

# The Plastic Human Brain Cortex

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Annu. Rev. Neurosci.  
2005. 28:377–401

doi: 10.1146/  
annurev.neuro.27.070203.144216

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0147-006X/05/0721-  
0377\$20.00

## Key Words

stroke, blindness, neurorehabilitation, neuromodulation,  
crossmodal plasticity, cortical stimulation, functional  
neuroimaging

## Abstract

Plasticity is an intrinsic property of the human brain and represents evolution's invention to enable the nervous system to escape the restrictions of its own genome and thus adapt to environmental pressures, physiologic changes, and experiences. Dynamic shifts in the strength of preexisting connections across distributed neural networks, changes in task-related cortico-cortical and cortico-subcortical coherence and modifications of the mapping between behavior and neural activity take place in response to changes in afferent input or efferent demand. Such rapid, ongoing changes may be followed by the establishment of new connections through dendritic growth and arborization. However, they harbor the danger that the evolving pattern of neural activation may in itself lead to abnormal behavior. Plasticity is the mechanism for development and learning, as much as a cause of pathology. The challenge we face is to learn enough about the mechanisms of plasticity to modulate them to achieve the best behavioral outcome for a given subject.

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## THE CONCEPT OF PLASTICITY

“Plastic” is derived from the Greek word  $\pi\lambda\alpha\sigma\tau\acute{o}\sigma$  (plastos), which means molded. According to the Oxford English Dictionary, being plastic refers to the ability to undergo a change in shape. William James (1890) in *The Principles of Psychology* was the first to introduce the term plasticity to the neurosciences in reference to the susceptibility of human behavior to modification.

Plasticity [...] means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once. Each relatively stable phase of equilibrium in such a structure is marked by what we may call a new set of habits. Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of

plasticity of this sort; so that we may without hesitation lay down as our first proposition the following, that the phenomena of habit in living beings are due to the plasticity. (p. 68)

Some years later, Santiago Ramón y Cajal (1904) in the *Textura del Sistema Nervioso* argued that behavioral modifiability must have an anatomical basis in the brain and thus extended the notion of plasticity to the neural substrate. Considering the acquisition of new skills, Cajal wrote

La labor de un pianista [...] es inaccesible para el hombre ineducado ya que la adquisición de nuevas habilidades requiere muchos años de práctica mental y física. Para entender plenamente este complejo fenómeno se hace necesario admitir, además del refuerzo de vías orgánicas preestablecidas, la formación de vías nuevas por ramificación y crecimiento progresivo de la arborización dendrítica y terminales nerviosas.<sup>1</sup> (p. 296)

We argue that plasticity is an intrinsic property of the nervous system retained throughout a lifespan and that it is not possible to understand normal psychological function or the manifestations or consequences of disease without invoking the concept of brain plasticity. The brain, as the source of human behavior, is by design molded by environmental changes and pressures, physiologic modifications, and experiences. This is the mechanism for learning and for growth and development—changes in the input of any neural system, or in the targets or demands of its efferent connections, lead to system

<sup>1</sup>The labor of a pianist [...] is inaccessible for the uneducated man as the acquisition of new skill requires many years of mental and physical practice. In order to fully understand this complex phenomenon it becomes necessary to admit, in addition to the reinforcement of pre-established organic pathways, the formation of new pathways through ramification and progressive growth of the dendritic arborization and the nervous terminals.

reorganization that might be demonstrable at the level of behavior, anatomy, and physiology and down to the cellular and molecular levels.

Therefore, plasticity is not an occasional state of the nervous system; instead, it is the normal ongoing state of the nervous system throughout the life span. A full, coherent account of any sensory or cognitive theory has to build into its framework the fact that the nervous system, and particularly the brain, undergoes continuous changes in response to modifications in its input afferents and output targets. Implicit to the commonly held notion of plasticity is the concept that there is a definable starting point after which one may be able to record and measure change. In fact, there is no such beginning point because any event falls upon a moving target, i.e., a brain undergoing constant change triggered by previous events or resulting from intrinsic remodeling activity. We should not therefore conceive of the brain as a stationary object capable of activating a cascade of changes that we call plasticity, nor as an orderly stream of events driven by plasticity. Instead we should think of the nervous system as a continuously changing structure of which plasticity is an integral property and the obligatory consequence of each sensory input, motor act, association, reward signal, action plan, or awareness. In this framework, notions such as psychological processes as distinct from organic-based functions or dysfunctions cease to be informative. Behavior will lead to changes in brain circuitry, just as changes in brain circuitry will lead to behavioral modifications.

The mapping between behavioral modifiability (James 1890) and brain plasticity (Cajal 1904) is not one to one. Therefore, depending on the circumstances, neural plasticity can confer no perceptible change in the behavioral output of the brain, can lead to changes demonstrated only under special testing conditions, or can cause behavioral changes that may force the patient to seek medical attention. There may be loss of a previously acquired behavioral capacity, release of behaviors normally suppressed in the unin-

jured brain, takeover of lost function by neighboring systems (albeit perhaps incompletely or via different strategies and computations), or the emergence of new behaviors that may prove adaptive or maladaptive for the individual. Plasticity at the neural level does not speak to the question of behavioral change and certainly does not necessarily imply functional recovery or even functional change. The challenge we face is to learn enough about the mechanisms of plasticity and the mapping relations between brain activity and behavior to be able to guide it, suppressing changes that may lead to undesirable behaviors while accelerating or enhancing those that result in a behavioral benefit for the subject or patient.

In this review we first discuss mechanisms of plasticity and strategies for its modulation in the motor system during the acquisition of motor skills and the recovery of function after a stroke. Then we focus on crossmodal plasticity following sensory loss, i.e., blindness, to illustrate the fundamental nature of plasticity and emphasize the principles that are applicable across systems.

## TWO-STEP CHANGES

Cajal (1904) predicted that with the acquisition of new skills the brain would change through rapid reinforcement of preestablished organic pathways and later formation of new pathways. We hypothesize that the first of these processes is in fact a necessary requirement for the development of the second. Formation of new pathways is possible only following initial reinforcement of preexistent connections. Therefore, the scope of possible plastic changes is defined by existing connections, which are the result of genetically controlled neural development and are ultimately different across individuals. Reinforcement of existing connections, on the other hand, is the consequence of environmental influences, afferent input, and efferent demand.

These two steps of plasticity are illustrated by the following experiment (Pascual-Leone 1996, Pascual-Leone et al. 1995). Normal

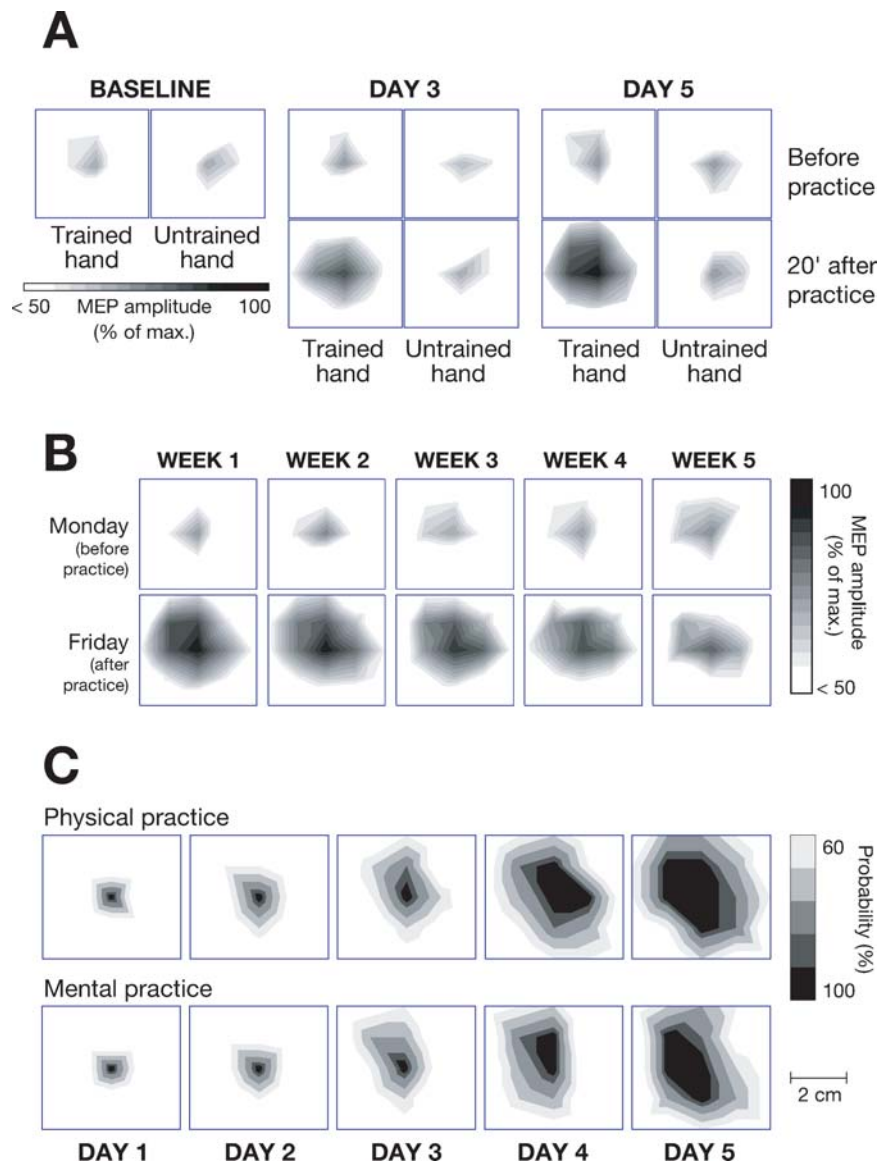
subjects were taught to perform with one hand a five-finger exercise on a piano keyboard connected via computer musical interface. The subjects were instructed to perform the sequence of finger movements fluently, without pauses, and without skipping any keys, while paying particular attention to keeping the interval between the individual key presses constant and the duration of each key press the same. A metronome gave a tempo of 60 beats per minutes for which the subjects were asked to aim, as they performed the exercise under auditory feedback. Subjects were studied on five consecutive days, and each day they had a two-hour practice session followed by a test. The test consisted of the execution of 20 repetitions of the five-finger exercise. The number of sequence errors decreased, and the duration, accuracy, and variability of the intervals between key pushes (as marked by the metronome beats) improved significantly over the course of the five days. Before the first practice session on the first day of the experiment and daily thereafter, we used focal transcranial magnetic stimulation (TMS) to map the motor cortical areas targeting long finger flexor and extensor muscles bilaterally. As the subjects' performance improved, the threshold for TMS activation of the finger flexor and extensor muscles decreased steadily. Even considering this change in threshold, the size of the cortical representation for both muscle groups increased significantly (**Figure 1A**). However, this increase could be demonstrated only when the cortical mapping studies were conducted following a 20- to 30-min rest period after the practice (and test) session (Pascual-Leone 1996). No such modulation in the cortical output maps was noted when maps were obtained before each daily practice session (**Figure 1A**).

