Rehabilitation of Brain Damage: Brain Plasticity and Principles of Guided Recovery

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Rehabilitation of the damaged brain can foster reconnection of damaged neural circuits; Hebbian learning mechanisms play an important part in this. The authors propose a triage of post-lesion states, depending on the loss of connectivity in particular circuits. A small loss of connectivity will tend to lead to autonomous recovery, whereas a major loss of connectivity will lead to permanent loss of function; for such individuals, a compensatory approach to recovery is required. The third group have potentially rescueable lesioned circuits, but guided recovery depends on providing precisely targeted bottom-up and top-down inputs, maintaining adequate levels of arousal, and avoiding activation of competitor circuits that may suppress activity in target circuits. Empirical data are implemented in a neural network model, and clinical recommendations for the practice of rehabilitation following brain damage are made.

The Clinical Problem

Many tens of millions of people worldwide suffer brain damage. Hundreds of thousands of professionals treat this brain damage using a variety of rehabilitation therapies. Yet in spite of this enormous endeavor, there is no agreement as to how these therapies work, though it can be concluded that at least some have been shown to be effective (Antonacci et al., 1995; Bütefisch, Hummelshain, Denzler, & Mauritz, 1995; Ottenbach, Hummelshain, Denzler, & Mauritz, 1995; Robertson, 1993; Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995). Without understanding how rehabilitation works, the refinement and improvement of rehabilitation methods on scientific principles will be difficult if not impossible. The aim of this article is to present a theoretical framework within which rehabilitation after brain damage can be understood and to elaborate some principles that may be used to guide and accelerate the natural processes of recovery of function.

Although the neural processes underlying recovery of brain function have been studied extensively (e.g., Sofroniew, 1993), the neuropathological level of analysis is limited in its ability to generate hypotheses about the appropriate behavioral strategies needed to accelerate recovery of function. Yet it is at the behavioral level where rehabilitation operates. Furthermore, given the growing evidence, which we review below, that behavioral interventions can have important neural effects, the need for a neuropsychological level of analysis of the processes involved becomes more pressing.

In one important respect, the neuropsychological level of analysis has already been established, principally by Luria (Luria, 1963; Luria, Naydin, Tsvetkova, & Vinarskaya, 1975), who argued strongly for a compensatory process known as functional reorganization or functional adaptation underlying recovery. In his view, given the fact that central nervous system (CNS) neurons outside of the hippocampus do not regenerate, recovery of neuropsychological functions is achieved largely by the reorganization of surviving neural circuits to achieve the given behavior in a different way. Although there is clear evidence that this is one important type of mechanism underlying recovery of function, which has recently been well described (Bäckman & Dixon, 1992) in the context of recovery of function following brain damage, we concentrate in this article on the possibility of rehabilitation-induced plastic reorganization of lesioned brain systems. In so doing, we use the term circuit to refer to a network of synaptically connected neurons or sets of neurons that are functionally connected, such that they reliably become activated together when a particular cognitive activity occurs. For the purposes of this discussion, circuits may be highly anatomically localized or widely distributed in the brain.

Recent advances in the knowledge about the plasticity of the adult CNS (e.g., Nudo, 1996) as well as developments in connectionist models of neuropsychological function (see review in Plaut, 1996) require that a new attempt be made to formulate a theory of recovery of function that allows not only for compensation as a mechanism of recovery but also for partial restitution of the impaired neuropsychological processes themselves. In other words, we argue that not only do brain-damaged individuals learn...
to do things in different ways, they may also learn to do what they
did before in more or less similar ways as before; we also argue that
the basis for some of these changes is experience-dependent
brain plasticity. Furthermore, we attempt to establish some prin-
ciples by which such experience-dependent plasticity may be
helped or hindered.

