Full title: **The homeostatic homunculus: rethinking deprivation-triggered reorganisation**
Short title: **The homeostatic homunculus**

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Highlights:

- Homeostatic mechanisms may sustain persistent representation of a missing hand
- Recent evidence indicates distributed latent activity across the homunculus
- Deprivation uncovers pre-existing latent activity, that can manifest as remapping
- Remapping could in some instances correspond to stabilising homeostatic mechanisms

Abstract:

While amputation was considered a prominent model for cortical reorganisation, recent evidence highlights persistent representation of the missing hand. We offer a new perspective on the literature of amputation-triggered sensorimotor plasticity, by emphasising the need for homeostasis and emerging evidence of latent activity distributed across the homunculus. We argue that deprivation uncovers pre-existing latent activity, which can manifest as remapping, but that since this activity was already there, remapping could in some instances correspond to functional stability of the system rather than reorganisation. Adaptive behaviour and Hebbian-like plasticity may also play crucial roles in maintaining the functional organisation of the homunculus when deprivation occurs in adulthood or in early development. Collectively, we suggest that the brain's need for stability may underlie several key phenotypes for brain remapping, previously interpreted as consequential to reorganisation. Nevertheless, reorganisation may still be possible, especially when cortical changes contribute to the stability of the system.

BALANCING BETWEEN PLASTICITY AND STABILITY

Seminal work on sensorimotor plasticity has established the notion that the adult cortex is extremely plastic. For example, following amputation of a finger [1] or deafferentation of an arm [2], the deprived primary somatosensory cortex (SI) of monkeys becomes activated by inputs of the cortically neighbouring finger or face, resulting in shifted map boundaries. It has long been assumed that such cortical remapping has direct consequences on perception and action, for example in the context of rehabilitation following stroke or amputation [3,4]. This notion of a 'soft-wired brain' contrasts with the fact that the brain needs stability and balance to maintain network coherence and cortical dynamics that are essential for its functioning. Indeed, one cannot navigate in a city if its streets keep changing names and directions, as they walk. Similarly, acquisition and preservation of higher-level skills require stable lower sensory representations to draw from. Worse, if not balanced, local plastic changes could theoretically lead to activity overload [5]. Therefore, an appropriate balance between stability and plasticity must be maintained.

Homeostasis corresponds to the ability for a cell or network to detect a perturbation and generate a compensatory response that restores baseline function, thus maintaining stable internal states and balance. At the brain level, homeostatic plasticity often refers to neuronal feedback mechanisms which maintain neural activity within a functional range [6]. In particular, deprivation has been shown to trigger a rapid modulation of inhibitory networks, followed by a relatively slower mechanism of synaptic scaling in excitatory networks [7]. While the first, rapid, process leads to disinhibition that can enable some features of Hebbian plasticity [8], the second, slower, process is mediated by synaptic scaling, which regulates and restores mean firing rate of excitatory neurons to normal levels, associated sometimes with homeostatic adjustment of intrinsic excitability, also in excitatory neurons [7]. Here, we define brain homeostasis as the mechanisms that would either strengthen or weaken activity that is respectively above or below what is necessary to maintain baseline function and activity balance at either a local or network level. While homeostatic control of neuronal activity at the cellular level has been widely investigated in the last two decades [9,10], the study of biological mechanisms underlying homeostatic control of neural network function is receiving attention only more recently [11–13]. In this context, development, deprivation and activity-dependent plasticity constitute real challenges to maintaining balance within the sensorimotor system, without over-constraining plasticity that is vital for adaptive changes.

