

PLP	=	phantom limb pain
S1	=	primary somatosensory cortex
fMRI	=	functional magnetic resonance imaging
M1	=	primary motor cortex
MEG	=	Magnetoencephalography

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Abstract:
Limb loss provides a key model for studying brain reorganisation as it combines two main drivers of brain plasticity - sensory input loss and altered behaviour. Here we explore how the highly structured and consistent hand representation in the primary somatosensory cortex (S1) changes following hand loss. We review classical findings demonstrating that following amputation, the neighbouring body part representations 'invade' the deprived hand area. We review potential perceptual consequences of such reorganisation, both maladaptive (e.g. phantom limb pain) and adaptive (e.g. compensatory strategies). We highlight recent evidence demonstrating that the functional organisation in the deprived cortex is preserved even decades after amputation, consistent with the view that S1 reorganisation reflects plasticity occurring at the brainstem level. We finally highlight alternative models of deprivation-driven S1 plasticity (hand transplantation, temporary deafferentation, congenital handlessness and neuroprostheses), providing further insights into the scope and functional consequences of S1 reorganisation.

1. Introduction

Our brain is an extremely dynamic organ, constantly updating its responsiveness and connectivity based on our experience. This ability to change, known as *brain plasticity*, enables us to develop from infants to adults, learn new skills, recover from injury and adjust to ageing. Here we will focus on extreme cases of plasticity, where an entire brain area is presumed to change its functional affiliation (otherwise known as *brain reorganisation*).

A striking demonstration of brain reorganisation, both at the microscopic (e.g. synaptic) and macroscopic (e.g. cortical) level, is observed following peripheral injuries that deprive the brain of a major source of sensory input, e.g. limb amputation. After amputation, the brain suffers an extreme loss of sensory input in tandem with dramatic alterations to motor behaviour to compensate for the disability (e.g. employment of a prosthetic limb, over-reliance on the intact limb). Amputees, therefore, provide a key model for studying brain plasticity – they allow us to investigate brain reorganisation patterns induced by sensory input loss and changed behaviour. Furthermore, by comparing reorganisation patterns in individuals who lost a limb in adulthood (amputees), and individuals who have been born without a limb (congenital one-handers), we can investigate how reorganisation is affected by development, and the critical period in particular (an interval of time during infancy where the central nervous system is extremely sensitive to environmental stimuli; see section 6.4).

We start by surveying seminal work of cortical reorganisation in non-human primates, demonstrating that neighbouring brain regions 'invade' the deprived area in primary somatosensory cortex (S1) after amputation. We outline research in human amputees to assess the potential perceptual correlates of such reorganisation (see section 4.1), and whether reorganisation may be maladaptive and/or adaptive for the individual. Benefiting from the ubiquitous phenomena of phantom limb sensations, we then examine the possibility that 'missing' representations persist after amputation, i.e. preserved organisation, and elaborate on what processes may be sub-serving S1 'reorganisation'. Lastly, we provide a brief overview of alternative models that researchers use to probe sensorimotor brain plasticity following input loss, and how they may provide further insights into the extent, and perceptual consequences, of reorganisation. But before we can talk about brain reorganisation, we will begin by outlining normal organisation within S1.

2. Primary somatosensory cortex organisation in healthy individuals

S1 encompasses the central sulcus (excluding the anterior bank) and postcentral gyrus (see Figure 1 for the main input pathway to S1). Primary sensory regions such as S1 are organised in a map-like fashion, showcasing cortical representations in a highly structured manner (Figure 2A). This architectural characteristic is termed *topographic organisation* and reflects spatial activity patterns along the cortical sheet, corresponding to the inputs from a physical variable (e.g. a body part for S1, a sound's frequency for primary auditory cortex). Topographic representation is considered to arise from a combination of genetic blueprints and peripheral sensory information (Grove and Fukuchi-Shimogori, 2003), and is therefore spatially invariant across healthy individuals, to a certain degree.

In comparison to the neighbouring primary motor cortex (M1), which shows broad topography (e.g. crude representations of the legs, hand and mouth), organisation in S1 is highly topographic, particularly concerning the hand (e.g. segregated representations across fingers), allowing us to make reasonable estimates of brain reorganisation after sensory input loss. In this chapter, we will therefore focus on (re)organisation in S1 following arm amputation. However, the ability to draw orthogonal distinctions between S1 and M1 is tricky, as both

cortices share an abundance of reciprocal connections (Pavlides, Miyashita and Asanuma, 1993), processing outputs (Penfield and Boldrey, 1937), and are both involved in fine motor-control. Moreover, many contemporary techniques for studying brain organisation in humans are not well equipped to accurately delineate S1 from M1 spatially. Therefore, where it is not easy to disentangle the individuated contributions of S1 and M1, we will refer to the findings as relating to the *sensorimotor* cortex.

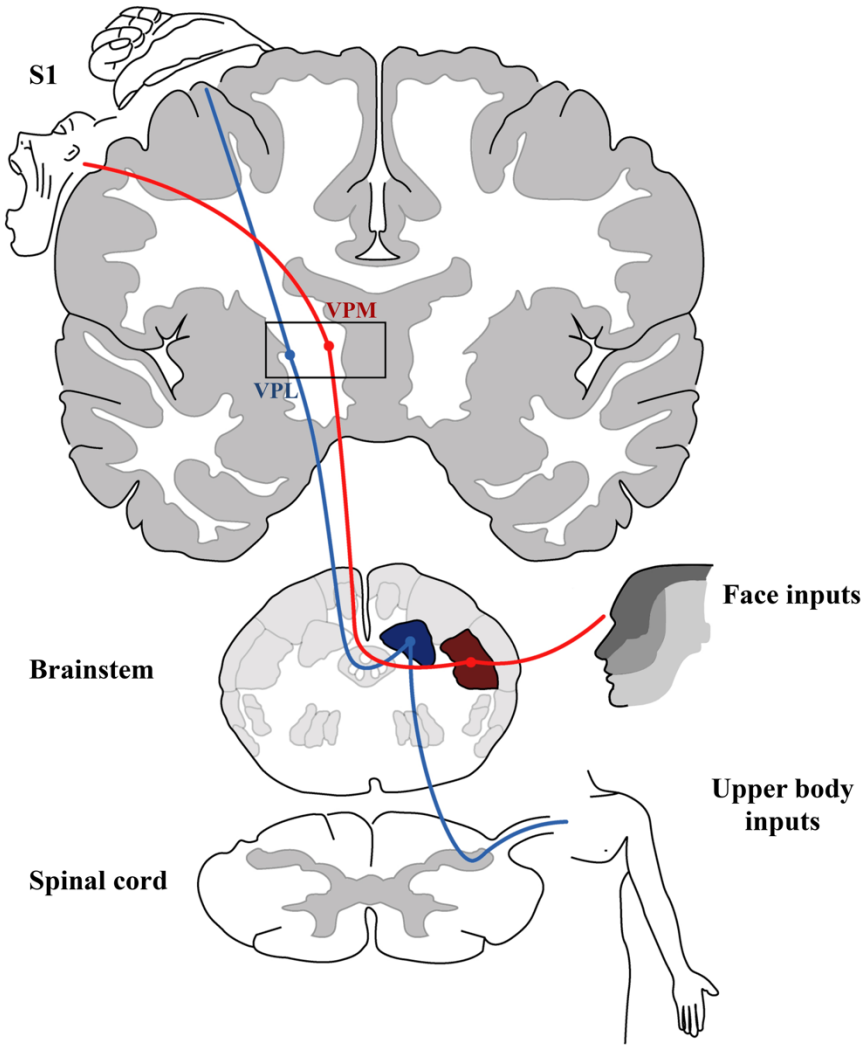

Figure 1. The somatosensory processing stream. *Afferent signals from the nerves of the hand (blue line) reach the primary somatosensory cortex (S1) after having relays in the dorsal column of the spinal cord, the cuneate nucleus (dark blue) of the brainstem, and the ventroposterior lateral nucleus (VPL) of the thalamus. Afferent signals from the face (red line) project from the trigeminal nucleus (dark red) in the brainstem to the ventral posteromedial nucleus (VPM) of the thalamus before reaching S1. Adapted from Pasha Parpia, 'Reappraisal of the Somatosensory Homunculus and Its Discontinuities', Neural Computation, 23:12 (December, 2011), pp. 3001-3015 © 2011 by the Massachusetts Institute of Technology.*

2.1 The development of the homunculus

The organisation of S1 was first characterised in detail by the seminal work of Penfield and colleagues (Penfield & Rasmussen, 1950; Penfield & Boldrey, 1937). They directly stimulated the cortical tissue of awake human patients undergoing brain surgery for epilepsy (carried out under local anaesthesia). Based on patients' self-reports of the induced sensations, Penfield and colleagues (1950; 1937) described a detailed body map in S1, where adjacent body parts were

represented next to each other (i.e. *somatotopically*), displaying the characteristic topographic organisation previously demonstrated in other primary sensory regions. This body atlas was termed the *cortical homunculus* (derived from Latin, meaning "little person"), and was draped in a medial-to-lateral fashion across the somatosensory and motor regions (Figure 2A). This famous observation was recently replicated using modern-day electrostimulation techniques, showing little inter-individual variance in patients undergoing neurosurgery to remove brain lesions (Roux, Djidjeli and Durand, 2018).