Before embarking on this endeavor, however, an important
caveat is required. Conceptually attractive as this distinction be-
tween compensation and restitution may be, there can be signifi-
cant difficulties in making it. We argue that compensatory pro-
cesses are implicated in recovery where the pattern of behavior in
a given domain is clearly produced by a quite distinct set of
neuropsychological processes compared with non-brain-damaged
participants. Examples of this follow later in the article. To dem-
strate that restitution and not compensation has occurred, on the
other hand, we cannot rely on this type of behavioral—experimental
test. Logically, though one may be able to show that a recovered
behavior appears identical to that shown by normal participants,
one can never exclude the possibility that a difference does exist
and that the correct experimental manipulation to demonstrate this
difference has simply not has been found. In short, proving that
restitution and not compensation has occurred using behavioral
methods demands the logically impossible proof of the null hy-
pothesis. The demonstration that restitution has occurred must
therefore depend on physical measures of brain structure and
function, showing that neuroanatomical structures known to be
involved in the impaired function are activated when the relevant
behavior is produced. We give examples of this type of evidence
below.

Heuristically, however, the distinction between compensation
and restitution has proved useful in developing the arguments of
this article. And in pragmatic clinical terms, it is also hard to avoid.
Faced with someone who cannot move her arm, for instance, does
one devote limited rehabilitation resources to trying to get her to
move that arm or to developing compensatory strategies to allow
her to live as normal a life as possible while avoiding the use of
that arm? Faced with someone showing severe expressive dyspha-
sia, do we as rehabilitationists try to train him to produce spoken
words, or do we teach him alternative means of communication?
Confronted with dysexecutive problems, do we focus our efforts
on structuring the environment to support more organized behav-
ior, or do we struggle to retrain at least some internally mediated
attentional control skills? These are real dilemmas for clinical
assumptions for the purposes of this article.

With this caveat in mind, we now make the following five
assumptions for the purposes of this article.

1. The brain is capable of a large degree of self-repair through
synaptic turnover and may in fact continuously be engaged in this,
even in the absence of overt damage. By synaptic turnover, we
mean the ongoing change in the dendritic branches of neurons,
with associated changes in the pattern of synaptic connectivity (cf.

2. This synaptic turnover is to some extent experience-
dependent and is a key mechanism underlying both learning and
recovery of function following brain damage.

3. Recovery processes following brain damage share common

Section A—Cortical Plasticity and
Hebbian Learning Mechanisms

There is abundant evidence to show that normal associative
learning and experience evoke changes in cortical sensory and
motor representational fields (Bailey & Kandel, 1993; Jenkins,
Merzenich, Ochs, Allard, & Guic-Robles, 1990; Kaas, 1991; Karni
et al., 1995; Merzenich et al., 1996; Nudo, Jenkins, & Merzenich,
1990; Nudo, Milliken, Jenkins, & Merzenich, 1996; Pascual-
Leone & Torres, 1993; Sugita, 1996; Wang, Merzenich,
Sameshima, & Jenkins, 1995; Weinberger, David, & Lepan,
1993), and it has been argued that the mechanisms underlying such
normal learning may be fundamental to the mechanisms involved
in recovery of function following acquired brain damage (Bailey &
Kandel, 1993; Kolb & Whishaw, 1989). There is also evidence
interpreted as experience-dependent changes in dendritic sprouting
beyond the somatosensory cortex (e.g., in Wernicke’s area; Jacobs,
Schall, & Scheibel, 1993), as well as behavioral evidence of
experience-dependent improvements in certain linguistic abilities
(Tallal et al., 1996) that may be underpinned by changes in
synaptic connectivity in the relevant language areas of the cortex.
Recent research also shows the possibility of brain cell regenera-
tion in the adult human hippocampus (Eriksson et al., 1998), and
in mice, such regeneration can be influenced by experience (Kem-
permann, Brandon, & Gage, 1998).