Here we will use the framework of homeostasis to offer a new perspective over classical and recent findings associated with deprivation-triggered plasticity within the human SI. While our focus will be on SI, we will also review relevant studies in the primary motor cortex (M1), in view of their tight functional and anatomical link [14]. We will first report converging evidence for persistent representation of the missing hand in the deprived cortex of amputees, that we propose may be sustained by homeostatic mechanisms. We will next

highlight recent evidence indicating that latent activity across the homunculus is more distributed than previously considered. We will argue that deprivation uncovers this pre-existing latent activity, which can manifest as remapping (see Glossary), but as this latent activity was already there, remapping could in some instances correspond to functional stability of the system rather than reorganisation (see Glossary). Finally, we will emphasise the potential importance of activity-dependent plasticity in maintaining the functional organisation of the sensorimotor cortex when deprivation occurs in adulthood (i.e., in amputees), and in early development (i.e., in congenital hand absence). We will suggest that in the latter case, large-scale alteration of the innate sensorimotor topography is possible, but that this form of 'remapping' might be driven by homeostatic preservation of function rather than topography. Collectively, we suggest that the brain's need for stability might be underlying several key phenotypes for brain remapping, previously interpreted as a consequence of reorganisation.

Glossary

Homeostasis: mechanisms that can either strengthen or weaken activity that is respectively above or below what is necessary to maintain baseline function and activity balance at either a local or a network level.

Remapping: changes to cortical map boundaries or topography, quantified based on activity measures. e.g., activity for one body-part identified in the cortical area of another body-part.

Reorganisation: activity changes that introduce new local representational content and readout to downstream brain areas; likely to impact behaviour related to the original or revised function.

Unmasking: uncovering of latent activity by removal of the dominant activity elicited by the primary input. While generally regarded as an active mechanism, the same outcome may be obtained by passive removal of the primary input without additional updating of activity profiles, if latent activity is indeed more distributed than previously considered.

PERSISTENT REPRESENTATION DESPITE CORTICAL REMAPPING

Contrary to the prevalent view of cortical remapping but consistent with the concept of homeostasis, recent accumulating evidence demonstrates that the canonical representational structure and function of the deprived cortex persist after amputation. This research draws on the lingering sensations arising from the missing limb that affect about 90% of adult upper-limb amputees [15]. By taking advantage of amputees' ability to voluntarily move their phantom hand, the signals elicited both centrally and at the periphery were found to differ from those produced by movement imagery [16]. This experimental approach, combined with advanced fMRI methods, uncovered SI finger maps of the missing hand, even decades after amputation [17]. Canonical hand representational structure was

found in all tested amputees, regardless of the vividness of their phantom sensations or pain [18](**Figure 1A**). Phantom hand activity was successfully used to decode a range of hand gestures performed with the phantom hand, suggesting a rich representational content of the missing hand in the deprived cortex [19]. Further support for preserved phantom hand representations is provided by assessing the sensations elicited by direct stimulation to the cortex [20] or to the peripheral nerve [21](**Figure 1B**). Perhaps most strikingly, intracortical micro-stimulation within the SI hand area of a tetraplegic patient elicited tactile sensations localised to the insensate hand, and not any other body-part [22,23](**Figure 1C**). Together with the high incidence of phantom sensations, these studies illustrate a high level of functional preservation across the sensorimotor pathway, with stable processing both at the representational and phenomenological levels, consistent with a homeostasis framework.