It is important to note, however, that Penfield and colleagues (1950; 1937) also reported discontinuities within S1's somatotopic organisation. They found that body parts were represented in a way that was not proportional to body mass, thereby producing a distorted, or exaggerated, 'little man'. For example, in humans the hand representation is much larger than the arm or trunk and exhibits a highly detailed map of the palm and fingers.

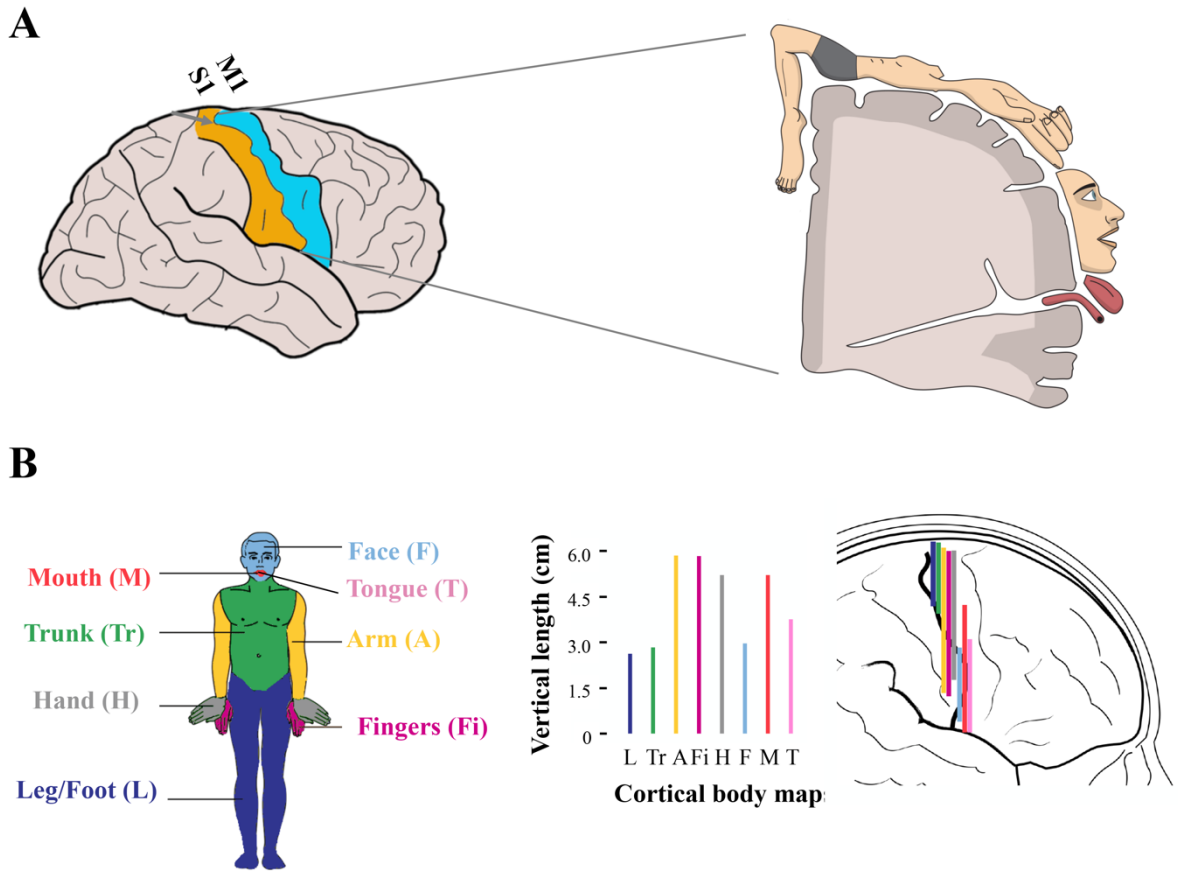

Figure 2. Somatotopic organisation in the primary somatosensory cortex. *A) Left: The primary somatosensory cortex (S1; orange) and primary motor cortex (M1; blue) are located on both sides of the central sulcus (CS; grey arrow). Right: An illustration of the somatosensory homunculus. Photo credit from 'The Homunculus Mapper'; Max Planck Florida Institute of Neuroscience. B) Representational overlap across body parts, as reported by Penfield and colleagues (1937). The histogram within this figure reflects the vertical length of the surface map for each body part within the somatosensory homunculus: face (F; blue), tongue (T; pink), arm (A; yellow), Fingers (Fi; bright pink), leg/foot (L; dark purple), hand (H; grey), trunk (Tr; green), mouth (M; red). These distances are projected onto the cortex, highlighting the great deal of overlap of representations within the homunculus. Adapted from Marco Catani, A little man of some importance, Brain, 140 (11), pp. 3056, Supplementary Figure 1, doi.org/10.1093/brain/awx270 © Marco Catani, 2017. Published by Oxford University Press.*

These enlarged cortical representations of body parts within S1 have been suggested to reflect the degree of peripheral innervation in the extremities. The size of each body part's representation, therefore, is thought to be relative to the density of cutaneous tactile receptors within that body part (Kaas, Nelson, Sur, Lin, & Merzenich, 1979). This phenomenon is termed *cortical magnification*, whereby certain body parts with high densities of receptors (i.e. the hands and lips) have enlarged S1 representations. Magnified representations within S1 have also been suggested to link with the functionality of that body part in terms of everyday use. For example, spider monkeys who use their tails for manipulating objects show increased S1 representation of their tail pads, whereas rats that rely on their whiskers for palpating the near environment show increased S1 representation of their whiskers. This functionality-driven enlargement is termed *afferent magnification*, whereby the increased size of the representation is not related to mechanoreceptor density, but rather to the ecological frequency or significance of the afferent input. With this in mind, the hand representation within the somatosensory homunculus is an especially interesting target for studying brain organisation. It is a body part which not only exhibits a high density of cutaneous tactile receptors but is also used frequently in daily life to carry out functionally meaningful actions. Upper-limb amputees, therefore, provide a unique opportunity to investigate what happens to the exquisitely detailed hand map following sensory input loss.

The fine-tuning of brain representations within S1 are characterised by a delicate balance between *representational selectivity* to specific body parts, and *representational overlap* across related representations (Graziano and Aflalo, 2007). In their canonical visualisation of the homunculus, Penfield and colleagues (1950; 1937) emphasised representational *selectivity*, i.e. individuated body part representation. However, it was also reported that a great degree of *overlap* also exists between representations (Figure 2B), such that stimulation of one part of the homunculus also induced sensation in an adjacent body part. For this reason, Penfield and colleagues (1937; 1950) proposed the homunculus as more of a visual aid than a binding cortical rule.

How does selectivity of representations co-exist with representational overlap? Recent research has suggested that body parts used more frequently together in daily life benefit from increased overlap. For example, single fingers used frequently together tend to show increased commonality of representations within S1 (Ejaz, Hamada and Diedrichsen, 2015). The resulting topographical organisation in S1 is therefore not only a product of inherent anatomical constraints, but also from the usage of body parts in daily life, i.e. the modulation of sensory input to the body map.

