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Adult brain plasticity – what is revealed is exciting, what is hidden is critical

A major discovery of modern neuroscience is that the brains of adult mammals are plastic. Here, I define plasticity as the ability of the brain to change beyond the variability observed in a population with diverse normal experiences. Although there had been earlier reports (e.g. Wall and Egger 1971; Kalaska and Pomeranz 1979), it was the two seminal papers published nearly two decades ago that created excitement in the neuroscience community by clearly and unambiguously demonstrating reorganization in the brains of adult primates following peripheral nerve injuries (Merzenich *et al* 1983a,b). The authors showed that when part of the hand representation in the primary somatosensory cortex or area 3b of owl monkeys is deprived of its normal inputs by cutting one of the three peripheral sensory nerves to the skin of the hand, neurons in the deafferented region do not remain unresponsive, but begin to respond to the stimulation of adjacent normally innervated parts of the hand (figure 1a). A large number of papers have since been published establishing the generality of these observations by extending them to visual, auditory and motor systems, to subcortical regions of the brain including nuclei in the thalamus and lower brain stem, and to other mammalian species (see Jain *et al* 1998b). In order to determine the limits of the ability of the brain to change, sensory deprivations have been done in a variety of ways. Examples include cutting multiple peripheral nerves in different combinations, amputation of one or more fingers, and temporary deafferentations by injections of anaesthetics.

Adult brain plasticity caught the popular imagination as a potential therapeutic tool following publication of a paper by Pons and colleagues showing the ability of the brain to reorganize far beyond what was previously believed (Pons *et al* 1991). They found expansion of the face representation in the primary somatosensory cortex of macaque monkeys over long distances into the forelimb region when all the sensory inputs from the arm were deafferented by transection of the dorsal roots. Such 'large-scale' changes are also seen after extensive deprived by transection of the dorsal columns of the spinal cord (Jain *et al* 1997) or amputation of an arm (Florence and Kaas 1995). The observations were later extended to humans using surface recording and imaging techniques (Flor *et al* 1995).

However, many questions remain beyond the establishment of the basic phenomenology and determining the limits of plasticity. First, the underlying mechanisms of plasticity are not completely understood. Experiments on monkeys with dorsal column injuries showed that plastic changes in the brain follow a specific time course (figure 1). The initial changes are restricted to the expansion of the remaining, nearby inputs from the hand, while expansion of the more distant face inputs requires months of recovery. This suggests that there are likely multiple mechanisms of brain plasticity. One group of possible mechanisms are synaptic mechanisms for example those mediated by NMDA receptors (Rema *et al* 1998) and changes in the levels of GABAergic inhibition (Garraghty *et al* 1991). Such mechanisms can reveal preexisting inputs that are not normally expressed. Other synaptic mechanisms include neosynaptogenesis and synapse withdrawal. The second class of mechanisms involve the growth of dendritic or axonal arbors. Restricted growth has been found in the cat primary visual cortex where branching of dendritic arbors increases without increasing the overall area of the arbor (Darian-Smith and Gilbert 1994). More extensive growth that crosses nuclear boundaries has been shown in the lower brain stem (Jain *et al* 2000). However, direct causal relationships between the changes in the topographic maps and any of these mechanisms are still lacking.