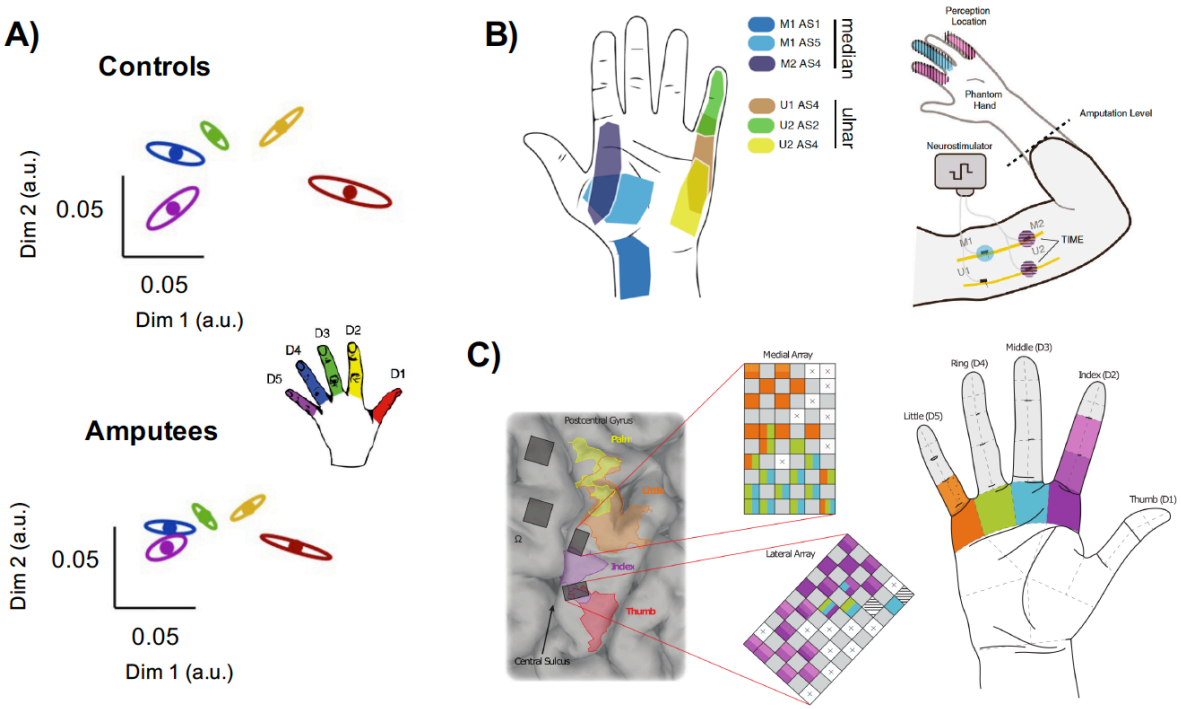

Figure 1: Evidence for persistent representation. A) From [18]. Representational structure of the non-dominant hand in controls (upper panel) and of the missing (phantom) hand in upper-limb amputees (lower panel) as measured by fMRI representational similarity analysis. The structure is portrayed by two-dimensional projection using multi-dimensional scaling. Dissimilarity is reflected by the distance in the two dimensions; individual digits are indicated by different colours (see insert); and ellipses show the between-subject standard error after Procrustes alignment. The representational structure of the phantom hand was statistically similar relative to controls. **B)** From [21]. Distribution of phantom sensations evoked by intraneural stimulation in an example amputee. The implantation of electrodes on the median (M1-2) and ulnar (U1-2) nerves is shown on the right schema. The colour code used to depict evoked sensations corresponds to specific electrodes (see insert). Peripheral stimulation causes sensations on the missing (phantom) hand. **C)** Adapted from [22]. Projected field maps for the hand of a tetraplegic patient in response to intracortical micro-

stimulation of SI. The left panel shows the electrode implantation in the cortex. The middle panel displays the two electrode arrays that were implanted in SI. The colour code corresponds to the parts of the hand where sensations were elicited. The right panel shows the hand regions in which evoked sensations were reported. SI stimulation causes sensations on the deafferented hand.

CORTICAL REMAPPING DESPITE PERSISTENT REPRESENTATION

How can we resolve the classical notion of remapping with this newly accumulating evidence for persistent representation? While these two processes are intuitively contradictory, it is important to point that they are not mutually exclusive, and can in fact co-exist [17,18,24]. Here we suggest that in the context of the brain's need for homeostasis, these processes are more complementary, in particular when considering the functional organisation of the sensorimotor cortex.

Following on Graziano's pioneering work [25], recent evidence in non-human primates and human M1 [26–29] and SI [30,31] suggests that body-part information is more distributed along the homunculus than commonly thought. Consistent with Penfield's emphasis of high overlap between body parts, this implies that some local activity might be latent relative to a more dominant activity elicited by its primary input (e.g., mouth and feet information in the hand cortical area, see [27]) (**Figure 2A**). If confirmed in SI, this evidence introduces a shift in our conceptualisation from a 'homunculus' with rigid body-part boundaries, to complex maps containing information from different body parts that are co-recruited in our daily life. This new perspective has two main consequences.