Remarkably, mental practice resulted in a similar reorganization of the motor outputs to the one observed in the group of subjects that physically practiced the movements (**Figure 1C**). Mental simulation of movements activates some of the same central neural structures required for the performance

of the actual movements (Roland et al. 1987, Decety & Ingvar 1990). In doing so, mental practice alone may be sufficient to promote the plastic modulation of neural circuits placing the subjects at an advantage for faster skill learning with minimal physical practice, presumably by making the reinforcement of existing connections easier and perhaps speeding up the process of subsequent sprouting and consolidating of memories.

Once near-perfect level of performance was reached at the end of a week of daily practice, subjects were randomized into two groups (**Figure 1B**). Group 1 continued daily practice of the same piano exercise during the following four weeks. Group 2 stopped practicing. During the four weeks of follow-up, cortical output maps for finger flexor and extensor muscles were obtained in all subjects on Mondays (before the first practice session of that week in group 1), and on Fridays (after the last practice session for the week in group 1). In the group that continued practicing (group 1), the cortical output maps obtained on Fridays showed an initial peak and eventually a slow decrease in size despite continued performance improvement. On the other hand, the maps obtained on Mondays, before the practice session and following the week-end rest, showed a small change from baseline with a tendency to increase in size over the course of the study. In group 2, the maps returned to baseline after the first week of follow-up and remained stable thereafter.

This experiment reveals that acquisition of the necessary motor skills to perform a five-finger movement exercise correctly is associated with reorganization in the cortical motor outputs to the muscles involved in the task. The rapid time course in the initial modulation of the motor outputs, by which a certain region of motor cortex can reversibly increase its influence on a motoneuron pool, is most compatible with the unmasking of previously existing connections (Jacobs & Donoghue 1991, Sanes et al. 1992). Supporting this notion, the initial changes are quite transient: demonstrable after practice, but



**Figure 1**

Changes in cortical output maps associated with learning a five-finger exercise on the piano (modified from Pascual-Leone 1996, Pascual-Leone et al. 1995). *A*: Cortical output maps for the finger flexors of the trained and the untrained hands of a representative subject (see text and Pascual-Leone et al. 1995 for details on mapping method). Note the marked changes of the output maps for the trained hand following practice and the lack of changes for the untrained hand. Note further the significant difference in cortical output maps for the trained hand after the practice sessions on days 3–5. *B*: Serial cortical output maps to finger flexors in a representative subject during five weeks of daily (Monday to Friday) practice of the five-finger exercise on the piano. Note that there are two distinct processes in action, one accounting for the rapid modulation of the maps from Mondays to Fridays and the other responsible for the slow and more discrete changes in Monday maps over time. *C*: Average cortical output maps for the finger flexors of the trained hand in subjects undergoing daily physical versus mental practice. Note the similarity in output maps with either form of practice.

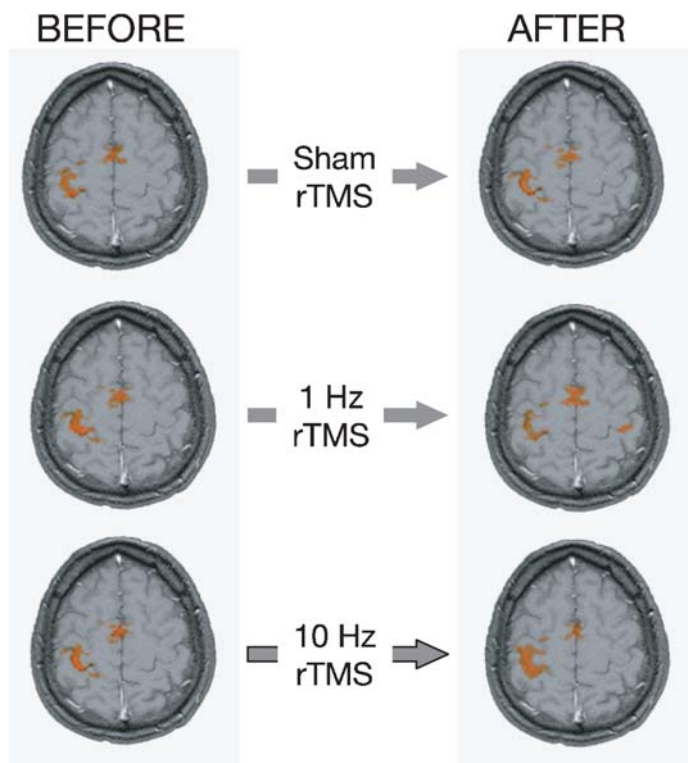
returning to baseline after a weekend rest. As the task becomes overlearned over the course of five weeks, the pattern of cortical activation for optimal task performance changes as other neural structures take a more leading role in task performance. We suggest that flexible, short-term modulation of existing pathways represents a first and necessary step leading up to longer-term structural changes in the intracortical and subcortical networks as skills become overlearned and automatic.

A growing number of neuroimaging studies have suggested a similar two-step process (Seitz et al. 1990; Grafton et al. 1992; Jenkins et al. 1994; Karni et al. 1995, 1998).

### THE RAPIDLY SHIFTING MAPPING BETWEEN BRAIN ACTIVITY AND BEHAVIOR

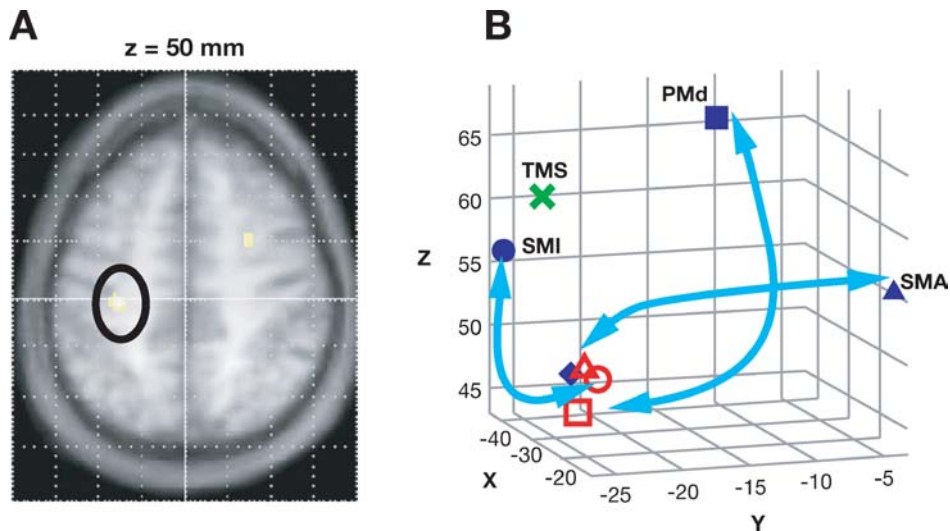
Behavior is the manifestation of the coordinated workings of the entire nervous system. As long as an output pathway to manifest the behavior is preserved (even if alternate pathways need to be unmasked or facilitated), changes in the activity across a distributed neural network may be able to establish new patterns of brain activation and sustain function. These notions are illustrated by the following experiment (**Figure 2**). We asked normal subjects to open and close their fist deliberately at a self-paced rhythm of approximately one movement every second while lying in an fMRI scanner. As compared with during rest, during movement there was a significant activation of the motor cortex (M1) contralateral to the moving hand and of the rostral supplementary motor cortex (SMA). If motor cortex activity is modified by repetitive TMS, the pattern of brain activation changes as behavioral integrity is maintained. Application of slow, repetitive TMS to the contralateral M1 (presumed to suppress neuronal firing; Walsh & Pascual-Leone 2003) results in increased activation of the rostral SMA and of M1 ipsilateral to the moving hand. Conversely, increasing excitability in the contralateral M1 (by application of fast, repetitive TMS) leads to a decrease in activation of rostral SMA.

