Evidence for Four Forms of Neuroplasticity

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Summary

We suggest that at least four major forms of functional neuroplasticity can be studied in normal human subjects and patients. The four forms of functional neuroplasticity are homologous area adaptation, cross-modal reassignment, map expansion, and compensatory masquerade. Homologous area adaptation is the assumption of a particular cognitive process by a homologous region in the opposite hemisphere. Cross-modal reassignment occurs when structures previously devoted to processing a particular kind of sensory input now accept input from a new sensory modality. Map expansion is the enlargement of a functional brain region on the basis of performance. Compensatory masquerade is a novel allocation of a particular cognitive process to perform a task. By focusing on these four forms of functional neuroplasticity, several fundamental questions about how functional cooperation between brain regions is achieved can be addressed.

Introduction

Recent research in cognitive neuroscience has made great strides in mapping the functions of the human brain and in determining the knowledge, representational elements, and processes that are subserved by cognitive maps (Merzenich et al. 1996a). Although much work remains to be done to provide a mature functional cartographic atlas of the cerebral cortex and subcortical structures, some assumptions about how representational knowledge is stored are generally agreed upon. The brain appears to be composed of modular neural networks (for the purposes of this chapter, their "penetrability" will be ignored) within which a defined representational unit is homogeneously represented. Such units may range from edge detectors, used in visual processing (Gilbert 1996) and stored in the occipital cortex, to high-level plans used to guide behavior and stored in

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Building a Bridge from the Laboratory to the Clinic

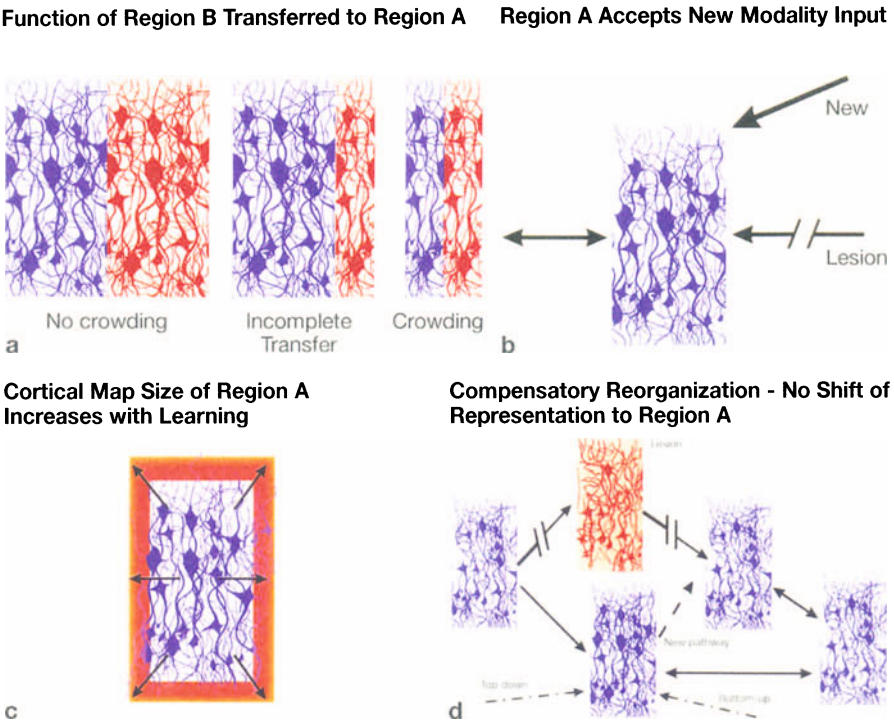

Fig. 1. Illustration of four major forms of neuronal system plasticity. The first form of plasticity (**a**) indicates that, during childhood, the functions of a particular region may be literally transferred to another brain area (homologous region adaptation). The second form (**b**) indicates that a particular brain region may accept input from another modality that, although ordinarily processed elsewhere in the brain, is now diverted to that region for specific information processing purposes (cross-modal reassignment). The third form of plasticity (**c**) indicates that changes in cortical map topography can occur for a variety of reasons, including skill learning and passive invasion of neighboring cortical tissue following trauma to that tissue or its input system (map expansion). The fourth form of plasticity (**d**) indicates that a spared brain region has assumed a primary role in performing a task after an injury to a focal brain region that previously played the prominent processing role (compensatory masquerade). See the text for more details.

the prefrontal cortex (Grafman 1995). To perform a typical human function, sets of modules are cooperatively activated. Thus, the human brain can be subdivided into its constituent functional (subcomponent) modules, sets of which must be combined in order to perform a task.

