ment fulfill at this stage of developmental progression? The answer to this question is not clear, but an analogous event, positive selection, occurs during the development of T lymphocytes. Positive selection promotes the survival and maturation of T cells with a high likelihood of being functionally responsive. By analogy, the purpose of such a regulated step during B cell development could be to enhance the potential functionality of all peripheral B cells by ensuring that each B cell expresses a functional BCR or potentially useful antibody.

The two new checkpoints (see figure) may reflect distinct signaling thresholds and requirements for different developmental stages and differentiation events. The earlier new checkpoint revealed by the ablation of Ig-β appears not to require the Ig-α ITAM, although Ig-α may participate; alternatively, Ig-β may serve a different regulatory function. The checkpoint at the pre-BI to pre-BII transition is also satisfied reasonably well in the Ig-α mutant, although there was a small decrease in the number of pre-BII cells. Finally, exit of newly generated B cells from the bone marrow did require Ig-α cytoplasmic domain function and thus may have a higher threshold of Ig-α function than do the earlier checkpoints. Additional experiments are needed to test this possibility. Finally, these studies emphasize the central role of the BCR in regulating B cell development and provide new insights into the regulation of B cell development by defining two new checkpoints unlocked by BCR function.

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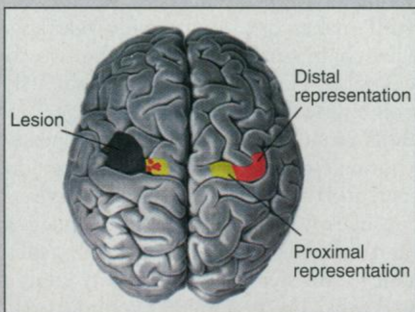
UPDATE

Remapping the Brain

Hans-Joachim Freund

The connections in the brain of a growing child are clearly shaped by experience—the learning of one's native language, for example—but evidence has shown that adult brains can also change dramatically when the inputs are altered. This became clear when researchers removed some of the sensory input to the brains of animals, and the "map" on the surface of the brain of the removed body part reorganized significantly (*1*). What happens when there is damage to the brain itself—a frequent result of stroke or traumatic injury? If such an injury is in the part of the motor cortex that controls hand movement, there is loss of "hand territory" in the cortical map that goes beyond the damaged tissue, extending into healthy cortex (*2*). In this issue, Nudo and co-workers (*3*), by mapping the motor cortex of squirrel monkeys before and after small ischemic lesions in the hand territory, show that the subsequent loss of hand representation around the lesion can be prevented by intensive retraining of hand skills starting 5 days after the injury.



Changing the brain map. Schematic view of reorganizational changes that occur as a result of cortical lesions in the human motor cortex [modified from (*9*)].

Progressive derangement of tissue around affected areas and the subsequent development of dysfunctional zones is frequent in experimental animals and stroke patients (*4, 5*). This process can be modified by use of the affected body part, but the success of the training depends critically on when training begins. Overuse of the affected limb during the first week after the lesion can increase the volume of the lesion (perhaps by glutamatergic excitotoxicity), whereas overuse during the second week does not (*6*).

But even without the training, the monkeys all eventually regained use of their hands. So, does it matter that the hand representation around the lesion could be preserved by training? In fact, there is mounting evidence that the reshaping of functionally useful circuits is facilitated by certain rehabilitative procedures. Highly stereotyped, repetitive training of the same movement is superior to conventional physiotherapy (*7*). The rhythmic proprioceptive and cutaneous input of repetitive training induces long-term potentiation in the sensorimotor cortex, a possible mechanism for motor learning. Relearning of disturbed hand skills is further reinforced by combining physiotherapy with the application of noradrenergic drugs that stimulate the reticular activating brain-stem system (*8*).

For true clinical benefit, the optimal time window and types of training for functional recovery have to be defined. Brain imaging methods, which allow the effects of various manipulations to be monitored, will facilitate this process: In patients with lesions of the motor cortex, movements of the contralesional hand activate areas outside the former hand representation (see figure). In patients with tumors, the activation occurs even outside the motor cortex (*9*), indicating the potential for large-scale plasticity after longer time periods. The modification of cortical maps around lesions by specific treatment protocols and their meticulous correlation with functional improvement will define the interplay between neural and behavioral events, setting the stage for new approaches to rehabilitative medicine.

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