Review

Experience, cortical remapping, and recovery in brain disease

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ABSTRACT

Recovery of motor function in brain and spinal cord disorders is an area of active research that seeks to maximize improvement after an episode of neuronal death or dysfunction. Recovery likely results from changes in structure and function of undamaged neurons, and this plasticity is a target for rehabilitative strategies. Sensory and motor function are mapped onto brain regions somatotopically, and these maps have been demonstrated to change in response to experience, particularly in development, but also in adults after injury. The map concept, while appealing, is limited, as the fine structure of the motor representation is not well-ordered somatotopically. But after stroke, the spared areas of the main cortical map for movement appear to participate in representing affected body parts, expanding representation in an experience-dependent manner. This occurs in both animal models and human clinical trials, although one must be cautious in comparing the results of invasive electrophysiological techniques with non-invasive ones such as transcranial magnetic stimulation. Developmental brain disorders, such as cerebral palsy, and embryonic abnormalities, such as dysmelia, demonstrate the potential of the human brain to remap the motor system. Future therapies may be able to use that potential to maximize recovery.

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Introduction

Neurological disorders and diseases are a major source of disability and mortality. Some of the most significant disorders include stroke (cerebral infarction and hemorrhage), multiple sclerosis, traumatic brain injury, and spinal cord injury. In all of these, and many more, the disease process may cause dysfunction that reaches a nadir and then

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improves. This improvement is often insufficient to restore satisfactory function and has caused many to seek methods by which improvement can be accelerated and maximized. In every disorder mentioned above, disability is caused by dysfunction of neurons or neuronal elements. Recovery could therefore occur by multiple mechanisms: (1) restoration of function of damaged neurons, (2) change in structure and function of remaining undamaged neurons (and related glia), and (3) formation of new behavioral strategies to accomplish the affected functions. Because metabolic recovery of neurons is not likely to take place over the course of more than a few days, much of the recovery that is seen after that period is likely to represent one of the latter two mechanisms.

Change in function of spared neurons

While the ability to change behavior has long been recognized as having a neural basis (by William James, for example) the mechanisms by which such plasticity occurs have been discovered in only the last few decades. This began with the discovery of long-term potentiation in the hippocampus (Bliss and Collingridge, 1993), and then in other areas (Aizenman et al., 1998), including motor cortex (Iriki et al., 1989). More recently, complementary processes have been discovered that maintain neuronal activity in the face of changing synaptic activity. These homeostatic mechanisms have the potential to restore neuronal function even when a large part of the synaptic input is lost (Nitsche et al., 2007). They include synaptic scaling and changes in intrinsic excitability. Such mechanisms are likely to reverse the phenomenon of diaschisis, or loss of neuronal function due to partial deafferentation (Finger and Almli, 1985; Feeney and Baron, 1986). Yet the contribution of diaschisis to actual disability is still unclear (Bowler et al., 1995; Seitz et al., 1999).

Mapping recovery

Maps of surface and external world representations have been discovered in the brain in motor and sensory systems (Knudsen et al., 1987; Merzenich et al., 1988). The map concept has been fundamental to understanding brain function, development, and plasticity (Blakeslee and Blakeslee, 2007). The idea of a map is useful for many reasons. Because representations of the environment are located in an orderly manner, researchers can find a particular representation by systematic searches. This is in contrast to the random search for neurons with a particular property that characterizes some neuronal systems. And because a map is ordered, local connectivity is easier to test and understand. For instance, the concept of lateral inhibition is a mechanism that can sharpen the specificity of individual representations (Lukasiewicz and Werblin, 1990). In a motor system, lateral inhibition can result in selection of one movement pattern with suppression of the others (Krasne and Lee, 1988).

An example of sensorimotor map plasticity

There are many examples of the instructive role of experience in brain anatomy and physiology. One of the most elegant and relevant is the role of combined auditory and visual experience in the auditory map of space in the barn owl (Knudsen and Konishi, 1978). If a juvenile barn owl experiences a shift in visual field through prisms or a change in auditory input through monaural ear plugging, visual and auditory receptive fields in the superior colliculus realign (Knudsen, 1985). The maps of space for visual and auditory input in such an animal are overlaid precisely, but only so long as the interventional device (prism or plug) is in place. This occurs only during a sensitive period during development; adults do not experience such realignment and cannot correct a previous realignment imposed during the sensitive period. The process of re-registering the two maps causes measurable shifts in the projections of neurons in one inferior

colliculus nucleus to another (Feldman and Knudsen, 1997). (The inferior colliculus projects to the superior, but this projection is not changed.) When a new mapping is first learned, it is dependent on NMDA receptors (Feldman and Knudsen, 1998) but if unlearned is tonically suppressed by inhibitory input (Zheng and Knudsen, 1999).