Current thinking about neuroplasticity suggests that there are at least *four major kinds of potential neuroplastic changes* operating at the representational module level (Fig. 1a–d). These are *homologous area adaptation, cross-modal reassignment, map expansion,* and *compensatory masquerade.*

Four Forms of Neuroplasticity

One form of neuroplasticity, *homologous area adaptation,* appears most active during an early, critical stage of human development and underlies the notion that damage to a particular brain region and its cognitive operation(s) can be compensated for by shifting the individual (or set of) operation(s) to other brain areas that do not include the affected module (e.g., the function is usually shifted to another module in the homologous region of the opposite hemisphere; Chugani et al. 1996). The result of this neuroplastic change has led to the idea that the new brain area accepting a new cognitive operation is now more "crowded" with distinct cognitive representations. This crowding leads to a sparser representation of knowledge within the shifted module and increases the likelihood of dual-task interference when two tasks to be performed simultaneously involve adjacent "modules" in the cortex – one of which has been shifted from its former and "natural" location in the brain. This form of neuroplastic change is reported less often in adults.

In a single-case study (Levin et al. 1996), we studied an adolescent who had incurred a severe right parietal lobe brain injury as a young child. Despite the severity and location of the injury, our evaluation showed that the adolescent had developed relatively normal visuospatial skills but had impaired arithmetic skills. The inference is that, at the time of the injury, the left parietal region assumed some of the responsibilities of the functions normally stored in the right parietal lobe. Since much of arithmetic computation is learned in school, the injury and plasticity occurred prior to the age of arithmetic acquisition. Thus, we argued that spatial processes had claimed the left parietal region prior to arithmetic instruction, making it much more difficult for the patient to learn and store arithmetic facts. In essence, there was little room left in the left parietal lobe for the storage of arithmetic facts and concepts. Functional magnetic resonance imaging of this patient during arithmetic processing indicated that, in fact, he activated left parietal tissue (among other regions), showing that that region was still genetically programmed to store arithmetic facts even if it was now more committed to spatial processing.

Some investigators have claimed that there is a relationship between the proportion of a functional region that is damaged and the amount of homologous region adaptation that can occur. The homologous region to the one that is damaged is only able to reorganize and assume a new function when contralateral inhibitory input is removed. Given this logic, it would be more useful to have complete rather than incomplete damage to a region where a primary function was represented in order for an optimal transfer of function to a homologous area to occur.

We recently had a chance to study another patient who suffered a severe stroke destroying almost the entire left hemisphere, although he had some spared, functionally active islands in the left parietal and frontal cortices (Basso et al., manuscript in preparation; Grafman et al., manuscript in preparation). This patient could read words but not nonwords. He also had great difficulty per-

forming calculations. We studied him while he was performing behavioral tasks with functional magnetic resonance imaging. Word reading activated a broadly distributed network in the right hemisphere. Attempts to read nonwords activated widely scattered and punctate areas in the left hemisphere. This finding suggests that the right hemisphere could assume some functions of the left hemisphere after massive damage. It seems clear that the major reading pathways in the left hemisphere were destroyed, allowing the right hemisphere to assume its reading functions; however, phonological construction required for nonwords could not be transferred, highlighting some of the limitations of this form of functional neuroplasticity in adulthood. Interestingly, during fMRI scanning while the patient was performing arithmetic fact verification, we found both right and left parietal lobe activation. Even with this bilateral activation pattern, the patient performed poorly, although his performance slightly increased in accuracy after a week's worth of training (with a concomitant increase in cortical activation). It can be inferred that, in this case, the remaining left parietal tissue was inhibiting the right parietal cortex from assuming more of a role in calculation, leading to a less-than-adequate (if at all) transfer of function to the right hemisphere. Although this case study is suggestive of the limits of homologous region adaptation, much more work is needed to confirm this speculative hypothesis, since an alternative view could be that both areas are needed to perform this complex task.

A second form of neuroplasticity, *cross-modal reassignment*, involves the introduction of new inputs into a representational brain region that has been deprived of its main inputs. For example, PET and fMRI studies of tactile discrimination ability have shown that subjects who became blind early in childhood, but were tested as adults, have somatosensory input redirected into area V1 of the occipital cortex, whereas normal controls do not show evidence of any V1 activation during the same task (Sadato et al. 1996). Perhaps, in the blind, such input succeeds in activating the representations stored in area V1 because such representations are in an "abstract format", that is, the cognitive operations are independent of the modality of input. For example, discrimination of meaningful geometric forms (such as Braille letters) could occur in previously defined primary visual areas if the new modality of input required the same kind of geometric form discrimination that is ordinarily handled by the "visual system." In the study referred to, only tactile discrimination of raised Braille dots that revealed geometric form (as opposed to simply passing the hand across a raised homogeneous field of tactile stimuli) or language activated V1 in the blind. In contrast, in normal subjects exposed to the same stimuli and tasks, not only was V1 activation not found, but there was evidence of decreased activation in area V1, suggesting that attention devoted to brain regions processing the tactile features of stimuli (e.g., parietal cortex) ordinarily inhibit competitive brain systems (such as the visual system). This inhibitory activity also suggests that – even in adults – there may be a pre-existing pathway (currently used for inhibition) that potentially could be transformed for facilitation during the processing of alternatively presented information (such as tactual information).