The evidence for experience-dependent synaptic changes should
not be surprising given the evidence that “synapses in both the
peripheral and central nervous system are subject to ongoing
turnover in the absence of damage of the tissues and in some cases,
under natural environmental conditions” (Cotman & Nieto-
Sampedro, 1982, p. 382). Such a view is also supported by data
from the dorsal root ganglion of the mouse provided by Purves and
Voyvodic (1987). Many other reviews support the view that a
number of experience-dependent changes occur in the adult brain,
including modification of synaptic connectivity having a time
course of minutes (Dinse, Recanzone, & Merzenich, 1993),
through dendritic arborization and to axonal sprouting with its
much longer time course (Darian-Smith & Gilbert, 1994; Dono-
ghue, 1995; Kaas, 1995; Kolb, 1996). Although there is the pos-
sibility that some sprouting may have negative effects (e.g., in-
creased spasticity; McCouch, Austin, Liu, & Liu, 1958), other
studies have lesioned the newly sprouted tissue to show that the
lesion-induced sprouting has indeed underpinned the behavioral
recovery observed (Ramirez, 1997).

However, no matter the views about the use of sprouting mech-
anisms, and even if one declines to accept their functional use, the
fact of experience-dependent synaptic plasticity at least through
changes in synaptic firing probabilities is impossible to refute. The
point of the present article is to apply the concept of cerebral
plasticity heuristically as a basis for establishing some principles
of rehabilitative acceleration of recovery processes and not to
review all possible neurophysiological mechanisms of recovery of
function following brain damage.

With this caveat in mind, we now make the following five
assumptions for the purposes of this article.

1. The brain is capable of a large degree of self-repair through
synaptic turnover and may in fact continuously be engaged in this,
even in the absence of overt damage. By synaptic turnover, we
mean the ongoing change in the dendritic branches of neurons,
with associated changes in the pattern of synaptic connectivity (cf.
mechanisms with normal learning and experience-dependent plasticity processes.

4. Variations in experience and inputs available to damaged neural circuits will shape synaptic interconnections and hence influence recovery.

5. An analysis of the determinants of normal short- and long-term plasticity in the undamaged CNS will yield useful guides to the key variables determining whether and how recovery of function can be guided and shaped by rehabilitation methods.

The concept of Hebbian learning is an important one in providing a framework for analyzing interactions between the neural and behavioral levels of analysis. Hebb (1949) argued that strengthening of synaptic connections occurs when pre- and postsynaptic neurons are coactive. Two neurons or groups of neurons that have been disconnected by a lesion may become reconnected if they are activated at the same time. Simultaneous activation will take place if both neurons are separately connected to a circuit whose neurons themselves are functionally interconnected. When this net of neurons is activated, the two neurons that are disconnected from each other are simultaneously activated. With several repetitions of this process, these two neurons thus may become reconnected. Hebbian learning provides a model for how neural circuits that are partially lesioned may regain the original pattern of connections and hence the cortical functions that they subserve may be regained. There is abundant recent evidence to support the Hebbian principle that “cells that fire together, wire together,” including data from intracortical microstimulation, whereby electrically stimulating cortical cells to fire in temporal proximity is shown to strengthen synaptic connections between them (Dinse et al., 1993).

There is, furthermore, evidence that connections between neurons that repeatedly fire nonsynchronously may actually become inhibited (Fitzsimonds, Song, & Poo, 1997; Singer, 1990). In this article, we attempt to elucidate some principles of rehabilitation aimed at restitution of function, drawing on these five assumptions about the recovery process.