Methodologically, considering the presence of latent activity across the homunculus, the way we perform our mapping (e.g., which body parts we decide to map) is going to affect the structure of our maps (**Figure 2B**). For instance, both electrophysiological (e.g., [1,2]) and neuroimaging studies (e.g., [32,33]) usually engage a limited set of body parts to define maps and remapping in a winner-takes-all manner (i.e., by assigning a neuron/cortical unit to the most responsive body-part among the ones tested). By doing so, other potentially more dominant inputs (e.g. the phantom hand) are ignored, thus creating a 'bias' towards tested body parts (**Figure 2B**). For example, an apparent remapping obtained by omitting a finger from a finger map analysis strikingly resembles the remapping observed following local anaesthesia of that finger (Wesselink et al, unpublished; **Figure 2C**). This selection bias is further exacerbated by legacy research, as body parts previously implicated in remapping are more likely to be selected for further testing (e.g. lower face versus upper face in amputees). Therefore, some descriptions of remapping may be misleading.

Conceptually, under the framework of distributed activity, the notion of remapping (Glossary) does not entail reorganisation of inputs. Remapping can result from the elimination of the

primary (and most dominant) input via the phenomenon of 'unmasking' (Glossary) as initially suggested by Garraghty and colleagues [34]. Unmasking is commonly thought to be associated with plasticity, where the release of lateral inhibition allows neighbouring representations to 'invade' the deprived cortex. But rodent studies in SI indicate that this form of disinhibition-driven remapping occurs only transiently, with responses returning towards baseline levels either fully [35] or partially [36] within a week or two. In the case of long-term remapping, if the underlying activity was already present prior to deprivation, though latent, it stands to reason that homeostatic mechanisms will boost this activity in order to maintain network stability. As such, the fact that deprivation uncovered this activity to the experimenters does not mean that it has impacted the way the brain reads out this activity from the deprived area. In fact, deprivation-triggered remapping, as identified in amputees, has been argued to lack any behavioural relevance [37], further indicating that the local functional processing is relatively unchanged. This notion of stabilised local activity despite input loss is therefore not inconsistent with homeostatic principles.