In a very elegant study, Lee et al. (2003) combining TMS and positron emission tomography (PET) have provided supporting evidence to these notions and critically extended it by revealing the shifts in cortico-cortical and cortico-subcortical connectivity underlying the changes in cortical activation patterns (**Figure 3**). Following rTMS, task-dependent increases in rCBF were seen



**Figure 2**

Brain activation in fMRI while subjects performed the same rhythmic hand movement (under careful kinematic control) before and after repetitive transcranial magnetic stimulation (rTMS) of the contralateral motor cortex. Following sham rTMS (*top row*) there is no change in the significant activation of the motor cortex (M1) contralateral to the moving hand and of the rostral supplementary motor cortex (SMA). After M1 activity is suppressed using 1Hz rTMS (1600 stimuli, 90% of motor threshold intensity; *middle row*), there is an increased activation of the rostral SMA and of M1 ipsilateral to the moving hand. Increasing excitability in the contralateral M1 using high-frequency rTMS (20 Hz, 90% of motor threshold intensity, 1600 stimuli; *bottom row*) results in a decrease in activation of rostral SMA.



**Figure 3**

Areas of the brain showing differential movement-related responses and coupling after rTMS. Modified from Lee et al. 2003 (copyright 2003 by the Society for Neuroscience). *A*: Increased movement-related activity after 1Hz rTMS to the motor cortex. Results are displayed on an axial section of averaged anatomical MRI scans ( $p < 0.001$ , uncorrected). *B*: Circle, square, and triangle symbols indicating sites in primary motor cortex (*open symbols*) that are more strongly coupled to activity in sensorimotor cortex (SM1), dorsal premotor cortex (PMd), and supplementary motor cortex (SMA) after rTMS. The solid diamond indicates the position of the SM1 site circled in **Figure 3A**. X marks the site of stimulation with 1Hz rTMS.

during movement in the directly stimulated primary motor cortex and the dorsal premotor cortex in the unstimulated hemisphere, whereas motor performance remained unchanged. Analyses of effective connectivity showed that after rTMS there is a remodeling of the motor system, with increased movement-related connectivity from the SMA and premotor cortex to sites in primary sensorimotor cortex.

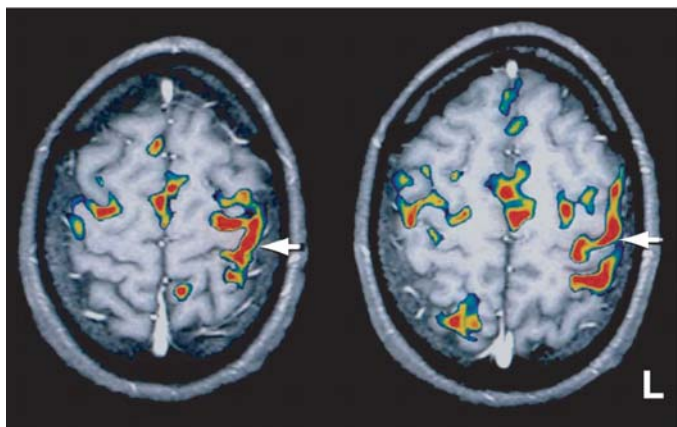
Both of these experiments demonstrate that in the face of a change in motor cortex activity (in these cases transient disruption induced by rTMS; Walsh & Pascual-Leone 2003) performance of a relatively simple movement task can be maintained by rapid operational remapping of motor representations, recruitment of additional motor areas, and task-related changes in cortico-cortical and cortico-muscular coherence (Strens et al. 2002, Chen et al. 2003, Lee et al. 2003, Oliviero et al. 2003).

### THE RISK OF CHANGE AND THE OPPORTUNITY FOR INTERVENTION

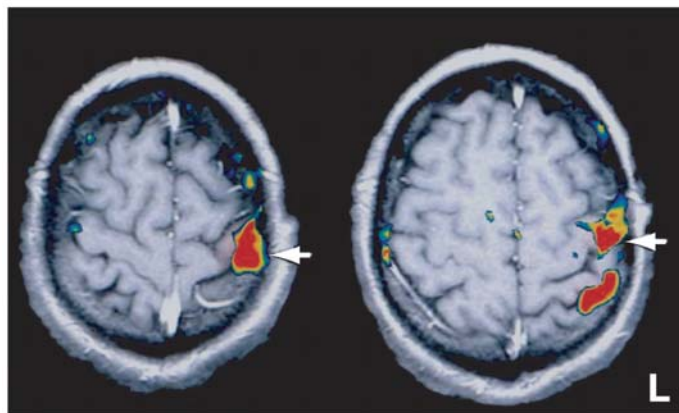
A system capable of such flexible reorganization harbors the risk of unwanted change. Increased demand of sensorimotor integration poses such a risk. Faulty practice or excessive demand in the presence of certain predisposing factors (for example, genetic) may result in unwanted cortical rearrangement and lead to disease. Focal hand dystonia in musicians (Chamagne 2003) is such an example of pathological consequences of plasticity.

We examined five guitarists using fMRI during dystonic symptom provocation by means of an adapted guitar inside the magnet (Pujol et al. 2000). As reference we used the activation pattern obtained in the same subjects during other hand movements and in matched guitar players without dystonia during the execution of the same guitar-playing

## NORMAL CONTROL



## DYSTONIA PATIENT



**Figure 4**

BOLD fMRI images of a normal and a dystonic guitar player executing right hand arpeggios in the scanner. Note the greater activation of the sensorimotor cortex (*arrows*) contralateral to the performing hand and the lack of activation of premotor and supplementary motor cortices in the dystonic patient. Modified from Pujol et al. 2000.

exercises. Dystonic musicians compared with both control situations showed a significantly larger activation of the contralateral primary sensorimotor cortex that contrasted with a conspicuous bilateral underactivation of premotor areas (**Figure 4**). Our results coincide with studies of other dystonia types because they show an abnormal recruitment of cortical areas involved in the control of voluntary movement. Our study demonstrates that the primary sensorimotor cortex in patients with focal dystonia is overactive when they are tested during full expression of the task-induced movement disorder. The implication is that the established mapping between brain activity and behavior is inadequate and

ultimately maladaptive, giving rise to symptoms of pathology. A sensory disturbance or sensorimotor mismatch may play a crucial role in contributing to the establishment of such an undesirable pattern of cortical activation (Hallett 1995, Bara-Jimenez et al. 1998, Elbert et al. 1998, Pantev et al. 2001).

Regardless of the role that sensory dysfunction may play, suppression of the task-specific excessive activation of the motor cortex has beneficial behavioral consequences for the symptoms of dystonia. For example, application of slow, repetitive TMS to the contralateral motor cortex suppresses cortical excitability by increasing intracortical inhibition and leads to a transient but significant improvement of dystonic symptoms in some patients (Siebner et al. 1999). Sensorimotor retuning (Candia et al. 1999, 2002), where motor activity is constrained using an individually designed splint so as to prevent dystonic posturing, is likely to induce its remarkable beneficial effects on dystonia by a similar mechanism of reducing task-specific motor cortical activation, thus promoting the establishment of a more adaptive mapping between brain activity and behavior (Candia et al. 2003). It is thus possible to induce shifts in brain activity either by guiding (and constraining) behavior or by directly modulating neuronal firing, for example through cortical stimulation. In either case, the plastic property of the nervous system is utilized to induce a behaviorally desirable outcome.