A Triage of Recovery Patterns

Some individuals appear to recover autonomously after brain lesions (e.g., Choi & Wellner, 1994; Davis & LeVere, 1979; Dettmers, Stephan, Lemon, & Frackowiak, 1996; Gronwall & Wrightson, 1974; Hier, Mondlock, & Caplan, 1983; Kertesz, 1979), while some show little or very incomplete recovery even over tens of years (Milner, 1975; Newcombe, Ratcliff, & Damasio, 1987; Wilson, 1991; Wilson & Davidoff, 1993). A third category shows recovery, but this recovery appears to be dependent on rehabilitative input (Antonacci et al., 1995; Bütefisch et al., 1995; Kerkhoff, Münßinger, Haaf, Eberle-Strass, & Stogerer, 1992; Öügenbacher & Jannel, 1993; Robertson, 1993; Robertson, North, & Giggsie, 1992; Robertson et al., 1995; Taub et al., 1993; Wiart et al., 1997; Wilson, 1988). Of this notional triage of spontaneous recovery, assisted recovery and no recovery, respectively (see Figure 1), the focus of this article is most heavily on the middle group, namely, assisted or guided recovery. This is where the challenge of establishing principles of restitution-oriented rehabilitation is present. In the no-recovery group, compensatory adjustment is the appropriate rehabilitation response, but this is not the subject of the present article and is dealt with in other reviews (Bäckman & Dixon, 1992; Wilson & Watson, 1996).

Though this triage has only descriptive and no explanatory value, it allows us to offer a context within which rehabilitation aimed at plastic reorganization of the brain can be analyzed. It also allows us to examine the theoretical limits to guided recovery of lesioned circuits by drawing on connectionist models of recovery that have been described elsewhere (Murre, DenDulk, & Robertson, 1999; Murre & Robertson, 1995).

Autonomous Recovery

The cell loss in the substantia nigra linked to Parkinson’s disease (PD) results in disruption of the nigro-striatal pathways. Electron microscope study of the caudate nucleus in three people who had had PD shows, however, that the number of synapses and the length of postsynaptic densities had increased, representing a plastic reorganization based on increased connections among a reducing number of surviving cells (Anglade, Mouaprigent, Agid, & Hirsch, 1996). This plastic reorganization following lesions to a circuit represents a common restitutive process whereby surviving neurons in a network maintain function through increasing connectivity.

In one sense, such sprouting can be regarded as compensatory, insofar as the additional dendrites compensate for the loss of neurons. This is not, however, the meaning of compensation that we intend in this article. An example from PD of what we would consider as compensation comes from a functional imaging study of people suffering from PD as they executed a finger-to-thumb motor task (Rascol et al., 1997). PD participants who were on medication showed a similar pattern of brain activation to that shown by age-matched control participants while doing this task. This consisted of a significant increase in bloodflow in the con-
tralateral primary motor cortex and in the supplementary motor areas, without any changes in brain activity in the cerebellum. The PD participants who were off medication, on the other hand, showed activation of quite different brain regions when doing this task, namely, the ipsilateral cerebellar hemisphere. They also showed a significant deactivation of the supplementary motor areas. Rascol et al. (1997) interpreted this as reflecting efforts to compensate for the impaired function in these patients, and this is in line with our use of the term compensation in the present article, namely, the use of quite different neuropsychological systems in the performance of a task, compared with non-brain-damaged controls. It seems very likely that both types of adjustment would be present in these off-medication patients. The restitutive dendritic sprouting (though not sufficient without medication to maintain "normal" behavior) was very likely in place as well as these compensatory adjustments underpinning the finger–thumb movements. Practically, it is likely that both restitution and compensation occur simultaneously in many cases but with differing degrees of potency in determining behavioral maintenance or recovery.

We argue in this section that sudden damage to the adult brain leading to loss of connectivity in a particular circuit should also be amenable to a similar process of reconnection to that shown in the striatum of some PD patients. Evidence exists that this does indeed happen in the primate brain. Owl and squirrel monkeys were trained to carry out a task requiring finger dexterity, and then those sensory brain areas (Area 3b) shown to be implicated in the skill performance were lesioned. With training, the skill was reacquired; this reacquisition was associated with reorganization of the sensory cortex, compatible with redistribution of representations to nondamaged areas of sensory cortex (Xerri, Merzenich, Peterson, & Jenkins, 1998). Other studies have shown similar plastic reorganization in motor cortex of primates (Nudo & Milliken, 1996).