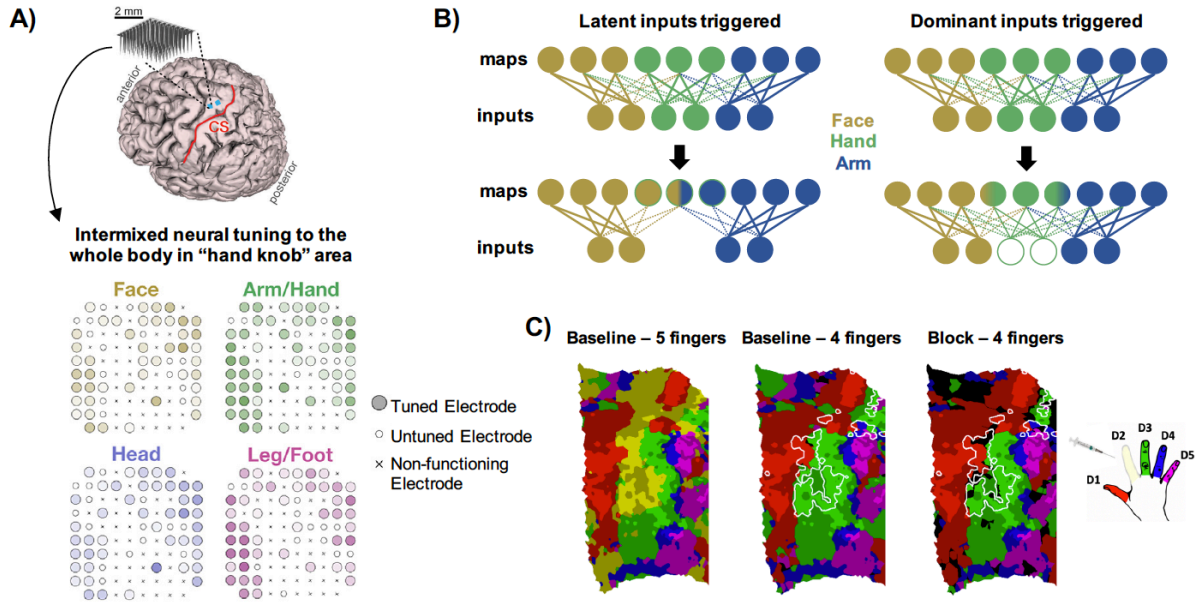

Figure 2: Evidence for distributed latent activity across the homunculus and its impact on mapping and remapping. A) From [27]. Activity recorded in the human M1 hand knob area when a variety of Face, Arm/Hand, Head and Leg/Foot movements were performed. This finding indicates that functional information for specific body parts is distributed across the homunculus **B)** Model adapted from [38] illustrating the distribution of latent activity (dashed lines crossing map boundaries) and the way this network is affected after hand amputation (bottom), when excluding (left) and including (right) stabilising inputs from the phantom hand. The unmasking of inputs does not necessarily impact the way the brain reads out this activity from the deprived area. **C)** From Wesselink et al, unpublished. SI winner-takes-all finger maps, using 7T fMRI, before and after local anaesthesia of digit 2. The map in the middle illustrates a winner-takes-all baseline map calculated when digit 2 is excluded from the baseline analysis. This middle map looks comparable to the post-anaesthesia map (on the

right), which suggests that remapping can correspond to experimental uncovering of underlying activity.

CONSIDERING ACTIVITY-DEPENDENT PLASTICITY AS A STABILISING PRINCIPLE

Plasticity in the adult sensorimotor cortex following deprivation has also been suggested to be triggered by contextual changes to the spared input, due to adaptive behaviour. For instance, unilateral arm amputees increasingly rely on their intact hand for daily functioning, and this over-use could relate to increased activity for the intact hand in amputees' (ipsilateral) deprived hand area, resulting in remapping of the intact hand's activity profile [39–41]. In the context of homeostasis, it has been suggested that this intact hand representation may help sustain the persistent representational structure of the missing hand underlying the same cortical territory [17], by providing highly organised inputs to maintain network stability. It is therefore possible that, similar to the case of remapping across cortical neighbours, some of the large-scale remapping observed in amputees (e.g., intact hand into the deprived cortex) may also reflect homeostatic mechanisms increasing latent activity levels to restore balance in the network. Importantly, this process does not necessarily change the representational content of the remapped activity [18] and thus does not necessarily have any behavioural relevance. It is also possible that behaviour does inform remapping in primary sensory cortex, but only transiently. In the longer-term, higher-order areas may adapt to support behaviour, allowing lower-level representations to return to their initial state. In line with this view, a recent study in twins suggests that while rapid short-term changes are more likely within primary sensory cortical areas, long-term structural changes seem to increase with cortical hierarchy [42].

ACTIVITY-DEPENDENT PLASTICITY IN EARLY DEVELOPMENT BRINGS A NEW PERSPECTIVE TO HOMUNCULUS ORGANISATION AND REMAPPING

While large-scale SI reorganisation might be more limited in adults than originally considered, early life development offers a more favourable environment for activity-dependent plasticity. This is because brain organisation is particularly sensitive to experience and activity during a critical period within development [43], and because white matter pathways are still under-determined (e.g. pruning). Additionally, homeostatic principles may be different for a developing brain and allow for more reorganisation [44–46]. Since hand representation is already established from birth [47], individuals with congenital hand malformations (either unilateral or bilateral – hereafter, one-handers and no-handers, respectively) provide a unique opportunity to examine the potential of SI for remapping and possibly reorganisation. Studies in these individuals revealed that their sensorimotor missing hand area is lacking an organised hand representation [18] and is instead activated more than controls by inputs from a range of body parts, such as the feet, mouth and residual arm [48,49](**Figure 3A,B**). Importantly, single-pulse TMS to the missing hand M1 area of no-handers elicits motor

evoked potentials on the feet, or interferes with foot movements [50,51], demonstrating that the missing hand cortex supports motor control of other body parts that are not necessarily cortical neighbours. This rare demonstration of a causal relationship between local processing in the missing hand cortex and behaviour indicates that reorganisation of motor output could potentially occur, and that this process is not restricted to cortical neighbours. Changes to the SI somatotopy were also found more locally within the foot area, with no-handers showing a detailed map of their toes, structured in a hand-like representational pattern, not found in typically-developed two-handed controls [52].