## PLASTICITY IN THE SETTING OF BRAIN INJURY

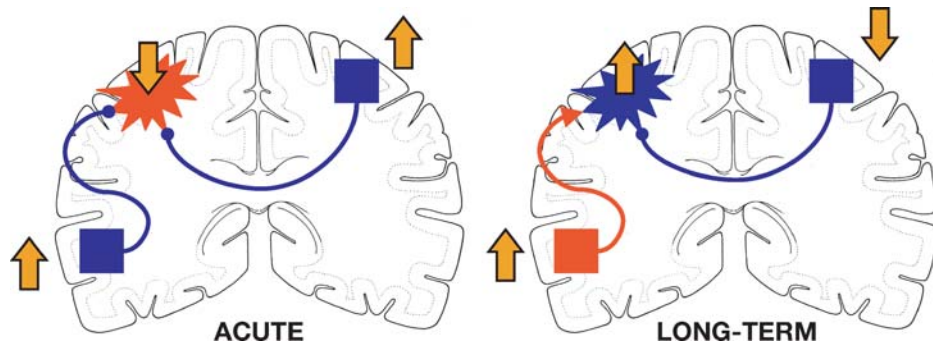
That plasticity is a capacity of the brain that can be activated in response to an insult to promote functional recovery or compensate for lost function is a misconception. Rather, plasticity is always activated. Following brain injury, behavior (regardless of whether normal or manifesting injury-related deficits) remains the consequence of the functioning of the entire brain, and thus the consequence of a plastic nervous system. Symptoms are

not the manifestation of the injured brain region, but rather the expression of plastic changes in the rest of the brain. After a lesion, just like after an rTMS-induced shift in activity in the primary motor cortex (see above), parallel motor circuits might be activated to establish some alternative input to the spinal motoneurons. These parallel circuits may originate from the contralateral, undamaged primary motor area (M1), bilateral premotor areas (PMA), bilateral supplementary motor areas (SMA), bilateral somatosensory areas, cerebellum, basal ganglia, etc. As long as efferent, cortico-spinal output pathways exist, cortico-cortical and cortico-subcortico-cortical interactions will shift weights across the involved functional network, aiming to establish a suitable brain activation map for a desired behavioral result. Conceptually it might be worth thinking of processes occurring after brain injury and leading to restoration of function as fitting different mechanisms that may proceed partly in parallel but which have variable time frames. Initial plastic changes aim to minimize damage. Rapid functional improvement is likely to occur as dysfunctional, but not damaged, neuronal elements recover from the postinjury shock and penumbra processes resolve. Partially damaged neural elements may be able to be repaired relatively quickly after the insult as well, thus contributing to early functional improvement. Subsequent processes, once the final damage has been established, involve relearning (rather than recovery) and will follow the two steps discussed above: initial unmasking and strengthening of existing neural pathways, and eventually the establishment of new structural changes.

These concepts can be illustrated by examining the role of the ipsilateral motor cortex in the recovery of hand motor function following stroke. After stroke, there is an increase in the excitability of the unaffected hemisphere, presumably owing to reduced transcallosal inhibition from the damaged hemisphere and increased use of the intact hemisphere. Several studies have demonstrated the in-

creased cortical excitability in the unaffected hemisphere after a stroke. For example, in patients with acute cortical stroke, intracortical inhibition is decreased and intracortical facilitation increased in the unaffected hemisphere (Liepert et al. 2000). Furthermore, the interhemispheric inhibitory drive from the unaffected to the affected motor cortex in the process of voluntary movement generation is abnormal (Murase et al. 2004). Interestingly, the duration of stroke is inversely correlated to the imbalance of the excitability between the hemispheres. A disease duration of more than four months after stroke onset results in a tendency to normalization of the intracortical facilitation (ICF) of the unaffected hemisphere (Shimizu et al. 2002).

Acutely after a stroke, increased inhibitory input from the undamaged to the damaged hemisphere makes conceptual sense if one considers it a manifestation of a neural attempt to control perilesional activity, reduce oxygen and glucose demands in the penumbra of the stroke, and thus limit the extension of the lesion (**Figure 5**). However, after an acute phase, and once the injury is stable, input to the perilesional area would seem to be best as excitatory in nature to maximize the capability of the preserved neurons in the injured tissue to drive behavioral output. If so, following the acute phase, we might expect a shift of interhemispheric (and many intrahemispheric) interactions, from inhibitory to excitatory. Should such a shift fail to take place, the resulting functional outcome may be undesirable, with limited behavioral restoration, in part owing to persistent inhibitory inputs from the intact to the damaged hemisphere (**Figure 5**). In fact, some neuroimaging studies demonstrate that long-term, persistent activation of the ipsilateral cortex during motor tasks is associated with poor motor outcomes, whereas a good motor recovery is associated with a decrease in activity in the unaffected and an increase in the affected primary sensorimotor cortex activity (Carey et al. 2002, Rossini & Dal Forno 2004). Furthermore, the pattern of activation



**Figure 5**

Schematic illustration showing that in the acute phase after a stroke, increased inhibitory input (within or across the hemispheres) may limit the extension of the lesion. Increased excitability (increased glutamatergic activity and reduced GABAergic activity) and posts ischemic LTP harbor an otherwise increased risk for further damage. However, after the acute phase, and once the injury is stable (long-term), excitatory input increases excitability and may further increase the efferent (e.g., motor) output. In contrast, inhibitory input at chronic stages is a maladaptive strategy, and the resulting functional outcome may be undesirable, with limited behavioral restoration. Note that the sources (intra- or interhemispheric) of such inputs may differ across neural systems and across individuals. Nevertheless, this provides a road map for neuromodulatory interventions whose aims differ in the acute and long-term stages (*block arrows indicate a desirable increase or decrease in excitability*).

in well-recovered patients is similar to healthy subjects (Ward et al. 2003). More longitudinal studies of patients following a stroke and correlation of interhemispheric interactions with functional measures are needed to explore these issues further. If correct, neuromodulatory approaches targeting the intact hemisphere may be useful to limit injury and promote recovery after a stroke.

For instance, suppression of the ipsilateral motor cortex through slow rTMS (Pascual-Leone et al. 1998, Maeda et al. 2000) may enhance motor performance in patients stable following the acute phase of a stroke. In patients 1–2 months after a stroke, Mansur et al. (2005) applied 0.5 Hz rTMS for 10 min to the unaffected hemisphere to suppress cortical activity and thus release the damaged hemisphere from potentially excessive transcallosal inhibition. The results of this pilot study support the notion that the overactivity of the unaffected hemisphere (ipsilateral hemisphere) may hinder hand function recovery, and neuromodulation can be an interventional tool to accelerate this recovery. The findings are consistent with results in normal

subjects, where ipsilateral motor cortex activation on functional MRI during unilateral hand movements is indeed related primarily to interhemispheric interactions (Kobayashi et al. 2003), and disruption of the activity of one hemisphere reduces transcallosal inhibition to the contralateral hemisphere and can indeed improve ipsilateral motor function (Kobayashi et al. 2004). However, Werhahn et al. (2003) conducted a similar study to evaluate the modulation effects of 1 Hz rTMS of the unaffected hemisphere on the paretic hand and found different results. In that study, 1 Hz rTMS of the unaffected hemisphere did not affect the finger tapping in the paretic hand in a small sample of five patients more than one year after a stroke. The time since the brain insult is likely to be a critical variable to consider. Studies with larger samples of patients are needed to investigate this question further.

Behavioral motor therapy may also shift cortical excitability balance between hemispheres and thus influence outcome. For example, the beneficial effects of constraint-induced therapy on motor function (Mark & Taub 2004, Grotta et al. 2004) are achieved

through immobilization of the unaffected arm, which results in a reduction of the excitability of the contralateral (undamaged) motor cortex owing to the decreased efferent demand and afferent input (Liepert et al. 2001). The reduced activity of the undamaged motor cortex may decrease transcallosal inhibition of the damaged motor cortex and thus promote recovery, ultimately by mechanisms similar to those recruited by suppressing cortical excitability through slow rTMS.

Of course, the alternative neuromodulatory approach, directly aimed to enhance excitability of the damaged hemisphere perilesionally, can also be entertained. Results of a pilot study in primates support the feasibility of using a therapy approach, combining peri-infarct electrical stimulation with rehabilitative training to alleviate chronic motor deficits and promote recovery from cortical ischemic injury (Plautz et al. 2003). Very early experiments with invasive cortical stimulation in humans reveal similarly encouraging results (Brown et al. 2003). However, non-invasive rTMS at appropriate parameters can also be applied to enhance cortical excitability (Pascual-Leone et al. 1998, Maeda et al. 2000, Huang et al. 2005) and thus may exert similar beneficial effects, particularly if coupled with physical therapy. In this setting, functional neuroimaging might be useful, among other things, to identify the perilesional areas to be targeted (Baron et al. 2004), and EEG or fMRI may allow investigators to define precisely and optimize the physiologic effects of TMS (Bestmann et al. 2004).

Similar principles of neuromodulation can be applied to the recovery of nonmotor strokes and other focal brain lesions as illustrated by studies on the effects of cortical stimulation on neglect (Hilgetag et al. 2001, Oliveri et al. 2001, Brighina et al. 2003) or aphasia (Knecht et al. 2002; Martin et al. 2004; Naeser et al. 2005a,b).

Therefore, functional recovery after a focal brain injury, e.g., a stroke, is essentially learning with a partially disrupted neural network. A main neural mechanism underlying

relearning of skills and preservation of behavior involves shifts of distributed contributions across a specific neural network (fundamentally, the network engaged in learning the same skills in the healthy brain). Intra- and particularly interhemispheric interactions may shift from being initially inhibitory (to minimize damage) to later excitatory (to promote functional recovery). Changes in the time course of such connectivity shifts may result in the establishment of dead-end strategies and limit functional recovery. Ultimately, activation of brain areas that are not normally recruited in normal subjects may represent a nonadaptative strategy resulting in a poor prognosis.