3. Seminal reorganisation studies in non-human primates

In 1983, Merzenich and colleagues first investigated what happens to the S1 hand map of adult non-human primates when it is deprived of sensory input. They performed a median nerve transection on the primate's hand and used microelectrode recordings to investigate changes in the somatotopic hand representation. 2-9 months after the transection, the former territory of the median nerve became occupied by expanded representations of skin surfaces innervated by the ulnar and radial hand nerves, areas that neighboured the now "freed-up" area. Importantly, the new representation followed the rules of topographic mapping, whereby neighbouring skin surfaces in space are represented next to each other in the reorganised map.

Following on this work, Merzenich and colleagues (1984) investigated what happens to the S1 hand map following finger amputation. Using microelectrode recordings in non-human primates, they demonstrated that within 2-6 months post finger amputation, the freed-up finger

area was taken over by the cortically adjacent fingers (Figure 3A). Pons and colleagues (1991) took this a step further and demonstrated that after long-term sensory input loss from the entire hand and arm, even more extensive reorganisation was observed: 12 years post upper-limb amputation in adult macaques, the missing hand area in S1 became responsive to touch on the lower part of the macaque's face (Figure 3B).

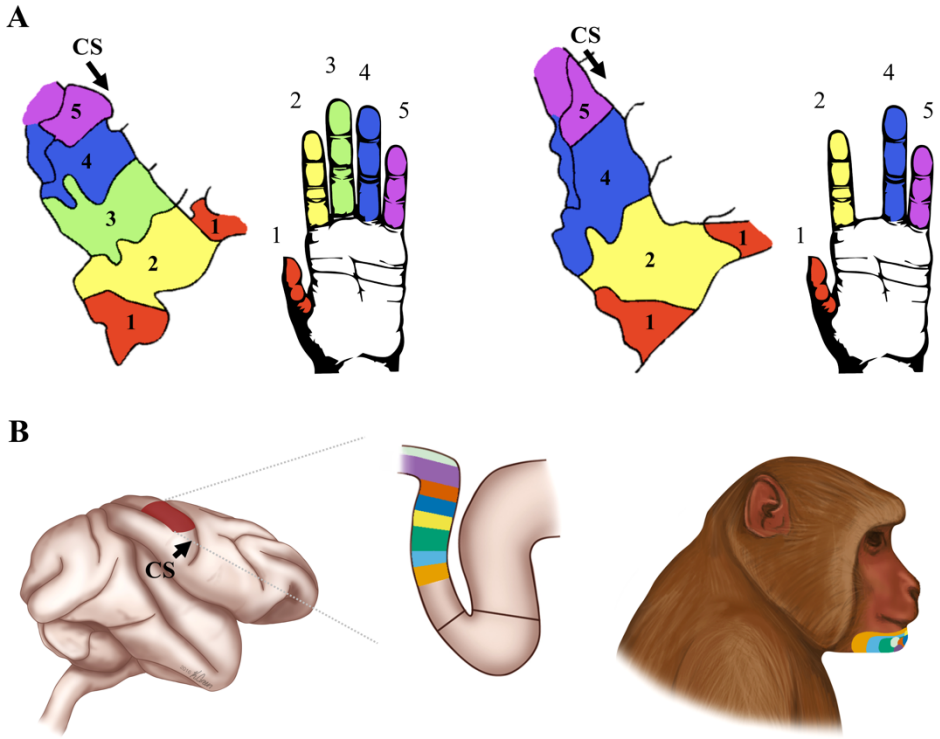

Figure 3. Reorganisation in primary somatosensory cortex of non-human primates, following major sensory input loss. *A) Left: S1 hand map, showing somatotopic finger representation. Right: 62 days post middle finger amputation, the former middle finger area became responsive to inputs from the neighbouring fingers (index and ring). Fingers 1-5: thumb (red); index (yellow); middle (green); ring (blue) and little finger (purple). Adapted from Michael M. Merzenich, Randall J. Nelson, Michael P. Stryker, Max S. Cynader, Axel Schoppmann, and John M. Zook, Somatosensory cortical map changes following digit amputation in adult monkeys, Journal of Comparative Neurology, 224 (4), p. 594, Figure 1a and b, doi.org/10.1002/cne.902240408. Copyright © 2004, John Wiley and Sons. B) 12 years post arm amputation, the S1 missing hand area became responsive to inputs from the chin, in a somatotopic fashion. Adapted from Trends in Cognitive Sciences, 21 (3), Tamar R. Makin and Sliman J. Bensmaia, Stability of Sensory Topographies in Adult Cortex, p. 196, Figure 1, doi: 10.1016/j.tics.2017.01.002. Copyright © 2017 Elsevier Ltd. All rights reserved.*

Reorganisation following major sensory input loss has also been documented following spinal cord lesions (Reed *et al.*, 2016), and whisker plucking/shaving in rodents (Feldman and Brecht, 2005). The golden-rule which arose from these studies is that the representation(s) neighbouring the 'freed-up' cortex will expand and 'invade' the region that is now deprived of inputs, following the topographic guidelines of cortical organisation. These observations led to the conclusion that the adult cortex has the potential to reorganise under extreme circumstances.

What are the functional consequences of the expanded representation of the neighbouring body parts onto the deprived cortex? Merzenich and colleagues (1984) speculated that reorganisation would improve tactile acuity and sensitivity of the newly expanded body part, in accordance with non-human primate learning studies by Recanzone and colleagues (1992). If *afferent*

magnification of inputs is associated with increased function (e.g. tactile acuity), then the expansion of the spared body part/skin surface representation into the deprived cortex should, theoretically, result in tactile gains (i.e. adaptive plasticity). A further speculation was that extensive reorganisation may drive the phantom sensations that are often reported in human amputees, as will be discussed below. These key questions have been addressed in human research, which will be the focus of the next section.

4. Reorganisation in human amputees and maladaptive reorganisation

4.1 Phantom sensations

Following amputation, individuals generally report experiencing vivid and continuous sensations of their missing limb. Phantom sensations are not necessarily painful, and are best described as a sensation that the missing hand is still present (Henderson and Smyth, 1948). Importantly, most amputees with phantom limb sensations are able to move their phantom limb to some extent. When instructed to move their phantom hand, amputees generally report detailed kinaesthetic sensations regarding the degree and extent of phantom movement. This is supported by empirical evidence demonstrating that phantom limb movements elicit both central and peripheral motor signals, that are different from those found during imagined movements (Raffin *et al.*, 2012; Raffin, Giraux and Reilly, 2012).

4.2 Referred sensations

Phantom sensations can be evoked through tactile stimulation of other body parts (referred sensations). In a famous series of studies involving three upper-limb amputees, it was reported that touch applied on the residual arm and lower part of the face elicited referred sensations of the missing hand (Ramachandran, Stewart and Rogers-Ramachandran, 1992; Ramachandran, 1993). Notably, stimulation of neighbouring sites of the face elicited referred sensations in neighbouring fingers of the phantom hand, suggesting a somatotopic organisation of referred sensations. The authors interpreted these findings as the perceptual correlate of expanded face activity in the territory of the missing hand (see section 3). It was hypothesised that if neurons in the S1 missing hand area become responsive to the face, then brain regions receiving input from this area will interpret this sensory input signal as resulting from the missing hand. Consequently, tactile face stimulation would elicit dual sensations of the face and the phantom hand.