The phenomenon of remapping is dependent on actual experience of visual and auditory targets. Although adults do not demonstrate the ability to precisely remap their colliculus based on alteration in visual or auditory experience, they do have the ability to re-express mappings learned prior to adulthood (Knudsen, 1998). The superior colliculus also has a map of head movement (Du Lac and Knudsen, 1990) so this system is truly a model of sensorimotor plasticity, with relevance to the issue of experience based remapping. In summary, changes in projections from one area to another appear to occur only during juvenile experience, but mappings learned as a juvenile can be reactivated by disinhibition in adults.

It is important not to generalize too much from this one example, as reorganization of long-range connections does appear to be possible in primate premotor cortex (Dancause et al., 2005), and the phenomenon of lesion-induced neurite outgrowth may be an important one for remapping the motor cortex (Carmichael and Chesselet, 2002; Kleim et al., 2002; Carmichael, 2003; Benowitz and Carmichael, 2010; Carmichael, 2010). But there may be limits to remapping in adults, particularly in motor cortex (Schieber and Deuel, 1997, and see section below on cerebral palsy.) While sensory remapping can occur in the multiple stages of processing prior to arrival in sensory cortex, output neurons in the primary motor cortex (M1) are just one synapse away from lower motor neurons, which are themselves dedicated to particular muscles in adults.

Geographical maps do not tell it all

There are two problems with maps as explanations in science: (1) geography is not everything, and (2) maps require users. The first problem can be fixed by including other markers on the map, so that a map of city populations includes bubbles in proportion to the population of each area. This tends to make the map messier, but more useful in finding resources. The second problem implies that maps are not a sufficient explanation by themselves. Just as a geographical map will not move you from one place to another, a map of movement representations will not move the body. The way in which the map is used is critical to its function. Remapping may have no effect on function, if the map user (i.e., motor executive function) does not use the newly remapped area correctly or at all.

While there are many types of brain maps, they can be divided into sensory and motor. The earliest studies on remapping in the adult brain were in the sensory system, but most work in human subjects recovering from conditions such as stroke have focused on motor maps. The majority of this review will concern motor maps, with some reference to work in sensory systems. The mechanisms of remapping in the two systems may be very different. Sensory systems have the potential for map self-organization based on the spatiotemporal structure of input (Linsker, 1988), while motor maps are likely to receive feedback of a more limited, and difficult to parse, kind.

The motor output map

An additional complication in the interpretation of cortical motor maps is the fact that the final common pathway for movement in the cortex never directly activates muscles, but rather causes lower motor neuron activity more or less directly. This means that remapping in the motor cortex could result from changes in the brain stem and spinal cord, areas that are more difficult to access experimentally. While M1 appears to make the greatest contribution to the corticospinal tract (CST), and appears to be crucial for the production of precise distal limb movements, there may be other important con-

tributions to the CST from non-primary motor areas, such as supplementary motor area (SMA) and the premotor areas (PMA) (Porter and Lemon, 1993). Motor cortical control of the hand in non-human primates may not be as direct as in humans (Maier et al., 1997) and studies of plasticity in such model systems need to be interpreted in that light.

The other issue regarding motor output maps is the question of what is represented in the motor cortex: muscles, postures, or movements. While this area remains controversial, the demonstration of population codes for movement in M1 has suggested that body centered movements are at least one feature represented. Reading the population code and translating it into reaching movements has proven to be useful, particularly in advancing cortical control of prosthetic devices (Schwartz, 2007). The fine structure of the motor map appears not to be map-like (Schieber, 2001) meaning that recovery processes within small areas may not be best interpreted as remapping. In fact, the characterization of changes in activity and connectivity that appear to support recovery as "reorganization" or "remapping" often seem overblown in situations in which synaptic strength and excitability of preexisting circuits are adjusted.

Knowns and unknowns in neural plasticity in recovery

The role of neural plasticity in formation and modification of maps has been described for decades, and is too large a topic to treat comprehensively here. However, the general theme is that maps are set up crudely by development, are refined by activity, and respond to changes in the environment. There is generally a critical period during which the map may be radically altered by environmental change, and then an adult period in which the maps is more static. Merzenich et al.'s (1983) groundbreaking work demonstrated that changes in somatosensory experience in adult non-human primates would change the primary sensory cortex map of the skin surface. Peripheral nerve lesions, amputation (Merzenich et al., 1984), and even yoking fingers together (Allard et al., 1991) could alter this map.