## THE OCCIPITAL CORTEX IN THE BLIND

The core principles of neural function that apply to the motor system should also apply to sensory systems. We now switch from the motor to the visual system and briefly discuss the impact of visual loss on occipital cortical function to illustrate the fundamental nature of plasticity.

We live in a society that relies heavily on vision. Therefore, blind individuals have to make striking adjustments to their loss of sight to interact effectively with their environment. One may thus imagine that blind individuals need to develop superior abilities in the use of their remaining senses (compensatory hypothesis). However, blindness could also be the cause for maladjustments (general-loss hypothesis). For example, the loss of sight could be detrimental to sensory perception/spatial information processing mediated by the remaining senses because of our strong reliance on vision for the acquisition and construction of spatial and form representations. Against the general-loss hypothesis is evidence that blind individuals show normal and often superior skills in tasks implicating touch and hearing as compared with the average sighted population (Rauschecker 1995; Hollins & Kelley 1988; Lessard et al. 1998; Van Boven et al.

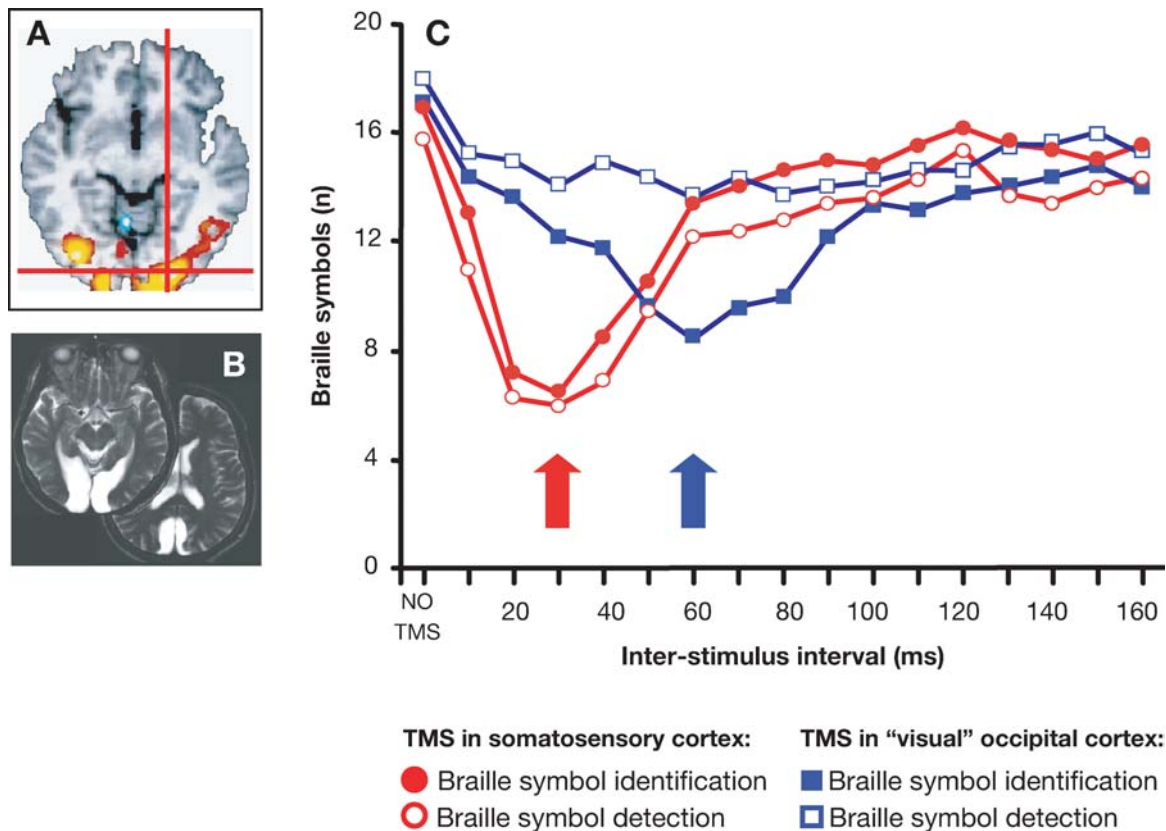
2000; Gougoux et al. 2004, 2005; Voss et al. 2004; Doucet et al. 2005). Growing experimental evidence suggests that in blind persons brain areas commonly associated with the processing of visual information are recruited in a compensatory cross-modal manner that may account for these superior nonvisual capabilities (Merabet et al. 2005, Theoret et al. 2004).

Phelps et al. (1981) and Wanet-Defalque et al. (1988) were among the first to suggest that the occipital cortex is active in the blind and furthermore, that puberty may represent an important developmental milestone for this activation. Using event-related electroencephalograph (EEG) recordings, Uhl et al. (1991) [and later confirmed by a follow-up study using single photon emission computerized tomography (SPECT) imaging; Uhl et al. 1993] provided early support for the notion of task-related (tactile) occipital cortex activation in blind subjects. Sadato et al. (1996, 1998) employed PET imaging and demonstrated that the primary visual cortex is activated in early-blind subjects performing a Braille reading task (**Figure 6A**). Specifically, they observed bilateral activation in medial occipital cortex (area 17) with concomitant activity in extrastriate areas. Activation of the primary visual cortex was also evident in non-Braille tactile discrimination tasks (e.g., discrimination of angle, width, and Roman-embossed characters encoded in Braille cells), though to a lesser extent. However, passive sweeping of the finger (without responding) over a homogeneous pattern of Braille dots (i.e., meaningless Braille symbols) did not result in activation of the primary visual cortex. Subsequent investigators have further refined and extended these early findings addressing the role of imagery, the differences between early and late blind, and the role of tactile versus verbal/linguistic aspects of the task (Büchel et al. 1998, Melzer et al. 2001, Burton et al. 2002a, Sadato et al. 2002, Amedi et al. 2003; for review see Merabet et al. 2005).

One must realize that functional neuroimaging at best establishes an association

between activity in a given region or network with task performance. Therefore, the observation of activity in visual cortical areas in the blind fails to prove that this activity is necessary for the sensory processing. In support of a causal link between occipital function and the ability to read Braille is the remarkable patient reported by Hamilton et al. (2000, **Figure 6B**). This congenitally blind woman (from retinopathy of prematurity) was once a highly proficient Braille reader (learning at the age of six and able to read at a rate of 120–150 symbols per minute). Following bilateral posterior cerebral artery strokes, she was rendered unable to read Braille despite the fact that her somatosensory sensation, peripheral motor, and sensory nerve functions were all intact. Even though she was well aware of the presence of the dot elements contained in the Braille text, she was “unable to extract enough information” to determine which letters and words were written. Despite her profound inability to read, she had no difficulty in performing simple discrimination tactile tasks, such as identifying the roughness of a surface, distinguishing between different coins, or identifying her house key from a given set. However, she was not able to judge distance between Braille dots or read Braille (Hamilton et al. 2000, Merabet et al. 2004b). This serendipitous experiment of nature (and tragic event for our patient) provides strong clinical evidence that a functioning occipital cortex is needed to carry out the task of Braille reading.

In an experimental setting, Cohen and colleagues (1997) used TMS to induce transient disruption of cortical function during a Braille identification task. Identification of Braille characters or embossed Roman letters was impaired following TMS to the occipital cortex in early-onset blind subjects but not in sighted subjects. In blind subjects, occipital stimulation with TMS not only induced errors in Braille identification, but also distorted tactile perceptions. Subjects knew that they were touching Braille symbols but were unable to identify them, reporting instead



**Figure 6**

Braille activation in the visual cortex of the blind and its functional relevance. *A*: Brain imaging (PET) of occipital activation during Braille reading in an early-blind subject (modified from Sadato et al. 1996). *B*: Braille alexia following a bilateral occipital stroke. T2-weighted structural MRI of a congenitally blind woman who was rendered unable to read Braille following a bilateral occipital stroke (modified from Hamilton et al. 2000). *C*: Effects of transient disruption of the occipital cortex using single-pulse TMS on tactile Braille character recognition in congenitally blind subjects. The TMS pulse was delivered at different times (interstimulus interval) after delivery of a tactile stimulus to the index finger pad. The graph displays the number of tactile stimuli detected (*open symbols*) and correctly identified (*filled symbols*). Disruption of somatosensory cortex leads to a decrease in the number of detected and identified letters at an interstimulus interval of 30 ms (*red arrow*). Disruption of occipital cortex does not affect detection but leads to a decrease in the number of identified letters at a later interstimulus interval of approximately 60 ms (*blue arrow*) (modified from Hamilton et al. 1998).