However, these reports illustrating referred sensations were not conducted systematically, and as such should be interpreted with caution. Further studies using more standardised approaches have shown that referred phantom hand sensations can be elicited by touching various body parts, including those that are not cortically adjacent to the missing hand area, e.g. trunk or shoulder contralateral to the missing hand (Knecht *et al.*, 1996). This suggests that the phenomenon of referred sensations does not adhere to S1 topography, weakening the hypothesis that referred sensations are a consequence of classic S1 reorganisation. Furthermore, the quality of sensory experience in the phantom limb frequently differed from the stimulation modality, e.g. both heat and vibration stimuli would elicit a tingling referred sensation in the phantom. Lastly, the commonly reported phenomenon that phantom sensations can be triggered by stimulating the residual arm, may simply reflect spontaneous peripheral reinnervation rather than cortical reorganisation (Nystrom and Hagbarth, 1981)

4.3 Phantom limb pain and the maladaptive plasticity model

About 80% of arm amputees experience painful phantom limb sensations (Weeks, Anderson-Barnes and Tsao, 2010). Phantom limb pain (PLP) is a neuropathic pain syndrome that is notoriously difficult to treat. It is typically unresponsive to conventional analgesic treatments,

posing a significant medical problem. An influential model ascribes PLP to *maladaptive* cortical reorganisation. Flor and colleagues (1995) were the first to identify a relationship between PLP and S1 reorganisation using magnetoencephalography (MEG). They investigated the distance between the lip representation and an estimated location of the S1 missing hand area in amputees. Results showed that the cortical distance between the lip and missing hand representation was reduced in amputees compared to controls, i.e. the lip representation was shifted towards the missing hand area. Importantly, a positive correlation was found between cortical reorganisation and amputees' self-reported PLP intensity levels: amputees with worse PLP had greater shifts in lip representation. This correlation between S1 reorganisation and PLP has subsequently been supported by various studies (see Flor, Nikolajsen and Staehelin Jensen (2006) for an overview).

Based on this initial report linking PLP and cortical reorganisation, it has been proposed that once S1 is deprived of a major source of sensory input, this will lead to degradation of the missing hand representation (Ramachandran and Hirstein, 1998). Consequently, neighbouring representations 'invade' the missing hand area, causing this deprived region to respond to inputs intended for adjacent cortical territories (i.e. the lips). This mismatch between body part representations (i.e. the missing hand and the lips) is thought to result in an 'error' signal that is interpreted by the brain as pain arising from the missing hand. This theoretical framework, known as *the maladaptive plasticity* model postulates that PLP can be relieved by reversing maladaptive reorganisation, i.e. by 'reinstating' the representation of the missing hand into its original territory. Over the past years, numerous treatments have been developed that aim to target and reverse the brain changes proposed by this model (Thieme *et al.*, 2016). A famous example of such a therapy is mirror box treatment, which uses illusory visual information of the missing hand (Ramachandran, Rogers-Ramachandran and Cobb, 1995), in an effort to restore the missing hand representation in S1. Further examples of treatments that aim to reverse maladaptive reorganisation are virtual reality (Ortiz-Catalan *et al.*, 2016) and graded motor imagery (Moseley and Flor, 2012).

Despite its popularity, a number of papers have been published in the past years that challenge both the assumptions behind this maladaptive plasticity model (Jutzeler, Curt and Kramer, 2015), and the effectiveness of the treatments that are based on this model (Barbin *et al.*, 2016; Thieme *et al.*, 2016). Most relevant to the current discussion is the finding that facial remapping in S1, assumed to be the main driver of PLP according to the maladaptive plasticity model, has been countered. Specifically, we and others have shown that any shifts in lip representations are minimal in human arm amputees, do not invade the missing hand cortex, and are restricted to the face area (Makin *et al.*, 2015; Raffin *et al.*, 2016; Philip *et al.*, 2017). A further assumption of the maladaptive plasticity model, that reorganisation is triggered by degradation of missing hand representation (i.e. through major sensory input loss), was also recently brought into question by us (see section 5.1). We used fMRI to demonstrate that activity elicited by phantom hand movements in amputees' S1 missing hand area was not significantly reduced compared to hand movements activity in healthy two-handed control participants. This suggests that the missing hand representation may not be deteriorated in amputees (see section 5 for further discussion). Finally, the notion that brain reorganisation in the missing hand area is harmful requires further qualifications, as discussed in detail in section 6.2. Indeed, new research emphasises compensatory daily behaviour as an alternative driver for reorganisation (Makin *et al.*, 2013; Philip and Frey, 2014), suggesting an adaptive rather than maladaptive relationship.

5. Preserved representations following major sensory input loss

A common feature across the key studies described so far is that scientists probe the invading representations to characterise the freed-up brain territory, leaving unexplored whether the original functional organisation of this region may be preserved, though latent. Amputees experiencing phantom sensations provide a unique, yet largely unexplored, opportunity for direct insights into the consequences of deafferentation and the possibilities of representational preservation decades following sensory input loss.

5.1 Persistent organisation in S1

Phantom hand movements are known to evoke signals in the sensorimotor system (Reilly *et al.*, 2006; Raffin *et al.*, 2012). While originally attributed to abnormal processing caused by the amputation (e.g. aberrant inputs (Makin *et al.*, 2013; Kikkert *et al.*, 2017, 2018) or peripheral reorganisation (Reilly *et al.*, 2006), evidence is now growing to show that the information content underlying S1 activity evoked by phantom hand movements is consistent with preservation of a normal hand representation (Kikkert *et al.*, 2016; Bruurmijn *et al.*, 2017). We recently used fMRI to examine whether the canonical somatotopic hand representation persists in arm amputees. If the S1 organisation is unchanged despite amputation, then activity patterns evoked by individual phantom finger movements should show characteristic S1 finger somatotopy. We found that the somatotopic representation of amputees' missing hand persisted even decades after arm amputation, and was similar to two-handed controls (Kikkert *et al.*, 2016; Figure 4A). Importantly, this preserved missing hand representation existed even in the absence of peripheral inputs, as demonstrated in an arm amputee suffering from brachial plexus avulsion injury (resulting in abolished communication between the residual arm and the central nervous system).

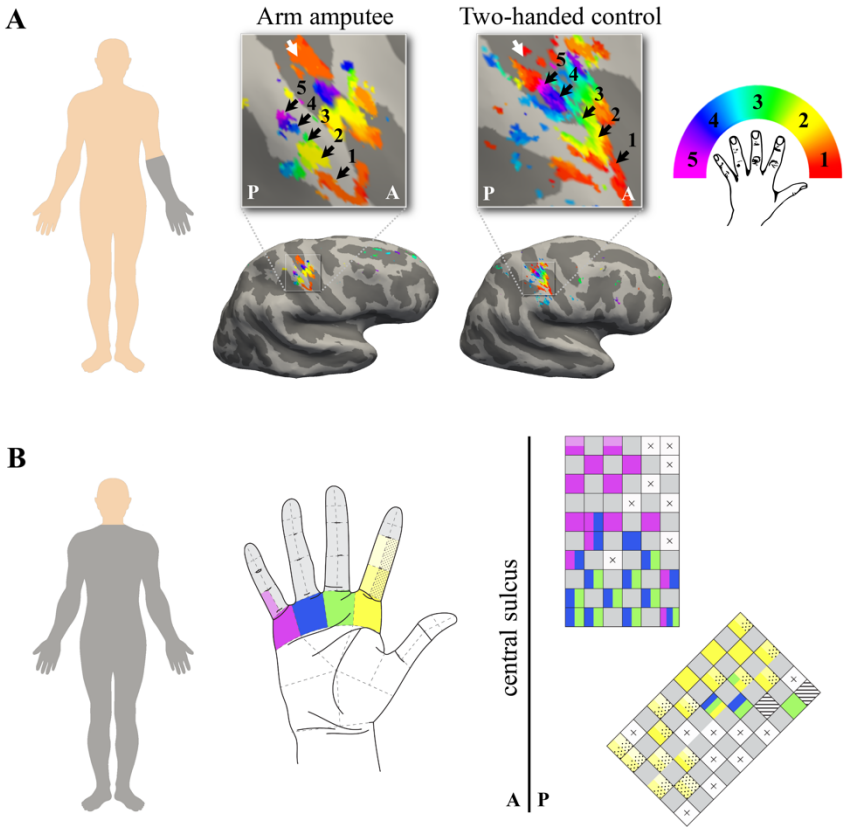

Figure 4. The somatotopic hand representation is preserved in the primary somatosensory cortex, despite decades of deprivation of hand inputs. *Grey area in the body drawings illustrate the body part from which sensory inputs were lost. A) Black arrows indicate representational selectivity for fingers 1-5: thumb (red); index (yellow); middle (green); ring (blue) and little finger (purple) in an above-elbow arm amputee (31 years post limb loss) and a representative two-handed control. Participants performed single digit flexion and extension*