A recent study using transcranial magnetic stimulation over the occipital cortex in blind subjects (Cohen et al. 1997) was also able to demonstrate interference with Braille reading in subjects blind from birth or shortly afterwards (within a few years of birth). However, there are probably limitations to the feasibility of this form of neuroplasticity. For example, color processing cells in the occipital cortex are specialized for visual input and would be unlikely to accept other forms of input.

The third form of neuroplasticity, *map expansion*, demonstrates the flexibility of brain regions devoted to a particular kind of knowledge or cognitive operation. Recent work has indicated that the size of cortical maps devoted to a particular information processing function may enlarge with skilled practice or frequent exposure to a stimulus. In two studies using two different techniques (transcranial magnetic stimulation and electroencephalography; Pascual-Leone et al. 1994; Zhuang et al. 1997), we demonstrated that implicit learning of a visuomotor sequence induced sensorimotor map expansion in the early stages of (implicit) learning. When learning became explicit, the cortical map size returned to baseline. This enlargement can be quickly seen over the first few minutes of practice or exposure. There is also evidence that this rapid enlargement of selected cortical maps can be persistent in individuals who develop or are trained in a particular skill that they need to utilize on a routine basis (Rosenzweig and Bennett 1996). The meaning of map expansion is still unclear (Donoghue 1995). It is possible that it could have two implications. One is that, with use, the cortical region devoted to a particular operation can expand into other regions usually dedicated to another function, in essence recruiting new neurons into the network. However, over practice, sometimes regions show increased activation and sometimes regions show decreasing activation. Another implication of map expansion follows from these observations. That is, when the exact unit of representation to be used to process the bottom-up or top-down information is still undecided, the entire network needs to be active. When the exact unit of representation is selected, the network can relax and less energy is expended.

The fourth form of neuroplasticity, *compensatory masquerade*, means that the novel use of an established, but intact, cognitive process to perform a task previously dependent upon an impaired cognitive process has occurred. This can be an insidious process whose discovery is dependent upon the utilization of fine-grained cognitive tasks. For example, there may be many ways to navigate a route from home to the office. One way may depend most upon a sense of spatial coordinates, is relatively implicit, and is performed rapidly. Another way may depend on verbal labeling of landmarks, is relatively explicit, and is performed more slowly. A brain injury may affect either process but spare one. The patient may then be able, over a short period of time, to use the strategy that is spared to navigate the same path. Unless a neuropsychological study evaluated both processes in some detail, the investigator could be misled into thinking that a more basic form of neuroplasticity had occurred (e.g., homologous area adaptation) rather than a realigned distributed network composed of previously existing

modules that played a previously minor role in performing the task now catapulted into a major role.

Discussion

These four major forms of neuroplasticity can be studied in normal human subjects and patients. Other levels of neuroplasticity that have been, and continue to be, thoroughly studied in in vivo and in vitro preparations include structural changes at the synaptic junction following repeated stimulation (Buonomano et al. 1997; Debanne 1996; Frotscher et al. 1997; Gu 1995; Ide et al. 1996; Kirkwood and Bear 1995). However, we believe that by focusing on the four forms of plasticity outlined above, several fundamental questions about how functional cooperation between brain regions is achieved can be asked. The implication of answering these questions for learning potential and recovery of function from brain injuries is profound, as we outline below.

Why does shifting the functional operations of a particular brain region to a more distant site seem to decline over development? We hypothesize that this may be directly due to increasing connectivity between maturing cortical and subcortical areas dedicated to a particular cognitive or information processing operation. The increasing magnitude and stability of the connectivity implies that highly sensitive distributed networks are formed which, when co-activated, lead to the performance of varied cognitive tasks. If functional substitution was permitted beyond the early stages of the formation of these distributed but connected and functionally committed modules, then a rather chaotic situation would emerge that could potentially require continual (and substantial) reorganization of distributed networks (potentially resembling the somewhat random and incompetent wiring of telephone lines that littered downtown Buenos Aires in the last decade). This situation would prove to be extraordinarily ineffective and disruptive to the ongoing process of learning and memory that development entails. Thus, we predict a direct association between the solidifying of connections between components of a distributed network and a decline in functional substitution ability of the involved components.