that the Braille dots felt “different,” “flatter,” “less sharp and less well-defined” (1997). Occasionally, some subjects even reported feeling additional (“phantom”) dots in the Braille cell. The functional significance of the occipital activation during Braille reading in the early blind has been further evaluated using single-pulse TMS to obtain information about the timing (chronometry) of in-

formation processing (Pascual-Leone et al. 2000, Walsh & Pascual-Leone 2003). A disruptive TMS pulse was delivered to the occipital or the somatosensory cortex (contralateral to the reading hand) at a variable interval after a peripheral stimulus was applied to the pad of the subject’s index finger (Hamilton & Pascual-Leone 1998). In normal sighted subjects, stimuli to the occipital cortex had no

effect, but TMS delivered to the somatosensory cortex  $\sim 20$ – $30$  ms after a tactile stimulus to a contralateral finger interfered with the detection of the peripheral somatosensory stimulus (presumably by disrupting the arrival of the thalamo-cortical volley into the primary sensory cortex; Cohen et al. 1991, Pascual-Leone et al. 1994). In congenitally blind subjects, TMS to the left somatosensory cortex disrupted detection of Braille stimuli presented to their right index finger at interstimulus intervals of 20–40 ms (**Figure 6C**). Similar to the findings in the sighted, in some cases the subjects did not realize that a peripheral stimulus had been presented to their finger. When they did realize it, they were able to identify correctly which Braille symbol was presented. On the other hand, TMS to the striate cortex disrupted the processing of the peripheral stimuli at interstimulus intervals of 50–80 ms. Contrary to the findings after sensorimotor TMS, the subjects generally knew whether a peripheral stimulus had been presented. However, they could not discriminate which Braille symbol had been presented. These results suggest that in early-blind subjects, the somatosensory cortex ap-

pears engaged in detection, whereas the occipital cortex contributes to the perception of tactile stimuli.

## UNMASKING CONNECTIONS: THE BLINDFOLD EXPERIMENT

Complete and transient visual deprivation in sighted subjects (i.e., five days of blindfolding) seems to be sufficient to lead to recruitment of the primary visual cortex for tactile and auditory processing (Pascual-Leone & Hamilton 2001). The speed of these functional changes is such that it is highly improbable that new cortical connections are established in these sighted individuals. Therefore, somatosensory and auditory connections to the occipital cortex must already be present and are unmasked under our experimental conditions (**Figure 7A**). These could be cortico-cortical connections, linking Heschl gyrus or post-central cortex and striate cortex directly, via cortical multisensory areas, through thalamic or other subcortical relay nuclei. Ultimately, the occipital cortex recruitment mechanisms in tactile processing in the blind and under blindfolded conditions are not likely to

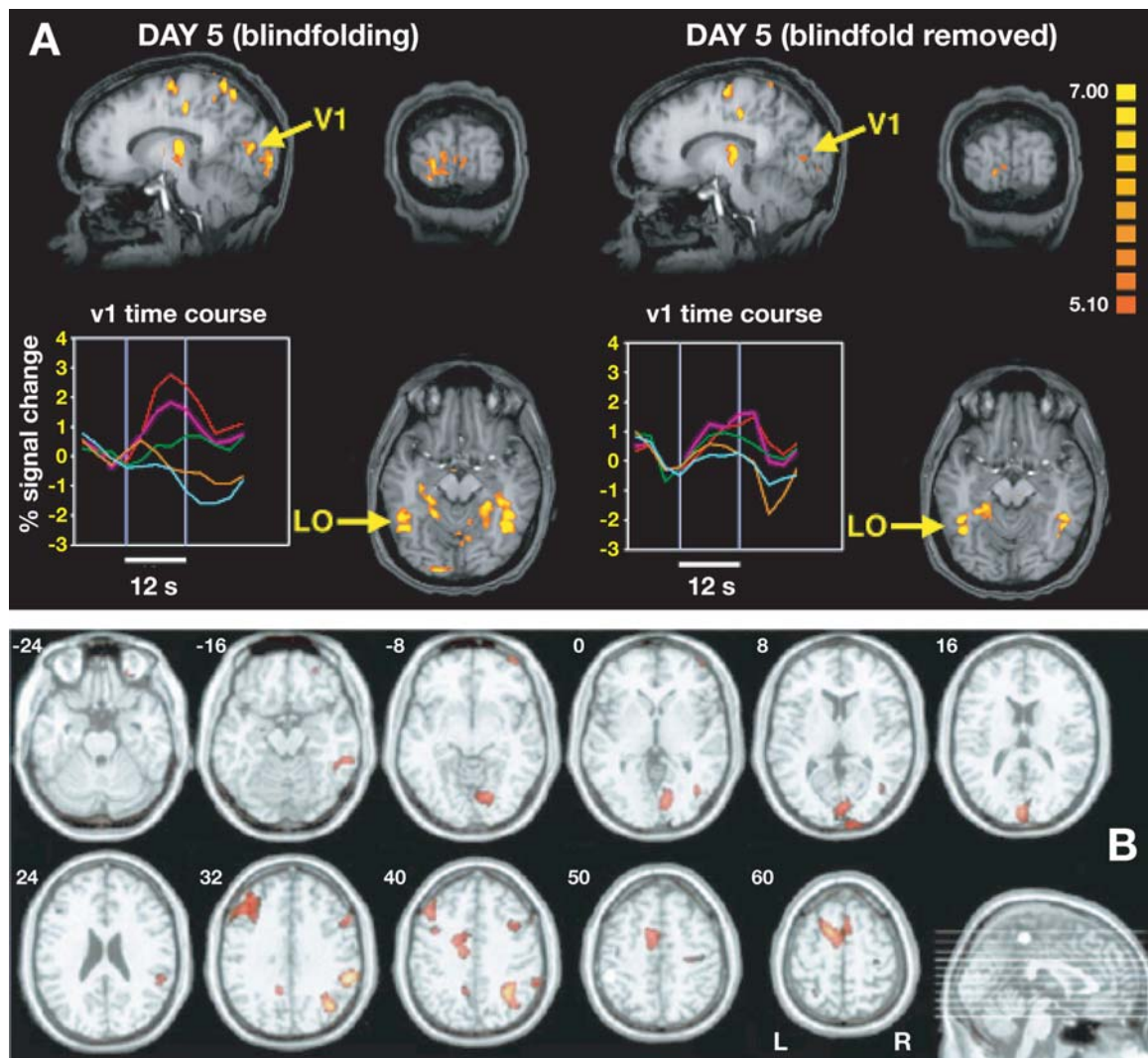
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### Figure 7

Changes in connectivity between somatosensory and visual areas in blindfolded sighted and early-blind subjects. *A*: BOLD fMRI activation focused on the calcarine sulcus (area V1) of a sighted subject undergoing complete visual deprivation for five days through blindfolding. During this period the patient was scanned conducting different tasks including tactile object recognition versus corresponding sensorimotor controls. This contrast results in negligible V1 activation during baseline (day 1 of blindfolding; *not shown*). Following five days of blindfolding robust V1 activation is evident in V1 (*left*). The V1 region of interest shows significant activation for tactile object recognition with either the left or the right hand (*red and purple time course, respectively*) but none during low-level sensorimotor control (imitating object palpation movements in the air with right or left hand; *orange and cyan colors, respectively*). This activation is dramatically reduced only hours following the removal of the blindfold (*right*). The speed of these functional changes is such that it is highly improbable that new cortical connections are established in these sighted individuals. Therefore, somatosensory connections to the occipital cortex, perhaps via the ventral pathway and the lateral occipital (LO) region, must already be present and are unmasked under our experimental conditions. *B*: Combined PET and rTMS study to probe the connectivity between primary somatosensory cortex (S1) and early visual cortex (V1 and neighboring areas). The figure presents the pattern of PET activation in early- versus late-blind subjects contrasting the effects of real versus sham rTMS to S1. Note significant activation in parietal, occipital, and occipito-temporal areas. Most striking, activation was found also in V1, which suggests that cortico-cortical connection between S1 and V1 is stronger in early-blind subjects, possibly supporting enhanced tactile information processing (modified from Wittenberg et al. 2004).

be identical. Fast changes during blindfolding reveal the capacity of the plastic brain to change in response to environmental changes (in this case, visual deafferentation) and maintain functional behavior (in this case, perceptual capturing of the world, for example, by enhancing auditory and tactile processing). Such shifts in connectivity are rapidly reversed with visual input restoration (Figure 7A). However, sustained and early sight loss may result in lasting structural brain changes with

the establishment of new pathways following the initial reinforcement of preestablished connections (just as Cajal predicted). Indeed, in early-blind subjects connectivity between primary somatosensory cortex (S1) and early visual cortex is changed, as recently shown in an elegant study combining rTMS with PET. Wittenberg et al. (2004) showed that rTMS over S1 evoked activation of peri-striate cortex in early-blind but not in late-blind or sighted individuals (Figure 7B).



## ESTABLISHING NEW CONNECTIONS: OCCIPITAL ACTIVATION IN HIGH-LEVEL COGNITIVE TASKS

Recent fMRI studies in the blind have demonstrated occipital cortex activation (including V1) during tasks requiring auditory verb-generation and similar linguistic tasks (Burton et al. 2002b, Amedi et al. 2003), semantic judgment tasks (Burton 2003, Noppeney et al. 2003), and speech processing (Röder et al. 2002). In a comparative analysis of brain activation in early and late blind during a verb-generation task, Burton et al. (2002b) instructed subjects to generate covertly a verb in response to reading a noun cue presented in Braille (e.g., reading the word “cake” would generate “bake”) or using auditory words. They found that occipital cortex activation (including primary visual cortex) was much more prominent in early- than in late-blind subjects (**Figure 8**).