movements with their non-dominant (controls) or phantom hand (amputees). Qualitatively similar digit topographies were found in amputees and controls (Kikkert et al., 2016). White arrows indicate the central sulcus. A = anterior; P = posterior. B) Electrode arrays implanted in S1 of an individual with long-term tetraplegic spinal cord injury, with respect to the central sulcus (solid black line). Coloured boxes in the grid represent the projected field on the paralysed hand for each electrode. Crosses and grey squares represent electrodes that did not elicit a reliable sensation or were not used for the microsimulation. Despite the long-term sensory deprivation of the hand due to the patient's spinal cord injury, intracortical microstimulation in the deprived hand area evoked tactile sensations perceived as originating from locations on the hand, in a somatotopic fashion. Adapted from Sharlene N. Flesher, Jennifer L. Collinger, Stephen T. Foldes, Jeffrey M. Weiss, John E. Downey, Elizabeth C. Tyler-Kabara, Sliman J. Bensmaia, Andrew B. Schwartz, Michael L. Boninger, and Robert A. Gaunt, Intracortical microstimulation of human somatosensory cortex, Science Translational Medicine, aaf8083, p. 2, Figure 1, DOI: 10.1126/scitranslmed.aaf8083. Copyright © 2016, American Association for the Advancement of Science Reprinted with permission from AAAS.

Further striking evidence for the immutability of S1 somatotopy despite input loss comes from cortical microstimulation studies in human tetraplegic patients (i.e. spinal cord injury patients affected from the neck down). Flesher and colleagues (2016) used in-vivo intracortical microsimulation within the hand area of S1 in a tetraplegic patient and investigated the sensory consequences of such stimulation (see also Armenta Salas *et al.* 2018). Despite the long term sensory deprivation of the hand due to the patient's spinal cord injury, the authors were able to reliably evoke organised tactile sensations that were spatially localised to the patient's insensate hand. Sensory input loss, therefore, did not result in replacement of the original representation. These findings are also consistent with studies investigating the perceptual consequences of peripheral nerve stimulation: stimulating amputees' residual nerves through e.g. electrical nerve stimulation evoked vivid phantom sensations (Anani and Körner, 1979; Dhillon *et al.*, 2004). Importantly, residual nerve stimulation can be used to evoke quasi-naturalistic sensations that are highly localised to spatially restricted regions of the missing hand (Tan *et al.*, 2014). Together, these findings suggest preservation across the somatosensory pathway from somatosensory nerves to their cortical targets, even decades after major sensory deprivation.

5.2 Implications for phantom limb pain

What are the implications of these persistent peripheral signals and S1 representations for PLP? Early theories proposed PLP to be due to peripheral aberrant signals, consequential to the peripheral nerve injury (Nystrom and Hagbarth, 1981). However, clinical approaches based on this theory that use local anaesthesia blocks aimed at eliminating this ectopic firing, are not effective in relieving PLP for all amputees (Nystrom and Hagbarth, 1981; Borghi *et al.*, 2010), potentially due to the challenges in blocking of nociceptive C-fibres (Serra *et al.*, 2015). For this reason, the central nervous system started taking a more prominent place as an explanation of PLP in the past decades, giving rise to the maladaptive plasticity model (see section 4.3). However, a recent study by Vaso and colleagues (2014) re-emphasized the importance of the periphery as a driver of PLP. They injected the dorsal root ganglion of lower limb amputees with a local anaesthetic, thereby preventing ectopic signals from the dorsal root ganglia reaching the central nervous system. This consistently led to a rapid and reversible attenuation, and often complete elimination, of PLP, as well as non-painful phantom limb sensations. The minimal duration of this effect was equal to the duration of the anaesthesia, while control (saline) injections in the dorsal root ganglia had no such effect.

Further work also favours the peripheral attributes of PLP (though indirectly) and questions a key assumption of the maladaptive plasticity model, i.e. that reorganisation is triggered by degradation of missing hand representation. We used fMRI to investigate activity elicited by phantom hand movements in the sensorimotor missing hand area in unilateral arm amputees

and its relationship to PLP. Contradictory to what one would expect based on the maladaptive plasticity model, and consistent with a peripheral origin to PLP, amputees with worse chronic PLP showed stronger maintained phantom hand movement activity in the S1 missing hand area (Makin *et al.*, 2013; Kikkert *et al.*, 2018). We propose that nociceptive inputs from the residual nerve form the basis of PLP and suggest that increased S1 activity does not causally drive PLP, but instead may be a secondary consequence of such peripheral disturbances. Continuous inputs from these nerves would lead to a more excitable missing hand area. As such, PLP would proportionately scale with brain excitability in areas normally receiving inputs from the missing hand.

6. Resolving the paradox: reorganisation versus persistent representations

How can findings of preserved somatotopy in the territory of the missing hand be allied with the wealth of evidence showing cortical reorganisation in the same area following sensory input loss? Afferent signals from the nerves of the hand reach S1 after having relays in the dorsal column of the spinal cord, the cuneate nucleus of the brainstem, and the ventroposterior lateral nucleus (VPL) of the thalamus (see Figure 1 & Figure 5A), and reorganisation may take place at any of these stages. In a recent study, Kambi and colleagues (2014) used electrophysiology in non-human primates with dorsal column lesions to investigate what may cause the expansion of intact chin inputs into the S1 deafferented hand area in macaques. They selectively inactivated either the cuneate nucleus in the brainstem (receiving inputs from the hand), or the native face area in S1. If cortical reorganisation is due to axonal sprouting or unmasking of lateral connections at the cortical level, then one would expect that silencing of the S1 face area would silence the expanded chin representation. Alternatively, if cortical reorganisation is caused by upstream effects of axonal sprouting at the brainstem level or spinal cord, then inactivation of the cuneate (normally transmitting information to the S1 hand area) would silence the expanded chin representation in S1. In agreement with the second prediction, the authors found that the chin remapping was only silenced when the cuneate nucleus in the brainstem was inactivated (see Figure 5). Therefore, reorganisation does not seem to take place in S1 itself, but instead reflects changes that occur earlier in the somatosensory processing stream.

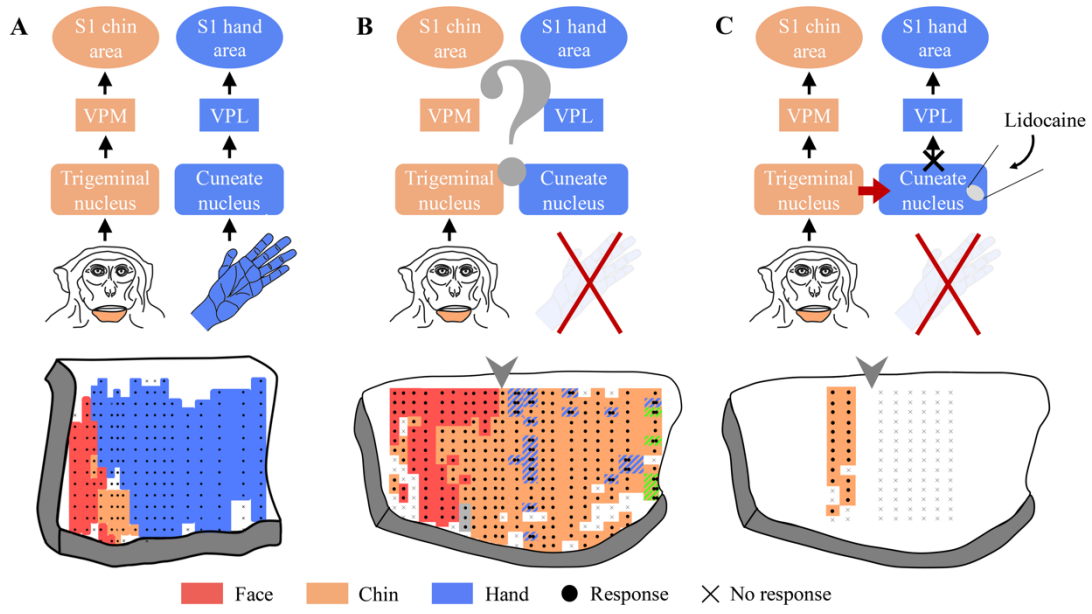

Figure 5. Reorganisation in the primary somatosensory cortex is due to brainstem plasticity. *A) In intact non-human primates, inputs from the chin (orange) ascend to S1 via the trigeminal nucleus of the brainstem and the*