A second hypothesis about plasticity emerges from the similarity in certain cortical operations across apparently modality-specific regions of sensory cortex, as described above as a second form of neuroplasticity. In the example we used, the occipital lobe, comprising several cortical areas concerned with discriminating among vertical and horizontal features of objects, was deprived of visual input. In this circumstance, should one expect atrophy and lack of activation across V1? There is now evidence that tactile input could be processed in area V1 if discrimination of the same stimulus properties was required, i.e., discrimination of width, angles, and feature conjunctions. In this case, a stable module (in terms of retaining its basic connecting paths to and from other cortical modules) takes over the processing of geometric stimuli, even though the input is now tactile and not visual. Thus, no dramatic restructuring of distributed networks is

necessary as further, more complex processing of such stimuli proceeds normally through the network.

The third form of neural plasticity reflects a functional "balkanization" of the cerebral cortex regions devoted to various cognitive operations. That is, there is a natural competitiveness among cortical regions which is reflected in constantly shifting boundaries between local cortical areas. This boundary shift is rather non-disruptive during normal learning, although an area that subserves a skill that is particularly valued by the person (e.g., guitar playing) can, over time, capture more cortical territory (e.g., cortical maps subserving finger representation in the hand that forms chords or plucks strings may enlarge). In the case of peripheral damage to a limb, cortical regions adjacent to territory representing the now lost limb invade the lost limb's previous cortical territory, staking out claims for the now uncommitted neurons (Aglioti et al. 1994; Melzack et al. 1997). Naturally, the most functionally active of the adjacent cortical regions will capture more cortical territory. However, some neurons may be activated by top-down processing, driving them to reincarnate, through mental imagery, images of the limb and sensation of its previous motoric capacity. Finally, when partial loss of an area occurs as a result of brain damage, adjacent cortical regions also may overlap with the damaged regions, affecting the ability of the patient to recover and perhaps causing interference during the simultaneous performance of tasks, requiring the participation of both affected and unaffected adjacent cortical regions.

In summary, we argue that there is evidence for four forms of functional plasticity: the first, homologous region adaptation, which is limited by the development of mature distributed neural networks; the second form allows novel sensory input into a module or set of modules previously receiving evolutionary determined primary sensory input; the third is present throughout the lifespan and allows the normal ebb and flow of modular boundaries depending on the frequency of use of that module in cognitive, motor, or sensory processing; and the fourth, compensatory masquerade, which is simply a reorganization of pre-existing functional neuronal networks.

There are many contemporary frameworks for conceptualizing neuroplasticity (DeLisi 1997; Goldman and Plum 1997; Kapur 1996; Leviton et al. 1995; Luders et al. 1997; Mirmiran et al. 1996; Plaut 1996; Seil 1997; Seitz and Freund 1997; Wolf 1996). Given the view of functional plasticity we subscribe to, in what direction should future research proceed? We suggest that emphasizing map topography manipulation and rerouting of input systems would give cognitive neuroscience research efforts the biggest immediate payoff. It is clear that map changes occur with learning and use, but the limitations of such topographic changes in functional reorganization are unknown. Are the map changes governed by a neurogeometric principle that is determined by the distance of neuronal columns from the epicenter of the neighboring functional region? Perhaps that geometric variable interacts with the overall size of the functional region as well as with the residual activation of neighboring functional regions to determine its neuroplastic capability. In any case, these hypotheses can be tested in

both normal subjects (during learning and dual-task paradigms that activate neighboring functional maps) as well as patients (looking at training-induced versus passively induced changes in cortical map size) and should be relevant for measuring functional improvement during and after participation in cognitive rehabilitation programs (Irvine and Rajan 1996; Merzenich et al. 1996b). The input substitution approach is also potentially very promising. It may be able to tell us which functional areas are able to accept a variety of primary sensory inputs based on a common input signal or that the receiving brain region is less concerned with the input modality than with processing a certain kind of coded input (e.g., geometric form). Although such a region may have a primary input based on evolutionary development, it may be able to accept atypical sensory input because of the similarity of the information being processed. These cross-modal reassignment studies can be administered to normal subjects (using sensory or cognitive deprivation paradigms) and patients with acquired sensory lesions (e.g., blind or deaf subjects).

Obtaining experimental control over paradigms designed to manipulate functional neuroplasticity in normal subjects and patients is advantageous since it allows for control over, and specification of, the conditions under which functional neuroplasticity can occur (Rauschecker 1997). This kind of control also allows for the eventual development of "challenge" studies using pharmacologic agents to facilitate or inhibit any functional neuroplastic changes that can be identified using the experimental procedures suggested in the previous paragraph. Indeed, the future looks promising as we probe the limits of functional neuroplasticity in the adult human while answering fundamental questions about the stable and dynamic topography of cortical and subcortical information processing maps.

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