If not exclusively driven or limited by somatotopy, one potential driver for remapping that has been proposed is adaptive behaviour, which is the utilisation of other body parts to substitute for the original function of the missing limb. For example, daily behavioural strategies of one-handers who use their residual arm, mouth and feet to substitute for their missing hand's function were reflected in brain activity and connectivity patterns [40,53,54](**Figure 3C**), suggesting Hebbian-like plasticity may be at play. Based on this evidence, it has been proposed that remapping may be facilitated or even limited by the functional role of the deprived brain region [53], such that only inputs by body parts that engage in the same functional role of the missing limb would be consolidated. This theory of function-dependent remapping (also termed domain-specificity; [55]) has been contested [49,56](**Figure 3B**) and awaits more direct empirical evidence. Nevertheless, it links the developmental findings for sensorimotor remapping to the broader context of homeostasis, whereby the functional balance in the network is maintained. Indeed, if we consider the sensorimotor homunculus more in terms of clusters of function than in terms of somatotopy, then the territory of a certain body-part region (e.g. the hand area) is in fact responsible for facilitating the function of that body-part (e.g. grasping, manipulating objects) rather than representing the body-part itself. While normally predominantly achieved with a given effector (e.g., the hands), some functions could be supported by other means (e.g., feet, mouth), suggesting that this area would already have the capacity to support these effectors (though in a reduced capacity, compared to the primary effector). Under congenital hand loss, this normally latent activity from effectors with homologous function would be unmasked and further boosted through homeostatic mechanisms. As such, the apparently dramatic remapping described in one/no-handers might be viewed as a network-level adaptation to ensure that the brain develops as stably as possible [57]. Thus, even though the developmental aspects render individuals with congenital hand malformation fundamentally different from amputees, these two populations may comply to similar homeostatic principles that stabilise latent activity, which may be more distributed than initially thought.