ventroposterior medial nucleus (VPM) of the thalamus. Inputs from the hand (blue) ascend to S1 via cuneate nucleus and the ventroposterior lateral nucleus (VPL). Representation of other parts of the face is shown in red. Dots mark locations of the recording sites where receptive fields of the neurons were mapped. B) After a dorsal column lesion, the deprived hand area became responsive to touch on the chin. The grey arrow marks the location of the hand-face border. Crosses illustrate recording sites for which no receptive field could be mapped. C) Inactivation of the reorganised (hand) cuneate nucleus silenced the expanded chin representation in the deprived hand area. This demonstrated that S1 reorganisation is due to upstream effects of axonal sprouting at the brainstem level or spinal cord. Adapted from Niranjan Kambi, Priyabrata Halder, Radhika Rajan, Vasav Arora, Prem Chand, Manika Arora, and Neeraj Jain, Large-scale reorganization of the somatosensory cortex following spinal cord injuries is due to brainstem plasticity, Nature Communications, 5, p. 3602, Figure 1, doi.org/10.1038/ncomms4602. Reprinted by permission from Macmillan Publishers Limited. Copyright © 2014, Springer Nature.

This discovery may resolve the seemingly contrasting results between the classical evidence showing face-related activity in the S1 deafferented hand area (due to brainstem reorganisation), and recent evidence in humans showing persistent representation of the missing or deafferented hand (due to stability of S1 structure and function, see section 5.1). It remains unclear, however, whether this brainstem reorganisation that is reflected in S1 has implications on functional processing. Additionally, the neural processes sub-serving preserved somatotopy despite deafferentation should be considered. We suggest that preserved somatotopy despite input loss may primarily be driven by motor (efferent) information. Indeed, while motor signals can no longer reach their final output terminal (the hand) following arm amputation, the motor cortex remains capable of sending out motor commands in amputees (Raffin, Giraux and Reilly, 2012) and spinal cord injury patients (Kokotilo, Eng and Curt, 2009). The motor system is thought to provide information about its descending commands to the sensory system by means of efference copies. When a motor command is sent out (e.g. in the form of a phantom or attempted hand movement), efference signals reach S1. This resulting corollary discharge is suggested to resemble the sensory feedback activity that would be expected from the movement (London and Miller, 2013). The persistence of efference signals in S1's cortico-cortical layers could contribute to the maintenance of preserved information content in S1, despite re-routed facial inputs to S1's afferent layer. As such, preserved topography may be overlapping with reorganised inputs in individuals suffering from deafferentation.

7. Alternative models for reorganisation

Alternative models of deafferentation provide further invaluable insight into the extent of reorganisation in S1 after input loss and its functional consequences for the individual. Here we explore what happens to S1 organisation when the 'lost' input is restored to the adult human brain (i.e. through arm transplantation or reversible sensory deprivation) and explore (re)organisation in those born without a hand (i.e. congenital one-handers). Finally, we consider brain machine interfaces as a novel window into probing the brain's capacity for reorganisation.

7.1 Hand transplantation in human amputees

Medical advancements have provided an alternative model to study reorganisation in human amputees. Hand loss can now be restored through surgical hand transplantation even years or decades after amputation, allowing scientists to address the question about what happens to the 'reorganised' S1 map when the original input to S1 is restored. Frey and colleagues (2008) used fMRI to demonstrate that tactile stimulation of an amputee's transplanted arm elicited activity within the previously deprived area which was comparable to that observed in two-handed controls. Furthermore, any extended face representation that may have existed prior to the hand transplantation was no longer present. Similar results have been reported following

bilateral arm amputation (Giraux *et al.*, 2001) and following toe-to-finger transplantations (Hadoush *et al.*, 2012). These findings of 'recaptured somatotopy' after restoring the original input to S1 were mostly interpreted as further evidence for the dynamic abilities of S1 to continuously reorganise based on changing experience. However, this result could also be interpreted as further evidence for potential preservation of the original cortical organisation, despite input loss, as described in section 5.1.

7.2 Temporary deafferentation

A primary way in which researchers have examined temporary deafferentation is by applying a 'cuff', or ischemic nerve block (INB), to the forearm or lower leg. Studies addressing the behavioural consequences associated with such transient deprivation tend to focus on perceptual gains in neighbouring and contralateral homogenous body parts, i.e. would sensory deprivation lead to topographically restricted improvements? Werhahn and colleagues (2002) found that tactile thresholds of the left index finger improved throughout the duration of a right arm INB and returned to baseline after recovery from the INB. No perceptual improvements were reported for the left hand when the INB was administered to the right foot, suggesting homogenously-restricted tactile gains within contralateral representations. It was later found that these perceptual improvements were associated with increased cortical excitability (as measured by motor evoked potentials using Transcranial Magnetic Stimulation) in both proximal and homogenous representations of the motor cortex (Werhahn *et al.*, 2002). The authors suggested that such topographical plasticity may result from disinhibition of sensorimotor inter-hemispheric connections, thereby increasing local excitability within the homogenous hand representation. The use of INB's to mimic cases of deafferentation, however, are questionable. Throughout the duration of an INB participants usually experience pain and discomfort as a side-effect of wearing the cuff, which could influence subsequent brain processing. A way in which to resolve these confounding factors is by using pharmacological nerve blocks, such as lidocaine.

Weiss and colleagues (2004) have reported perceptual advantages of proximal representations in parallel with S1 reorganisation when using a pharmacological nerve block to the radial and median nerve of the left upper-limb in healthy participants, that produced cutaneous anaesthesia of the left hand's thumb, index and middle fingers. Subsequent MEG showed that the S1 representation of the little finger (spared from the nerve block) and the lower lip had moved closer together, potentially reflecting an 'invasion' of neighbouring representations into the deafferented region. Björkman and colleagues (2009) also found that after applying an anaesthetic cream to the right forearm (resulting in mild cutaneous anaesthesia), tactile sensitivity of the cortically neighbouring right hand was improved. These improvements occurred in tandem with the expansion of the hand representation into the anaesthetised forearm region as shown using fMRI, suggesting that cortical reorganisation after deafferentation may not necessarily be *maladaptive* and can occasionally provide *adaptive* benefits for the individual. This notion has been harnessed by researchers aiding stroke patients who display sensorimotor impairments (e.g. Muellbacher *et al.*, 2002).

Together these results indicate that a brief period of sensory deprivation may induce sensorimotor gains due to cortical expansion of neighbouring representations. However, the perceptual correlates of reorganisation in these studies are tangled with the ensuing contributions from behavioural change, which may in turn give rise to changed brain representation. We therefore cannot say with certainty that deprivation-induced reorganisation is adaptive in and of itself, or whether behaviour also plays a role. In other words, the resulting behaviour may drive cortical changes, and not the other way around.

We recently attempted to tease apart the differing contributions of deafferentation and behaviour (i.e. training) in promoting adaptive plasticity after input loss (Dempsey-Jones *et al.*, Under Review). We administered a pharmacological nerve block to healthy participants' right index finger with or without a period of tactile training to the neighbouring middle finger (see Figure 6A). Deafferentation without training selectively enhanced tactile perception in the finger adjacent to the anaesthetised finger (see Figure 6B). This demonstrated that temporary deafferentation by itself can provide functional advantages for somatotopically neighbouring representations, as previously suggested by the aforementioned studies (Merzenich, *et al.* 1984; Werhahn *et al.*, 2002; Werhahn *et al.*, 2002; Weiss *et al.*, 2004; Björkman *et al.*, 2009). When deafferentation was combined with tactile training, however, widespread tactile improvements to untrained fingers were found, extending beyond the normal topographical spread of tactile learning (Dempsey-Jones *et al.*, 2016). Indeed, improvements were significantly more extensive when compared to a sham group, who underwent a period of training after a saline injection to the index finger. The use of training, therefore, can extend adaptive reorganisational benefits beyond the original topographical confinements (i.e. beyond the direct cortical neighbours and homologous partners of the deafferented body part).