The biological basis for recovery of function in brain disorders has been described in other reviews (Strick, 1988; Nudo et al., 2001; Hendricks et al., 2002; Cramer, 2004; Ward and Cohen, 2004) and in other contributions within this issue (Floel and Cohen, for example). The common features of mechanisms for recovery include (1) importance of experience/activity, (2) critical period immediately after neuronal/glial damage, (3) importance of error in learning, and (4) localization of function. Corollaries of 1 and 4 include (1) experience should change localization and (2) the more limited the area damaged, the greater the potential for recovery.

The evidence that experience is required for recovery includes the elegant work of Nudo, who demonstrated that the primary motor cortical map of movement (M1) evolved after focal M1 lesions (Nudo and Milliken, 1996; Nudo et al., 1996). Rehabilitation that encouraged use of the impaired hand led to relative enlargement of the M1 area devoted to the hand. This work in monkeys, which was based, of necessity, in small numbers of animals, has been reproduced in rodent models. While the smaller size and different organization of the rodent motor cortex maps mapping studies difficult, the experience dependence of M1 for recovery has been well-demonstrated (Kozlowski et al., 1996; Chu and Jones, 2000).

Non-primary motor areas also reorganize after primary motor cortex stroke. Hand maps shrink in ventral premotor area (PMAv) after an M1 hand lesion (Nudo, 2007) and PMAv remaps output to S1 after it loses its target in M1 (Dancause et al., 2005).

Probes for remapping in humans

The gold standard for determining the motor map in humans is direct stimulation, such as intraoperative motor mapping, performed as part of surgery for brain tumors. This technique dates back to

Sherington and is the basis for the concept of the motor homunculus in humans. Such studies have uncovered a more complex and rapidly reorganizing motor map than was previously recognized (Duffau et al., 2000; Duffau, 2001). But intraoperative stimulation is not practical in most studies and alternative methods of mapping have been used. These include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), particularly functional methods (fMRI) (Ashe and Ugurbil, 1994), and transcranial magnetic stimulation (TMS) (Barker et al., 1987; Chokroverty, 1990).

Determining connections within and between maps may also be accomplished by several means. In animal studies, paired stimulation and recording methods, or use of tracers transported axonally, have been used. In human studies, again, such methods are not practical, and non-invasive methods such as magneto-encephalography, resting state BOLD connectivity, diffusion tensor imaging, and tractography are used. Despite the technical achievement of such methods the quality of data is much more limited. The fine structure of maps such as investigated by Nudo in monkeys is not accessible by non-invasive techniques in humans. The ability to precisely measure a representation is reduced by factors such as thresholding, noise, spatial and temporal smoothing, brain motion, and multiple time-varying physiological processes.

PET studies

The use of PET to determine brain changes after stroke was pioneered by Weiller et al. (1992). These studies demonstrated abnormalities in brain activation with motor task performance that varied by individual (Weiller et al., 1993). However these studies cannot be considered to demonstrate changes in the motor maps, except in the broadest sense that they find the location of the motor system. The spatial resolution of PET is relatively poor, although could potentially demonstrate longitudinal differences by analyzing change in activation over time.

Measuring longitudinal change that occurred as a result of therapy was the goal of a study carried out at NINDS, with multiple collaborators (Wittenberg et al., 1999). Chronic subcortical stroke survivors were randomized to 10 days of constraint-induced movement therapy (CIMT) (Taub et al., 1993) vs. a more passive control method. Participants had PET scans to measure brain activation with finger movement, as well as TMS (see below) and EEG studies, before and after the intervention. The task-related increases in regional cerebral blood flow (rCBF) in these chronic stroke patients were greater than those of control subjects, likely because they required more motor cortical activity to produce muscle activation. Since they had subcortical lesions, interrupting the CST, much of this activity likely did not find its way to activation of lower motor neurons. The net change in task-related rCBF after CIMT was a decrease, mainly along the edges of the overly activated area (Fig. 1). The appearance of the longitudinal change was reduction in activation area, but size of an activated cluster of voxels in PET may be conflated with magnitude of activation in the core of the cluster, so the interpretation of this finding is ambiguous, but has reproduced subsequent studies using fMRI (Dong et al., 2006).