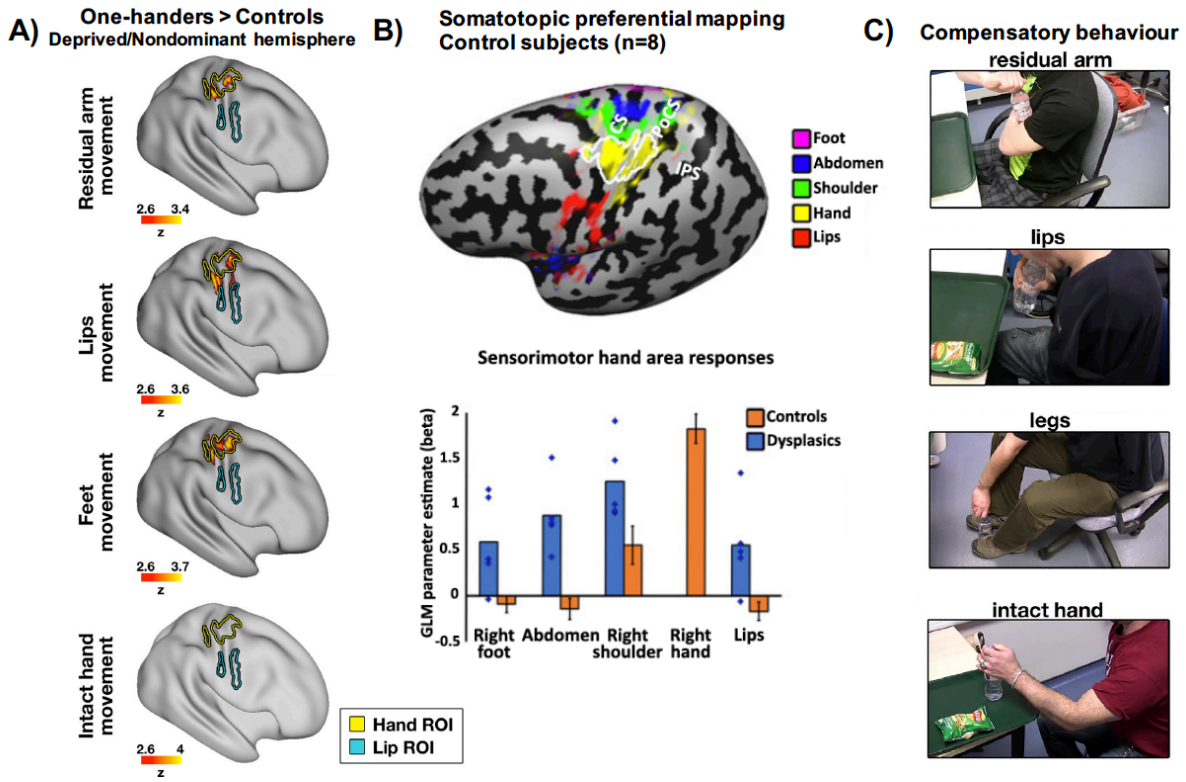

Figure 3: Remapping observed in individuals born with congenital hand malformations. A) From [48]. Univariate contrast maps between one-handers and controls during residual/non-dominant arm (one-handers/controls), lips, feet, and intact/dominant hand movements, projected onto an inflated surface of the hemisphere contralateral to the missing hand. In each of the arm, lips, and feet (but not intact hand) conditions, one-handers showed increased activity in the missing hand cortex compared with controls. Yellow/blue contours represent the hand/lip ROIs, respectively. **B)** From [49]. Sensorimotor maps obtained in control participants, illustrating the hand region (white contour) used to extract the underlying cortical activity in congenital no-handers. As shown in the bottom, increased activity was observed for all body parts compared to controls. **C)** From [53]. Illustration of the adaptive behaviour displayed by congenital one-handers when asked to open a bottle. The body parts used to compensate for the absence of the hand (i.e., residual arm, lips and legs) are those exhibiting increased activity in the missing hand cortex shown in A).

CONCLUDING REMARKS

Here we offer a new perspective on the literature of deprivation-triggered sensorimotor plasticity, by emphasising the brain's need for homeostasis and the presence of distributed latent activity across the homunculus. We suggest that these two guiding principles can unify disparate, and often intuitively contradictory evidence, relating to the sensorimotor system's response to deprivation following amputation. Persistent missing-hand representation and activity-dependent plasticity may both help maintain the functional organisation of the sensorimotor cortex following deprivation. Simply put – inputs that contribute to the stability of the sensorimotor system organisation could be consolidated via Hebbian plasticity while

other inputs are negated by homeostatic mechanisms. Importantly, under this framework, the notion of distributed latent activity implies that rather than triggering reorganisation via disinhibition, unmasking may trigger homeostatic mechanisms that help preserve the underlying pre-existing functional structure and processing of sensorimotor cortex in case of deprivation. As such, uncovering this latent activity may not necessarily alter the representational content in the deprived cortex or relate to behaviour. Thus, rather than being associated with reorganisation, remapping may (under some circumstances) correspond to stability of the system. Nevertheless, it is important to emphasise that under our suggested framework, reorganisation at a finer scale is not impossible to achieve, especially in the context of learning, so long as such changes do not threaten the stability of the network at a larger scale. Finally, using development as an extreme model for remapping, we showed that large-scale remapping may be possible, albeit under special circumstances. Here we suggest that although activity profiles might be modulated relative to typical development, the overall functional organisation of the brain is maintained, when considering homuncular organisation as guided by function rather than by specific inputs. However, the potential behavioural relevance of this large-scale remapping still needs to be clarified. This process could therefore also reflect the brain's overarching drive for stability across lifespan. Future efforts for restoring hand function, such as brain-computer interfaces for artificial limb control, biological hand transplantation, stroke rehabilitation and hand augmentation could harness and benefit from this functional and structural stability.

Acknowledgements: This work was supported by an ERC Starting Grant (715022 EmbodiedTech) and a Wellcome Trust Senior Research Fellowship (215575/Z/19/Z), awarded to TRM. We thank Avital Hahamy, Daan Wesselink, Hannes Saal, Ella Striem-Amit and Esther Kuehn for helpful feedback on the manuscript and Arabella Bouzigues for proof reading.

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