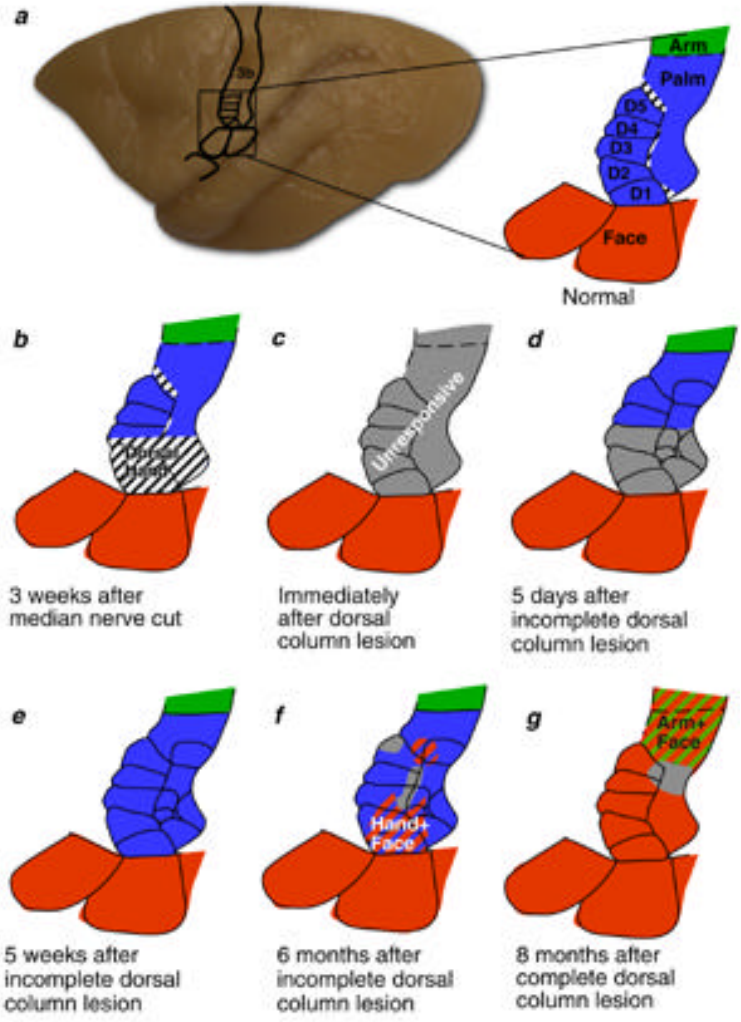

Figure 1. (**a**) Outline of the somatosensory area 3b of an owl monkey overlaid on a dorsolateral view of the brain. Details of the normal map shown on the right are boxed. In area 3b face is represented lateral to the hand representation. Within the hand representation the digits are mapped in a somatotopic order with digit 1 (thumb) adjacent to the face and digit 5 (little finger) medialmost. Most of the hand region in area 3b is occupied by the representation of the glabrous (palmar) surface of the hand. The representation of the hairy skin on the back of the hand occupies only small islands in the hand cortex. Outlines of area 3b and details of the hand and face regions are based on those revealed anatomically by staining sections of the cortex for myelin (Jain *et al* 1998a). Note that unlike the brains of humans and Old World monkeys such as macaque monkeys, the cortical surface of the owl monkey brain is almost entirely free of sulci. This exposes nearly all of area 3b on the surface making it easy to study it reliably and thoroughly using electrophysiological and histochemical techniques. (**b**) Reorganization of the hand region in area 3b following transection of the median nerve to the hand. Median nerve innervates the thumbward half of the glabrous skin of the hand. Immediately following transection of the median nerve, neurons in the deafferented hand cortex become unresponsive to peripheral stimulation. However, over a period of three weeks neurons in all of the deafferented cortex come to respond to the stimulation of the skin on the back of the hand which is innervated by the intact radial nerve. (**c–g**) Time course of reorganization of area 3b following unilateral lesions of the dorsal columns of the spinal cord at upper cervical (C3/C5) levels. Such lesions deafferent sensory inputs from the hand and other parts of the body below the level of the lesion. (**c**) Immediately after the lesion neurons in the deafferented cortex become unresponsive to peripheral stimulation. The adjacent face cortex remains normal. (**d**) If the lesion is incomplete, the deafferented parts of the hand region remain unresponsive for about a week, although it is possible that limited expansion of the undeafferented inputs might have occurred. (**e**) Five weeks after an incomplete lesion, the intact hand inputs expand into all of the deafferented cortex much like that shown in **a**. (**f, g**) Longer recovery periods result in expansion of the face inputs into the hand region. If the lesion is incomplete (**f**) expansion of the face inputs occurs in addition to the earlier occurring expansion of the intact hand inputs. Inputs from the upper arm which enter the spinal cord rostral to the site of the lesion also show a limited lateralward expansion (**g**).

A second, but related question concerns the exact site of plasticity along the neuraxis. Information from the periphery is transmitted to the cortex via a series of subcortical 'way stations'. The plastic changes could occur at any of these processing stations and then be reflected in upstream regions. Suppose that expansion of the face representation occurs in the medulla such that the cuneate nucleus, which normally gets inputs from the hand now gets inputs from the face, then neurons in the upstream hand regions in the thalamus and cortex will also begin to respond to the stimulation of the face (figure 2). However, the subcortical nuclei are more than simple repeater stations. They receive feedback connections from upstream regions and dynamically modify the information they transmit. Changes that occur upstream can modify the information content downstream. Higher regions can potentiate the effects of the changes occurring earlier in the processing stream or they can inhibit the expression of these changes. Although plastic changes have been independently shown to occur at various levels, it has been harder to establish the site of initial and major changes, if there is one.