fMRI

Functional MRI is a technique that allows better temporal resolution (in the range of seconds) and spatial resolution than PET, with a similar sensitivity to activity-related blood flow changes, but often with a lower signal-to-noise ratio, so that temporal and spatial smoothing are required. But it also does not expose subjects to ionizing radiation and is therefore particularly appropriate to longitudinal studies, with repeated scanning of the same individuals (Aguirre et al., 1998).
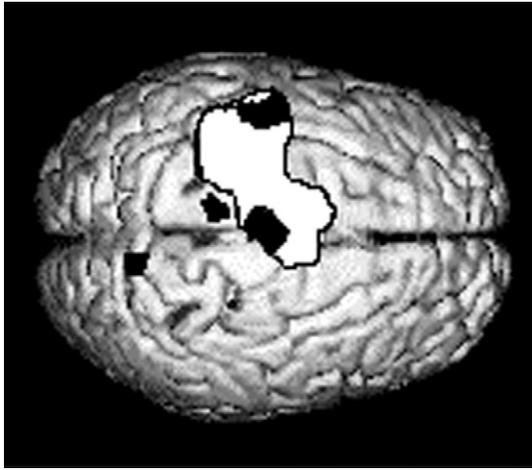
Fig. 1. Cerebral activation changes after CIMT. Superimposed on an underlay of a normal template brain are the areas of overactivation compared to normal volunteers ($p<0.001$, uncorrected for multiple comparisons, in white bordered in black). The black areas are those with a reduction in activation in subjects receiving CIMT compared to controls ($p<0.01$). See Wittenberg et al. (1999) for details.

Patients with upper limb amputation and phantom limb pain showed a shift of oral movement related brain activation into the hand motor area (Lotze et al., 2001). This suggests the ability to remap motor representation in adults, although in this case was associated with a pathological state rather than useful plasticity. In a striking recent study of adults with dysmelia (reduced or absent upper extremities due to thalidomide exposures), fMRI showed representation of foot movement on the expected hand representation. Upper extremity movements were still localized in this part of M1 so this was not a simple case of one representation expanding and another contracting due to peripheral abnormalities (Stoeckel et al., 2009). Given that this condition is present from the embryonic stage, it suggests that the motor representation has developmental limits, and that the concept of homunculus is an oversimplification of the complex representation of movements. So the hand area of M1, seen as a knob when viewed from the surface, may be specialized for dexterous movements, even by the foot.

TMS studies

Transcranial magnetic stimulation (TMS) is a technique that allows the closest non-invasive approximation to electrical cortical stimulation. There have been numerous general reviews of the technique (Hallett, 2007) and of the potential for TMS in studies and treatment in neurorehabilitation. TMS has long been used to map the motor representation, as stimulation evokes waves of activity in upper motor neurons (Awiszus and Feistner, 1994) and is effective at activating most muscles in normal individuals.

The spatial distribution of the evoked electrical field in the brain extends for a few centimeters, but maps may be obtained by repeated stimulation at precise locations. The peak electric field of a double circular (also called "figure 8") coil is near the intersection of the two circular winding, and falls off in a sinusoidal fashion. Therefore small movements of the coil change the location of this peak and can be exploited to reveal the spatial relationships of different functional areas. However, because TMS stimulation is much broader than intracortical microelectrode stimulation, responses are generated over several millimeters of tissue with actual spatial extent difficult to determine. Deconvolution is one approach to revealing the actual extent of a representation, but introduces errors (Bohning et al., 2001). While modeling TMS effects on the brain is an area of active research, the current standard approach is to examine a simple maps of responses and determine the center of gravity (CoG) and a metric of map size.

Technical aspects of TMS maps: The CoG is a useful metric because it gives each location stimulated a weight based on the size of the response there. Because the CoG is the result of so many data points, it has a low standard error and high degree of reproducibility. It can be determined with millimeter accuracy, but has no bearing on the spatial extent of the representation. For that purpose, the map volume is often used, which is a sum of the average MEP at each location stimulated, normalized to the average MEP at the location the largest response. The map volume thus varies from 1 indicates a response at only one location, to N, where N is the number of locations in which any response is measured. Stimulation is generally done at a fixed percentage of motor threshold, the stimulus strength that elicits measurable MEP at least half the time (Rossini et al., 1994). ("Map volume" can be a confusing term, as it refers to the volume of a contour graph constructed on the scalp surface, but represents the area in which stimulation evokes a response).