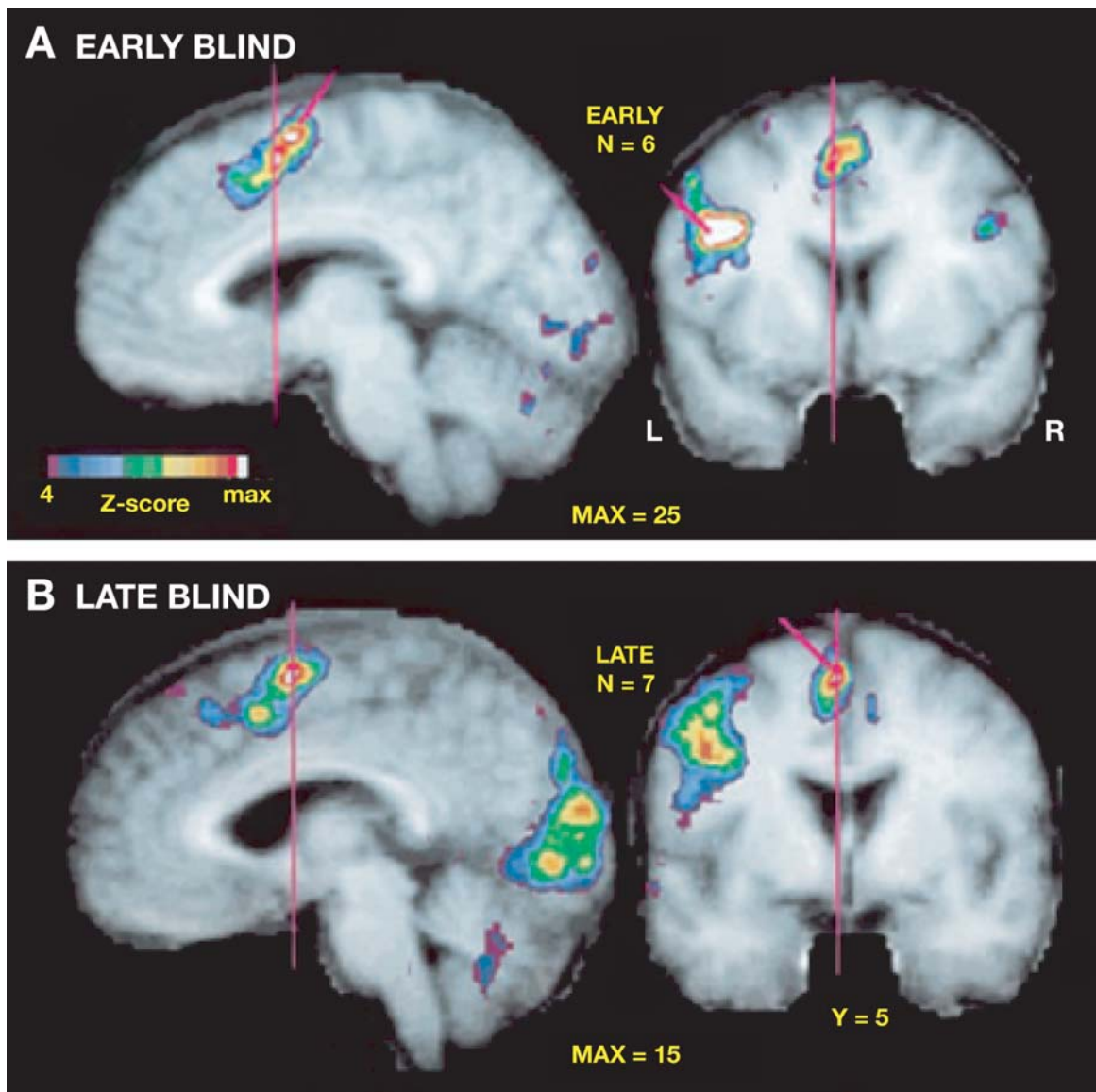
Amedi et al. (2003) observed robust left-lateralized V1 activation for a verbal-memory task requiring the retrieval of abstract words from long-term memory. The striking finding of this report is that contrary to previous studies, the observed occipital activation was demonstrated without introducing any tactile or auditory sensory input. Notably, blind subjects showed superior verbal memory capabilities compared not only with age-matched, sighted controls, but also with reported population averages (using the Wechsler verbal memory test). Furthermore, investigators found a strong positive correlation between the magnitude of V1 activation and the verbal memory capability in that the degree of activation increased with increasing word-recall ability (**Figure 9**).

The functional relevance of these findings was demonstrated with rTMS. When activity in the left calcarine sulcus or left occipitotemporal cortex was disrupted by rTMS, performance in a verb-generation task was impaired (the error rate increased) (Amedi et al. 2004). An analysis of error types revealed

that the most common error produced after rTMS was semantic (e.g., apple  $\Rightarrow$  jump, instead of eat, one possible correct response). Phonological errors and interference with motor execution or articulation (stuttering and slurring of the responses) were rare. Thus, in blind subjects, a transient virtual lesion of the left occipital cortex can interfere with high-level verbal processing, and not only with the processing of tactile stimuli and Braille reading. This finding suggests that beyond changes in connectivity across sensory systems, in early blind the visually deafferented occipital cortex becomes engaged in higher-order cognitive functions, presumably through establishment of new connections.

## DRAWING CONCLUSIONS FROM THE BLINDFOLDED AND THE BLIND

The functional and structural identity of the occipital cortex may change from processing visual information to processing information related to another sensory modality or even supramodal high-level cognitive functions (**Figure 10**). In comparison, the occipital cortex may inherently possess the computational machinery necessary for nonvisual information processing (Pascual-Leone & Hamilton 2001). Under specific conditions (such as blindness or prolonged blindfolding) this potential could be revealed. Burton (2003) suggested the definition of two distinct mechanisms: (a) “cross-modal plasticity de novo” in response to visual deprivation, and (b) “expression of normal physiology” that is normally inhibited or masked when sight is present. However, as discussed above, in the context of the intrinsically plastic brain, these two mechanisms are inextricably linked. The unmasking of preexisting connections and shifts in connectivity represent rapid, early plastic changes, which can lead, if sustained and reinforced, to slower developing but more permanent structural changes, with dendritic arborization, sprouting, and growth. This hypothesis can account for the findings in

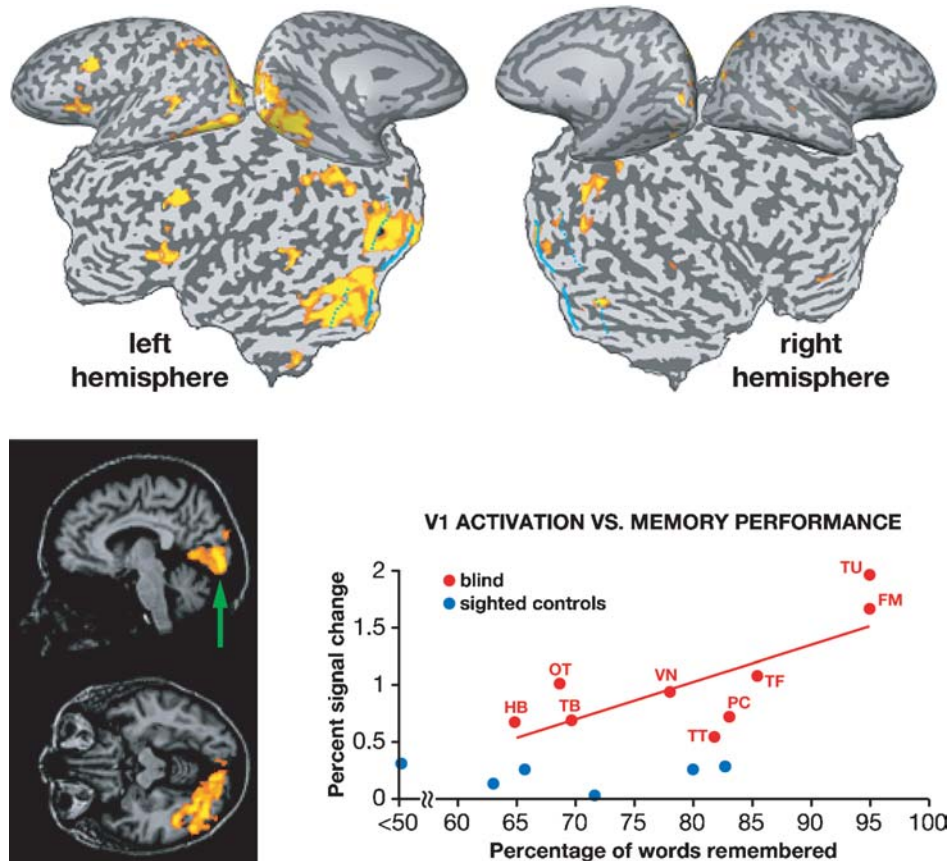


**Figure 8**

BOLD fMRI activation within occipital cortex in early- and late-blind Braille readers. Note that the magnitude of activation is greater in early-blind individuals. Scale denotes the Z-scores for BOLD responses (Z-max early-blind 25; Z-Max late-blind: 15; modified from Burton et al. 2002).