Parallel results in humans have also been obtained. For instance, in one study of patients who had a tumor in the hand area of the primary motor cortex, Positron Emission Tomography showed that in all patients, voluntary finger movements by the contralesional hand were linked to blood flow increases in adjacent areas of the motor cortex, premotor cortex, or parietal somatosensory cortex (Seitz et al., 1995). At the very least, the reorganization of representation within motor cortex in humans shown here gives a strong parallel to the primate data, clearly indicating the occurrence of restitutive reconnection and reorganization (as opposed to compensatory reorganization to quite different neural circuits, as was observed in the finger–thumb movement study of PD patients described above). The transfer of function outside primary motor cortex, to premotor and primary somatosensory cortex, is less easy to assign to restitutive versus compensatory categories. This is particularly so given that some areas of activation were as much as 43 mm distant from the lesion site.

It may well be, therefore, that both compensatory reorganization of neighboring circuits and restitutive reconnection within the motor cortex itself underpinned recovery. The fact that plastic reconnection can underpin recovery in at least some human cases is, however, clearly made in this article. Chollet and Weiller have reviewed other studies showing similar types of plastic reorganization (Chollet & Weiller, 1994), all of which indicate that plastic reorganization within primary motor cortex may underpin functional recovery following lesion.

Very significant recovery of function following lesions has been documented for many other types of disorder. These include acquired language disorders (Kertesz, 1979; Weiller et al., 1995; Zangwill, 1975), perceptual deficits (Wilson & Davidoff, 1993), unilateral neglect (Stone, Patel, Greenwood, & Halligan, 1992; Stone et al., 1991), attention deficits (VanZomeren & Burg, 1985), tactile discrimination (Weder et al., 1994) and many others. Compensatory processes of course may explain some of this recovery, but the possibility that plastic reorganization can underpin at least some of this observed recovery of function is strong.

Clearly, however, many other pathophysiological mechanisms influence the nature and course of recovery following lesions. Our argument here assumes that in terms of such variables as disturbed hemodynamics, intracranial pressure variations, glutamate cascades, and a score of other processes that can follow brain lesions, some sort of physiological stability has been reached. These processes are more prominent in the acute phase following a lesion, and the mechanisms of recovery that we are dealing with in this article are considered while partialing out these other complex changes to the brain.

There are two types of process that appear to underpin the type of plastic reorganization under consideration. One type is a rapidly occurring alteration in synaptic sensitivity, possibly related to unmasking of existing connections through change in the inhibitory dynamics. This can take place over seconds and minutes and is contrasted with structural changes taking days and weeks (Donoghue, 1995). Functionally, however, the effects appear quite similar, in phenomena ranging from phantom limb following amputation (Ramachandran, Stewart, & Rogers-Ramachandran, 1999), to cortical reorganization contingent on Braille learning (Hamilton & Pascual-Leone, 1998). The remodeling of connectivity in neural networks involves changes in the firing probabilities between groups of neurons. Such changes in connection strengths between groups of neurons can occur either through changes in synaptic sensitivity, or through structural changes in connections between groups of neurons, for instance, through dendritic sprouting.

von Monakow’s (1914) notion of diaschisis is relevant here. Diaschisis refers to depression of activity in remote, nondamaged brain sites that are functionally connected to lesioned areas. This can readily be interpreted in terms of a weakening of synaptic connections between the damaged and undamaged sites, contingent on the reduced level of activity in the lesioned area. As a result, cells in the two areas no longer fire synchronously to the same degree, and so synaptic connectivity between them is weakened. This loss of connectivity results in depression of function in the structurally undamaged but functionally partly disconnected remote site. Although initially such changes will consist of weight changes, over time these weight changes may translate into structural alterations in the connections between the partially disconnected sites. But the consequences of both mechanisms seem very similar, and in attempting to build a model of synaptic remodeling, a single weight-change mechanism should serve as a useful first approximation covering both types of change. Weight here refers to the strength or efficiency of connections.