Maps and recovery

A study conducted at Wake Forest University sought to examine the changes in TMS maps that occurred during the usual time period of in- and outpatient rehabilitation. Patients with first-ever ischemic stroke affecting motor function in one hand had serial TMS mapping and paired-pulse stimulation. Paired-pulse stimulation gives a measure of the effectiveness of intracortical inhibitory mechanisms. The results of the mapping studies, as yet unpublished, demonstrated in TMS maps evolve during recovery. In the most severely affected patients, no TMS responses could be elicited at the first visit, so changed in the maps could not be determined. In the group of patients who did have maps possible at the first visit, those who had severed impairments of dexterity, showed expansion of the map size over time, with the degree of map expansion correlating with improvement in motor ability (Fig. 2).

CIMT and TMS maps

Liepert was a pioneer in this area, first demonstrating that immobilization reduces map area (Liepert et al., 1995) and then that constraint-induced movement therapy (CIMT) increases the affected side motor map (Liepert et al., 1998). Briefly, CIMT is a therapy predicated on the idea that stroke leads to learned non-use of the affected limb, so that even when spontaneous recovery occurs, the motor executive system is less likely to use a stroke-affected limb (Taub et al., 1993). Liepert initially measured map area as the number of sites in which responses could be evoked, and used the unaffected limb to normalize map area.

In two studies that followed up on the TMS map finding in CIMT, the map volume measure was used, with careful attention to determination of the motor threshold, and stimulation at a fixed percent-
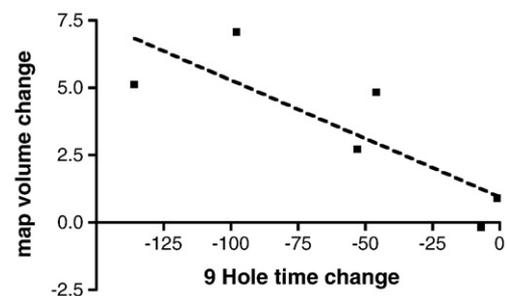

Fig. 2. Correlation of map size change with dexterity improvement. Subgroup of a stroke natural history study, those subjects with abnormal times on the 9 hole peg test but who had MEP in the hand at the earliest time measured (3–10 days). Change in MAP volume over 3 weeks is compared to change in 9 hole time for the affected hand. Improvement in speed showed a trended with increase in map volume ($r=-0.83$, $p=0.058$).

age (120% or 110%, respectively) of motor threshold (as was true in Liepert's studies.) This procedure should have eliminated any basic change in motor excitability as a cause for map volume increase, meaning that a change in map volume reflects an underlying change in the area that represents the target muscle. The first study, mentioned above (Wittenberg et al., 1999), demonstrated a significant increase in map volume only in chronic stroke subjects who underwent CIMT, not the control therapy, although the difference between groups was only a trend ($p = 0.08$), due to low numbers of control subjects with measurable maps. In the second study, subacute stroke patients (3–9 months) showed a similar difference between CIMT and control (usual care) therapy, with slight map volume shrinkage in controls (Sawaki et al., 2008). Interestingly, there was a significant correlation between the map volume increase and grip strength, suggesting a functional meaning for the map volume change.

Cerebral palsy

In studies of motor maps in cerebral palsy (CP), there are several reports of extreme abnormalities of the motor map, including super-imposed bilateral maps (Delvaux et al., 2003) and lateralized leg representation (Maegaki et al., 1999). A pilot TMS/fMRI mapping of both upper- and lower-extremity representations in children with cerebral palsy revealed a variety of abnormalities. Fig. 3 is an example that demonstrates both abnormalities, including superimposed hand motor maps from both left and right side and very similar activation locations for finger and foot movement. These studies demonstrate the limits of map reorganization, when a brain lesion occurs *in utero*. While CP may lead to significant participation of ipsilateral motor cortex and shifts in somatotopy, it is sobering to note the severity of motor abnormalities in the face of this map reorganization.

Do maps matter?