blindfolded subjects and for the magnitude difference of the reorganization between early and late blind. This hypothesis also results in the strong prediction that careful task choice and experimental design will reveal the nonvisual roles of the occipital cortex in the

sighted. Indeed, Amedi & colleagues (2001, 2002) reported convergence of visual and tactile object recognition in the ventral visual stream in an occipito-temporal area termed the lateral-occipital tactile visual area (LOtv). The defining feature of this region is that



**Figure 9**

Verbal memory fMRI activation in early visual cortex of congenitally blind subjects correlates with their superior verbal memory abilities. Congenitally blind subjects show robust activation in the left visual cortex during a verbal memory task of abstract word retrieval, which involves no sensory stimulation. The left-lateralized activity stretches from V1, via extrastriate retinotopic areas, to nonretinotopic areas such as the lateral occipital complex (LOC; *top panel*). This activation was correlated with the subjects' verbal memory abilities (*lower panel*). Subjects were tested on the percentage of words they remembered six months after the scan. In general, blind subjects remembered more words and showed greater V1 activation than did the sighted controls. The correlation between V1 activity and performance was significant only in blind subjects (modified from Amedi et al. 2003).

it is activated preferentially by object shape rather than by texture and scrambled images of the object. Similarly, TMS studies have revealed that the visual cortex of the sighted is functionally involved in tactile processing of orientation (Zangaladze et al. 1999) and judging of distance between Braille dots (Merabet et al. 2004a). Recent fMRI work even suggests that as compared with phonemic word generation, semantic word generation

involves (in addition to a series of other brain regions) activation of bilateral occipital cortices in sighted subjects (Press et al. 2004).

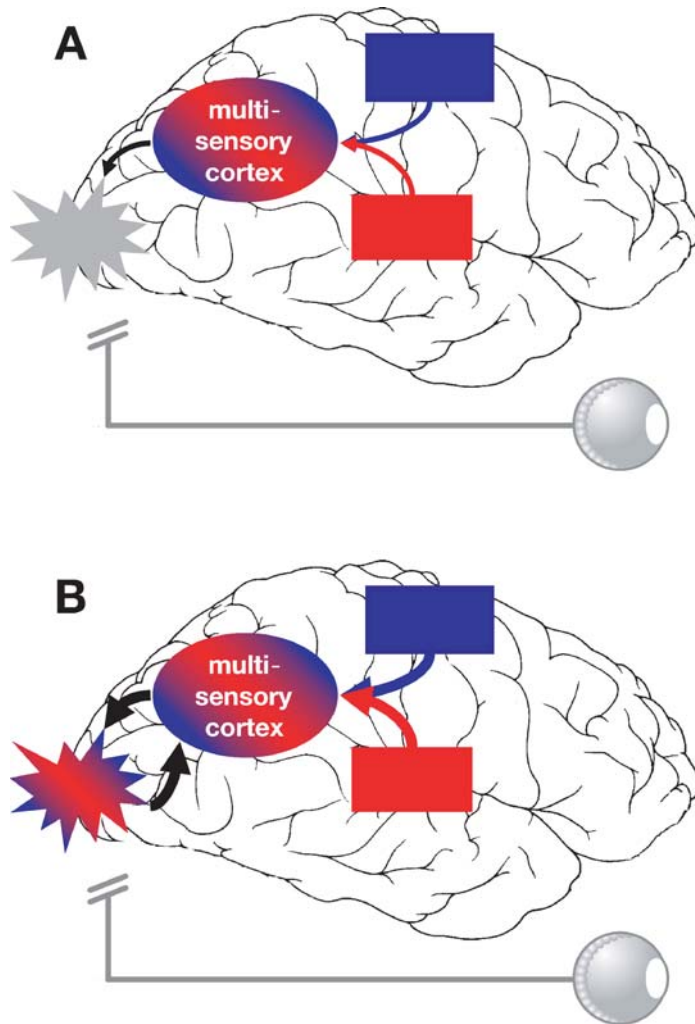
Therefore, in the visual system in response to loss of visual input, we encounter a similar situation to the one discussed in the context of the motor system: In a first step the nervous system is molded rapidly by shifts of strength in existing connections. In a second step new structural connections are

established giving rise to new capacities such as improved verbal memory through recruitment of the occipital cortex (Amedi et al. 2003); the remarkably high incidence of absolute pitch in early-blind subjects in the absence of the expected changes in planum temporal asymmetry (Hamilton et al. 2004); or the superior auditory localization ability of blind subjects, which correlates with the amount of striate cortex activation (Gougoux et al. 2005).

However, just as in the motor system, plasticity risks becoming the cause of pathology. For example, acutely after visual deafferentation, just as after a focal lesion of the occipital cortex, altered cortical excitability and rapid changes in cortico-cortical connectivity frequently lead to visual hallucinations and phantom vision (Merabet et al. 2004a). Such hallucinations can be suppressed by reducing cortical excitability through slow rTMS (Merabet et al. 2003). Eventually, hallucinations tend to subside, perhaps correlating with the long-lasting, cross-modal plasticity changes and the recruitment of the occipital cortex for high-order cognitive tasks. However, such plasticity, although aiding in the adaptation to blindness, poses difficult challenges to vision restoration. Appropriate delivery of electrical stimulation to the retina or the occipital cortex can evoke patterned sensations of light even in those who have been blind for many years. However, success in developing functional visual prostheses requires an understanding of how to communicate effectively with the plastically changed, visually deprived brain to merge what is perceived visually with what is generated electrically (Merabet et al. 2005). Similarly challenging is the situation for patients who recover sight through surgical approaches (for example, cataract removal or corneal stem-cell transplant) after long-term visual deprivation (Fine et al. 2003).

## SUMMARY

Plasticity in the motor system may be primarily driven by efferent demand, whereas in the



**Figure 10**

Schematic representation of changes affecting the occipital cortex after visual deafferentation. *A*: Following visual deafferentation, inputs from other sensory processing areas (red and blue) reach the occipital cortex via connections through multisensory cortical areas (and possibly through direct connections). *B*: The unmasking and strengthening of such connections (thicker lines) lead to enhanced multisensory processing at the level of the occipital cortex and may eventually lead to the establishment of new connections and functional roles.

visually deprived visual system it is the consequence of afferent input changes. Nevertheless, across systems the fundamental aspects of plasticity remain the same: Plasticity is an obligatory consequence of all neural activity (even mental practice), and environmental

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**ICF:** intracortical facilitation

**M1:** motor cortex

**LOtv:** lateral-occipital tactile visual area

**PMA:** premotor area

**PMd:** dorsal premotor cortex

**S1:** somatosensory cortex

**SMA:** supplementary motor area

**SPECT:** single photon emission computerized tomography

**TMS:** transcranial magnetic stimulation

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pressures, functional significance, and experience are critical factors. For example, the role of the occipital cortex for tactile processing in the blind is likely to be fundamentally different for those who learn Braille early and those who do not.

Two steps of plasticity can be identified: unmasking existing connections that may be followed by establishment of new ones. The former provides an opportunity to learn about core aspects of normal physiology (for example, the role of cross-modal interactions in visual perception). The latter can give rise to unexpected capacities (for example, supranormal auditory abilities or verbal memory in the blind).

Plasticity is an intrinsic property of the human nervous system, and plastic changes may not necessarily represent a behavioral gain for a given subject. Plasticity is the mechanism for development and learning, as much as a cause of pathology and the cause of clinical disorders. Our challenge is to modulate neural

plasticity for optimal behavioral gain, which is possible, for example, through behavioral modification and through invasive and non-invasive cortical stimulation.

So, what makes our dynamic plastic cortex possible? Experience and behavior correspond to the activity of all relevant neurons throughout the brain. Neuronal networks provide a most energy efficient, spatially compact, and precise means to process input signals and generate responses (Laughlin & Sejnowski 2003). Nodes in such networks, specific brain regions, are conceptualized as operators that contribute a given computation independent of the input (Pascual-Leone & Hamilton 2001). Inputs shift depending on the integration of a region in a distributed neural network, and the layered and reticular structure of the cortex with rich refferent loops provides the substrate for rapid modulation of the engaged network nodes. Ultimately, plasticity is a most efficient way to utilize the brain's limited resources.

## ACKNOWLEDGMENTS

Work on this review was supported by K24 RR018875, RO1-EY12091, RO1-DC05672, RO1-NS 47,754, RO1-NS 20,068, and RO1-EB 00,5047. E.F. is supported by a grant from the Harvard Medical School Scholars in Clinical Sciences Program (NIH K30 HL004095-03). L.M. is supported by a K 23 mentored career development award from the National Eye Institute (K23 EY016131-01) and A.A. by a Human Frontiers Science Program award. The authors thank Mark Thivierge for invaluable administrative support.

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