We have developed a model of self-repair in neural networks (Murre & Robertson, 1995; Murre et al., 1999) that enables us to test many of our basic assumptions and explore the importance of the parameters underlying the repair of damaged representations.
We obtain these results both with a biologically informed neural network model (based on the cortex part or trace system of the TraceLink model of amnesia, Murre, 1996, 1997) and with an approach based on Hopfield networks (Hopfield, 1982). We mention some of the results of our TraceLink simulations below as an illustration of our approach. In addition to the simulations, we have undertaken mathematical analyses of the network models. In these, we increase the level of abstraction and view a neural representation as a large set of neural units (groups or modules of tightly coupled neurons) with connective tracts between them. Such a set is called a graph. For the analyses we, furthermore, assume that the connectivity is random (relaxing this assumption does not significantly alter our results). We model brain lesions by randomly deleting connections in these networks. Repair is modeled by a three-step process, in which we (a) activate one neural unit, (b) allow its activation to spread to all other connected units, after which we (c) randomly add new connections between activated units (mathematical implementation of Hebbian learning). The mathematics of this type of random graphs has recently shown important developments (Bollobás, 1985) that allow us to derive a number of very fundamental properties of such systems. Moreover, we have explored the effects of relaxing our assumptions in simulation studies. Our primary aim was to see whether the fundamental properties of random graphs are altered if they are brought more into line with known neurobiology. For most parameter ranges, this does not seem to be the case.

Although we regularly refer to our modeling studies with random graphs and artificial neural networks (Murre & Robertson, 1995; Murre et al., 1999), the basic assumptions outlined above remain at the core of our theory. In this article, we do not aim to prove any specific points with our modeling work, but we rather view it as having a more supportive role. Specifically, the reasons for referring to it are threefold: (a) First, the modeling work has proven to be an important and useful heuristic for us in developing the theory. Connectionism is an excellent formalism to bridge the fields of (neuro)psychology and neurobiology. (b) Second, we feel that some of our simulations illustrate our theoretical positions, for example, regarding self-repair. (c) Third, the fact that we implemented our core assumptions in a set of models can be viewed as a quality check because implementation of a theory in a specific model has certain consequences: (a) It forces one to be explicit about what is meant by each theoretical concept. This may uncover hidden assumptions in the theory. (b) Theoretical implications can often be simulated. Sometimes, when trying to accomplish this, it becomes clear that aspects of the theory are underspecified, in particular with regard to structures and processes. (c) Sometimes, a theoretical implication or prediction that seems logically and intuitively plausible is not supported by the simulations. In such cases, the theorist receives a valuable warning to reconsider its logical derivation. Given that many different models can be developed, given a set of core assumptions, a successful simulation of an implication should be seen as an existence test, answering the question "Can this characteristic emerge from the basic assumptions?" Summarizing, we view the role of the modeling in this article as a heuristic, illustration, and quality check of the theory.

On the basis of our core assumptions and aided by simulations and analyses (Murre & Robertson, 1995; Murre et al., 1999), we make certain predictions about the process of plastic reorganization following brain lesions. We predict that the speed of such completion depends mainly on three factors: (a) total size of the lesioned neural circuit, (b) degree of connectivity within the network, and (c) size of lesion. Providing the lesioned circuit retains sufficient interconnections among the remaining cells or groups of cells, theoretically at least that circuit should be able, through Hebbian learning, to recomplete the pattern of connections as illustrated in Figure 2.

The mechanism illustrated in Figure 2 would be a plausible candidate to explain at least some of the abundant evidence of spontaneous recovery following various types of brain damage.