A focal stimulation technique, such as epidural stimulation, will only work if the appropriate brain area is being stimulated. Therefore, maps matter for such techniques, as they tell what neuronal resources are present in each location. But for more non-focal stimulation techniques, such as tDCS, or activity-based therapies, such as CIMT, the map may not be relevant. The more important point about maps is that they facilitate research, as changes are more interpretable in a well-ordered neural system.
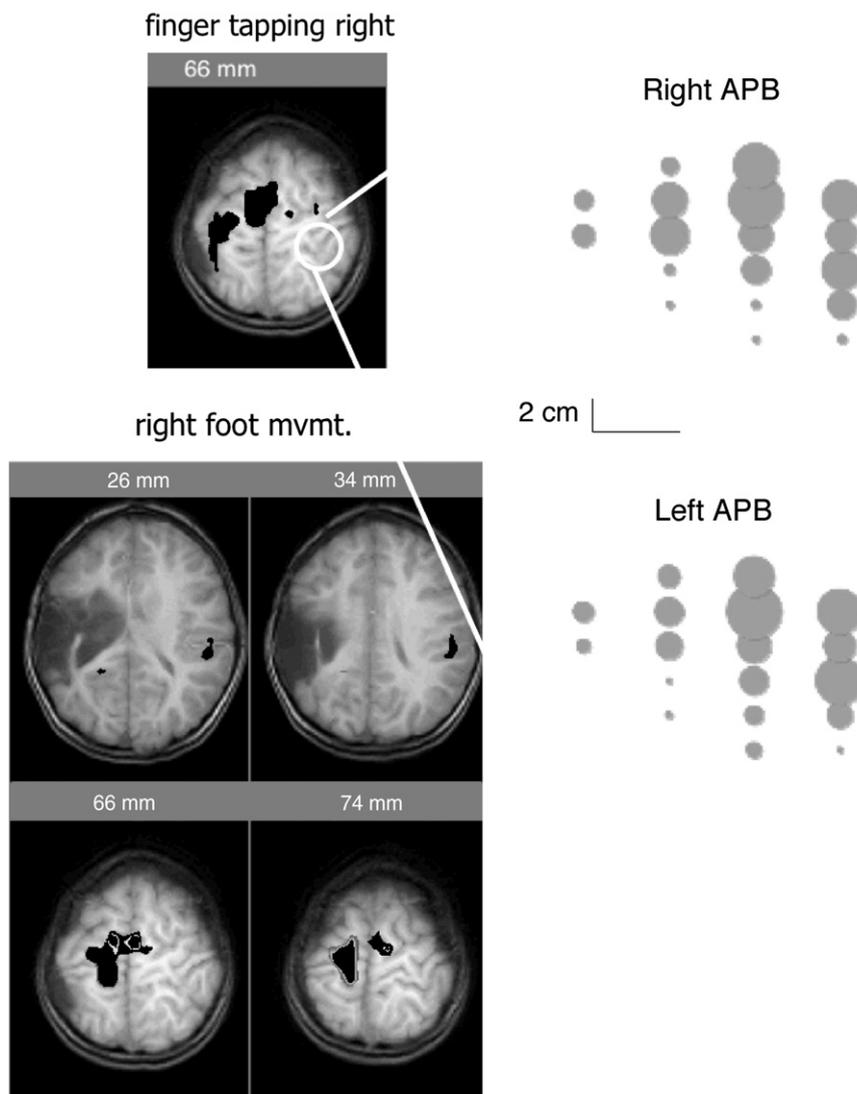

Fig. 3. Cerebral palsy example. The subject was a child with right hemiparesis and strong mirror movements of the left hand with right hand movement. The finger tapping activation reveals left M1 and SMA activity (in black) with M1 activation only slightly more medial for foot movement. (Left hemisphere is on the left of these images.) TMS demonstrated overlapping maps of right and left thumb muscle (APB) in the right brain, where no activation was seen for right hand movement. Subjects had anatomical and EPI-BOLD imaging in a GE 1.5 T MRI with archiving, reconstruction, and initial analysis by means of proprietary software of the Advanced Neuroscience Imaging Research Core (http://fmri.wfubmc.edu/). Further analysis used SPM (Welcome Department of Imaging Neuroscience, London, UK) and FSL (Oxford University).

Conclusions

The concept of remapping has led to significant advances in how we understand the multifactorial process of recovery after CNS injury. There are experience-dependent processes that likely involve disinhibition of previously inhibited connections as well as stabilization of new synapses. But the map metaphor has also led to an exaggerated conception of post-lesion plasticity. For example, the map expansion found by TMS that appears to be related to therapy may come about through changes in inhibition, excitability, and potentially spinal cord circuitry, and therefore may not represent the same kind of remapping as found in experimental motor cortical lesions. The idea of a map is useful only if we have somewhere to go; at times acting locally is more important.

Acknowledgments

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