The third question is, why are adult brains plastic? Perceptual consequences of plasticity have been harder to establish in animal models because of obvious reasons. In humans, expansion of the face representation into the hand region might underlie the phantom limb phenomenon (Flor *et al* 1995; Borsook *et al* 1998). Patients with amputation of a limb feel as if their missing limb is being touched

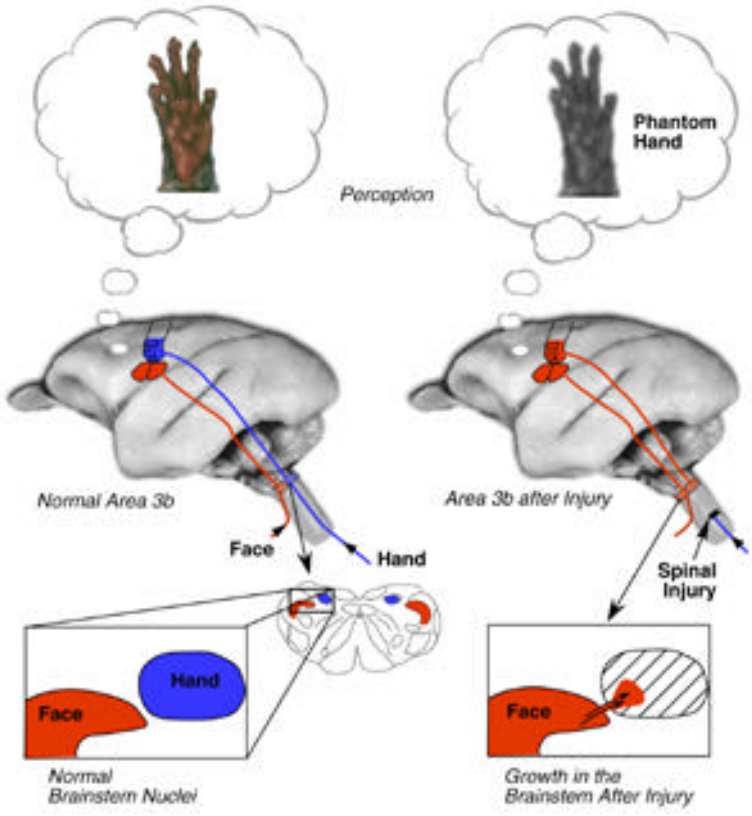

Figure 2. In a normal brain (left) the trigeminal nucleus of the brain stem, which receives inputs from the face, projects to the face region of area 3b, and the cuneate nucleus, which receives inputs from the hand, projects to the hand region. These nuclei project to the cortex via the ventroposterior nucleus of the thalamus (not shown). Following deafferentation by unilateral transection of the dorsal columns or amputation of an arm there is growth of the face inputs from the trigeminal nucleus into the cuneate nucleus (right; Jain *et al* 2000). These abnormal inputs to the cuneate nucleus, which can be further potentiated by changes in the thalamus or the cortex, will be reflected in area 3b as expansion of the face representation into the hand region. Moreover, if the areas processing outputs from the sensory cortex do not reorganize accordingly, activation of neurons in the hand cortex by a touch on the face will continue to be interpreted as a touch on the hand by the brain and will be perceived as a phantom sensation on the amputated hand.

when the skin of their stump or face is touched. An attractive hypothesis proposed to explain this is that since the hand region of the somatosensory cortex is receiving inputs from the face and the output circuits have not modified accordingly, a touch on the face is interpreted by the brain as a touch on the missing limb (figure 2). An analogous example from the visual system is filling-in of the scotoma (blind spot) in the visual field caused by retinal lesions. However, such misinterpretation of the self and surroundings are unlikely to confer any evolutionary advantage to the brain that undergoes plastic changes. Experiments involving temporary deafferentations by anaesthetics or those allowing nerve regeneration by suturing together ends of a cut peripheral nerve show that at least some of the plastic changes are reversible. Perhaps brain plasticity evolved as a mechanism to keep neurons in the deafferented regions of the brain active and therefore prevent them from degenerating while healing mechanisms repair the injury.

These questions need to be addressed if we are to develop effective therapeutic measures that use the capacity of the brain to reorganize. Such measures can help patients with injuries to the brain, spinal cord, or peripheral nerves, and enable us to build and effectively use intelligent or neuronally controlled prosthetic devices.

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