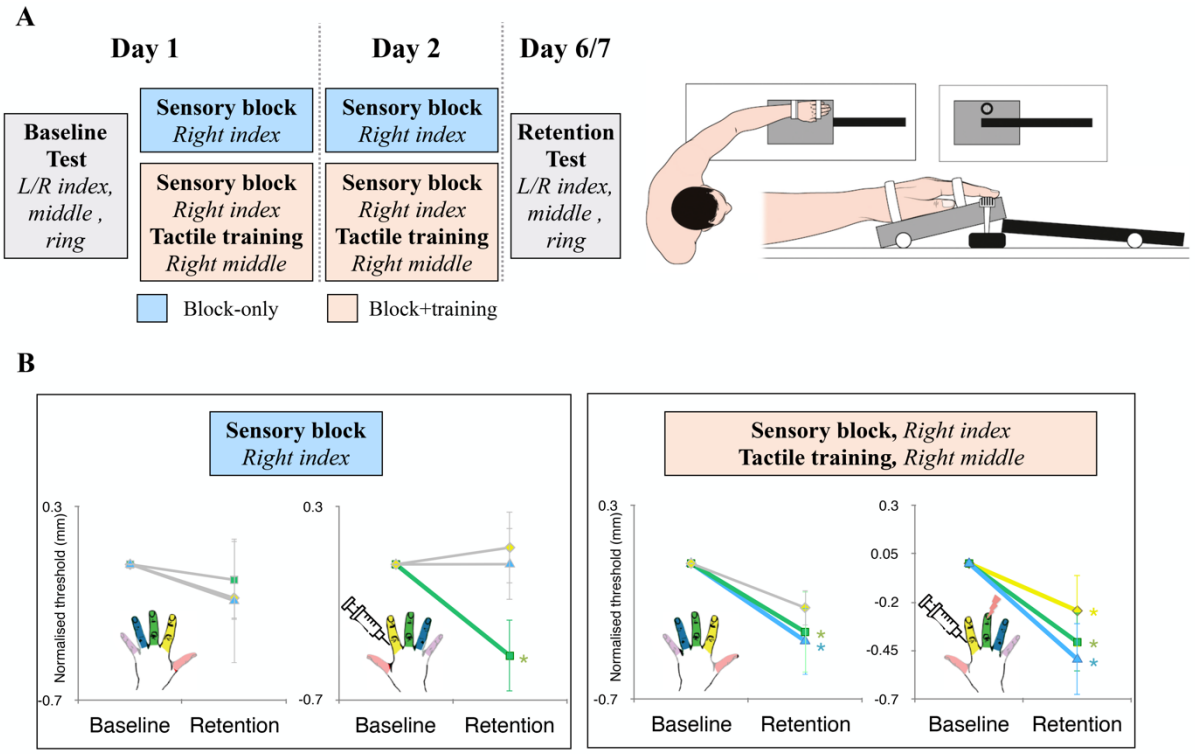

Figure 6. Temporary deafferentation in combination with tactile training can lead to perceptual gains beyond the normal somatotopic spread of tactile learning. *A) Tactile acuity was tested before, and several days after, a pharmacological block to the right index finger. Tactile thresholds were assessed using a Grating Orientation Task using grooved plastic domes to the index, middle and ring fingers of the left (L) and right (R) hands. Healthy participants were spilt into a block-only (blue), a block+training (pink), and a sham-block+training group (not shown here). B) For the block-only group tactile gains were found only for the middle finger adjacent to the block. However, when the block was administered simultaneously with tactile training to the adjacent finger, perceptual gains were reported in neighbouring, homogenous and untrained fingers extending beyond the normal topographical spread of learning. * = $p < 0.05$.*

These findings have implications for the interpretation of deprivation as a primary driver of reorganisation following sensory input loss. Amputees and spinal cord patients deploy a range of behavioural strategies to compensate for their disability, e.g. over-usage of the intact hand,

which tend to mirror that of perceptual learning, as it involves repeated exposure to the same stimulus and/or repetitive movements. Compensatory behaviour could therefore capitalise on deprivation-induced plasticity, leading to perceptual gains. Recent work highlights how changed behaviour in amputees may drive usage-dependent patterns of cortical reorganisation within S1 (Makin *et al.*, 2013; Philip and Frey, 2014; Van Den Heiligenberg *et al.*, 2018). However, it should be noted that research has not yet been able to demonstrate a causal relationship between cortical reorganisation patterns and functional benefits (e.g. in daily life), and so any conclusions suggesting a direct association between reorganisation and adaptive behaviour must be taken with caution.

7.3 Congenital one-handers

Pioneering work by Hubel and Wiesel (Daw, 2009) who investigated reorganisation following visual deprivation introduced the significance of *critical periods* – temporal windows during infancy where cortical responses to sensory input are extremely sensitive – in influencing brain (re)organisation. Here we review the consequences of congenital handlessness, (i.e. those born without a hand/s) on brain reorganisation: What happens to the cortical maps of individuals who never received sensory information of the hand(s) during this crucial time window?

Congenital one-handers tend to compensate for their disability by over-using an array of body parts, such as the feet, mouth, and residual arm, as a substitute for their missing hand (e.g. to stabilise objects; see Figure 7). As some of these body part representations neighbour the missing hand area (e.g. the arm) while others (e.g. the feet) do not, the repertoire of compensatory strategies allows us to address the role of behaviour in driving reorganisation – will over-usage of these body parts lead to reorganisation that extends beyond somatotopic relationships? We demonstrated using fMRI that when congenital one-handers moved each body part used for compensatory purposes (e.g. the feet, residual arm, lips), the induced activity was greater in the missing hand's sensorimotor cortex compared to two-handed controls (Makin *et al.*, 2013; Hahamy *et al.*, 2017; see Figure 7). We also found increased functional connectivity between the missing hand area and the lips and feet representations. Importantly, when congenital one-handers moved their intact hand – which does not substitute their missing hand function – this was not the case. We should note, however, that no significant correlations between reorganisation and behaviour were found, and therefore it cannot be said with certainty whether this reorganisation supported adaptive behavioural strategies in daily life. Regardless, these results demonstrate reorganisation beyond that of typical somatotopic boundaries.

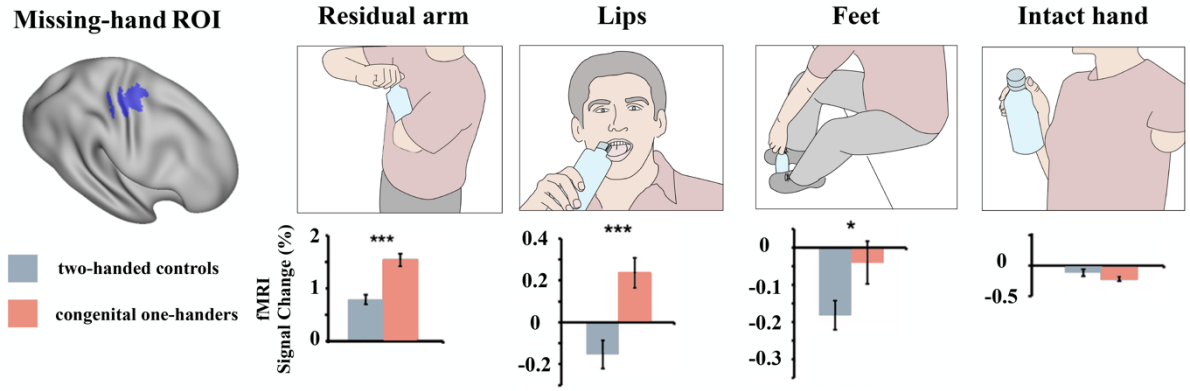

Figure 7. Movements of body parts used for compensatory behaviour activate congenital one-handers' missing hand area. *Top: Congenital one-handers tend to compensate for their disability by using various body parts (e.g. feet, lips and residual arm) to aid their intact hand while carrying out typically bimanual actions, e.g. opening a bottle. Bottom: We found using fMRI that when congenital one-handers (red) moved each of these compensatory*

*body parts the induced activity (y-axis) within the missing-hand S1 area (non-dominant hand S1 area for controls) was greater when compared to two-handed controls (grey). However, when congenital one-handers moved their intact hand, which is not used to substitute their missing hand's function, this was not the case. These results suggest that reorganisation can extend beyond that of typical somatotopy in those who persistently use body parts for compensatory usage early in life. Adapted from Hahamy et al., 2017. * $p<0.05$; *** $p<0.001$.*

Research has also been conducted addressing reorganisation in individuals born without any hands. These congenital *no*-handers tend to display remarkable dexterity with their feet, using them in a hand-like manner since an early age. Using fMRI, Stoeckel and colleagues (2009) found that toe movements elicited stronger activity in the sensorimotor missing hand area in congenital *no*-handers compared to two-handed controls, suggesting usage-dependent reorganisation. The authors further confirmed this foot-to-hand remapping in the deprived primary sensorimotor cortex using TMS in a choice reaction time task, where the congenital no-handers were asked to either flex or extend their big (dominant) toe in response to a visual cue. Application of TMS during the task resulted in delayed foot responses, hinting that the remapped foot representation was functionally relevant to the individual. As the foot and the hand area are not cortical neighbours, these results demonstrate that cortical reorganisation had again expanded beyond that of typical somatotopic organisation. However, it still remains unclear whether behaviour is a driver of cortical reorganisation, or whether the altered behaviour results as consequence of cortical reorganisation. Indeed, other research using fMRI found increased representation for various body parts in the sensorimotor missing hand area, regardless of everyday usage strategies (Yu *et al.*, 2014; Striem-Amit, Vannuscorps and Caramazza, 2018). These results suggest that even within the critical period reorganisation may not after all be behaviourally driven, and could arise instead from unmasking of functionally-irrelevant inputs, or reflect organisational changes at the brainstem level, as described in section 6 above.

7.4 Brain Machine Interfaces

Brain Machine Interfaces (BMIs) allow a user to control a device (e.g. a prosthetic arm) using direct neural signals. In BMIs, the experimenter explicitly defines the causal mapping between brain and behaviour, and it is up to the brain to learn this pre-defined mapping through trial and error. Currently, efforts are being made to selecting the neural signals most relevant for motor control of the limb that is replaced by the machine, to provide intuitive BMI learning and control (known as biomimetic BMI; Bensmaia and Miller, 2014). However, current BMIs rely on small populations of neurons, requiring some level of arbitrary assignment of neurons for the readout. This is even more the case when the neurons selected for BMI decoding are not necessarily behaviourally relevant for the ultimate function of the BMI at the start of learning (Carmena *et al.*, 2003). In such cases, the brain needs to associate a specific (often arbitrary) brain pattern with a novel behaviour. As such, the process of BMI learning provides a powerful new tool to study this relationship between brain plasticity and behaviour in a given circuit. BMI research therefore allows us to ask: under which conditions can brain activity be remapped to control the machine?

BMI learning in non-human primates has previously been shown to occur both short-term (within a daily session; i.e. short-latency reorganisation) and long-term (across days; i.e. long-latency reorganisation; Carmena *et al.*, 2003). Importantly, such short- and long-term BMI learning may occur through different processes. Sadtler and colleagues (2014) previously showed that short-term BMI learning is constrained by the current properties of the network of neurons that govern the behaviour, i.e. by generating activity patterns within pre-existing neural modes. Such short-term BMI learning is thought to be achieved by exploring patterns that can be readily generated (i.e. activity within the neural repertoire), indicating that at this

time-scale, across-network reorganisation is unattainable. Conversely, long-term learning is thought to rely on synaptic changes that let neurons behave in new ways, i.e. generating patterns outside the pre-existing neural repertoire. While it may be possible for such learning to occur outside the pre-existing neural network during guided learning over many days, this suggests that at least short-term reorganisation is limited to within-network changes (Gallego *et al.*, 2017).

BMI studies mostly focus on healthy two-handed non-human primates, not taking into account how the brain may change following an extended period of major sensory input loss. Balasubramanian and colleagues (2017) addressed this issue by investigating the neural consequences of BMI learning in non-human primates that had undergone a unilateral upper limb amputation early (at 2 months) or later in life (5 years of age). As in previous BMI studies with two-handed monkeys, they assigned different inter-connected clusters of recorded neurons in M1 to control different aspects of motor control of a robotic arm. They found that it was possible for the amputated monkeys to perform the BMI task, regardless of whether signals were recorded contralateral or ipsilateral to the amputation. Importantly, BMI learning occurring over days and weeks induced changes both within and across the clusters that were specified for the BMI decoding. These results indicate that network-wide plasticity can support learning to control a neuroprosthetic device, suggesting a form of *adaptive plasticity*.

While BMI studies provide an interesting perspective regarding reorganisation, they are not sufficient in explaining how the brain may naturally reorganise following major sensory input loss. Firstly, it remains unclear whether the brain can similarly reorganise in a meaningful manner on the macroscopic (cortical) level, progressing beyond architectural or topographical brain boundaries, as has been suggested to occur following limb amputation. Furthermore, BMIs are simple and artificial systems and do not reflect the complex changes the brain undergoes following naturally induced sensory input loss, such as limb amputation. Lastly, while BMIs give an interesting idea of how the neural activity may change during BMI learning, the readout of the system is predetermined and fixed, and as such does not accurately represent the working of a natural brain. Despite these reservations, this revolution in neurotechnology is promising both in terms of clinical applications and our understanding of neural reorganisation.

8. Concluding remarks

Multiple studies, using different methodologies and models, have demonstrated that following amputation (or other forms of major peripheral input loss), the missing hand area becomes responsive to displaced inputs. But despite this abundance of evidence for cortical reorganisation, many questions relating to the capacities and limits of reorganisation remain under investigation.

Physiological processes driving deprivation-driven remapping are still unclear. While plasticity has been well demonstrated to occur at the fine-scale synaptic level, the process of cortical reorganisation requires a complex and large-scale process that provides a large patch of cortex with altered inputs, which may not exist. Is the observed cortical remapping a mere reflection of subcortical plasticity? Or is the cortical somatotopic layout relevant for determining the scope of reorganisation? Is cortical remapping triggered primarily by input loss, i.e. passive unmasking and disinhibition? Or is this process refined by altered behaviour? It remains a challenge to tease apart the contribution of deprivation-induced and use-dependent plasticity, especially when considering the role of behaviour in early life (e.g. in congenital one-handers).

Furthermore, recent research in humans challenges the classical framework of reorganisation by showing that the representation of the missing hand is retained in the primary sensorimotor system even decades following amputation. This new discovery raises the question of whether the organisational stability of the so called "deprived" area impacts reorganisation. While it is conceptually plausible that both persistent representation and reorganisation co-exist (e.g. due to engagement of different layers in the cortical column, as elaborated in section 6), it is likely that these two processes may interact given the tight coupling of inputs and outputs in the S1 microcircuit. The main challenge when answering the question of preservation versus reorganisation is the issue of engaging the persistent S1 missing hand representation when phantom sensations are not present, e.g. in individuals with congenital limb loss or in animal models.

Perhaps the most critical outstanding question concerns the importance of such plasticity, i.e. what are the behavioural consequences of these representational shifts? When stimulating the deprived area, either directly or through restored peripheral input, acquired amputees report experiencing sensations relating to their missing hand. This suggests that, consistent with the uncovering of persistent representations of the missing hand, the functioning of the deprived area is unchanged. However, opportunities for functional reorganisation may exist when sensory deprivation occurs before the end of the critical period of development, e.g. re-mapping of body-part representations used for compensatory behaviour (see section 7.3). The proposition as to whether cortical change modulates daily behaviour is not only a crucial question within the field of brain plasticity, but also for clinical rehabilitation and assistive technology. Currently, there is no strong causal evidence proving that brain reorganisation impacts behaviour, both adaptively and maladaptively. However, note that a lack of evidence should not be taken as evidence in and of itself. Future research may shed further light onto the adaptive and maladaptive capacities of brain plasticity.

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