1 We concentrate on lost connections rather than on cell death, that is, on lesioning entire neurons, because if cell death is severe, an area must be considered lost and compensation strategies must be pursued. Furthermore, we do not attempt to model compensation strategies here, and the effects of moderate levels of cell death are modeled in several ways: (a) We look at the effects of the size of neural representations, which cell death tends to diminish (i.e., if many cells die, certain neural units will cease to function). (b) Our model assumes that connective tracts involve many intermediate neurons (cf. the work of Abeles, 1991; Bienenstock, 1995), which become inoperative on severe cell death. It should be remarked, however, that we observe that the direct effects of cell death alone (i.e., without separate lesioning of connections other than those lost with dying cells) are minor compared to those of even small lesions. (c) Finally, we also model the effect of focal lesions of cells on the reorganization of representations (Murre & Robertson, 1995; Murre et al., 1999).
Figure 2 shows how a well-connected neural circuit incurs a moderate, diffuse lesion, after which spontaneous recovery takes place. The recovery is driven (in this case) by random activation of one of the groups. While the activation is spreading through the circuit, neural groups become (re-)connected through a Hebbian learning process. In practice, many such activations would be necessary to achieve sufficient connectivity to cause significant recovery. After prolonged recovery, the circuit will be nearly as well interconnected as before the lesion, although we expect the average overall strength of the connections to be lower. We postulate that one of the main functions of the Hebbian (re-)connection process is to ensure that enough extra connections are available to recover from these types of lesions. In other words, the brain needs a certain percentage of redundant connections to withstand brain damage (see Murre & Robertson, 1995; Murre et al., 1999, for an analysis of how much redundancy is necessary).

**Serial lesion effect.** The nature of autonomous recovery as a result of pattern completion of lesioned circuits is strikingly demonstrated in the phenomenon known as the serial lesion effect. There are several studies showing that following certain types and location of brain damage, a given lesion created on a single occasion will have more detrimental behavioral effects than exactly the same type and size of lesion created in a stepped fashion over a number of occasions (deCastro & Zrull, 1988; Finger & Stein, 1982; D. R. Meyer, 1988; Nonneman & Kolb, 1979; Travis & Woolsey, 1956). This may be due to pattern completion within lesioned networks, which can take place more easily and more completely after a small compared to a large lesion. This is also supported by both our connectionist simulations and our analyses with random graph theory (Murre & Robertson, 1995; Murre et al., 1999). By this argument, the lesioned neural network will, through Hebbian learning, achieve some repair or reconnection in the interval before the second lesion is given. The second lesion attacks a partially recovered circuit and hence has a less severe effect than if the whole lesion were given at the same time. This phenomenon has been successfully represented by us (Murre & Robertson, 1995; Murre et al., 1999) and is illustrated schematically in Figure 3.

Although several small, serial lesions appear to have a less destructive effect on brain function than one larger lesion of the same total volume, a second lesion will in most cases exacerbate the effects of a previous lesion. In traumatic brain injury, for instance, a given injury usually has a more deleterious effect than if there has been a previous traumatic brain injury (Gronwall & Righton, 1975). This is to be expected, as the total amount of tissue damage is in this case greater, whereas the serial lesion effect assumes the same total amount of tissue damage between the two conditions.

Taken to its logical conclusion, the serial lesion hypothesis implies that if a lesion is big enough, then reconnection of the damaged neural circuit will never be possible, which indeed appears to be the case in some cases (Milner, 1975; Newcombe et al., 1987; Wilson, 1991; Wilson & Davidoff, 1993). That brings us to the other extreme of the recovery triage—failure of recovery.

**Failure of recovery.** Just as striking as those instances of apparently complete recovery following brain lesions are those cases where deficits remain permanent and unaffected by any rehabilitation attempts. The neuropsychological literature abounds with examples of neuropsychological disorders that do not recover over years (e.g., Kertesz, 1979) or even over many decades in the case of one study of penetrating missile injuries from the second World War (Newcombe et al., 1987). Disorders such as anosognosia (Humphreys & Riddoch, 1987), unilateral spatial neglect (Robertson et al., 1994) and many others can also be intractable.

Such cases may occur because neural circuits are so disconnected or so depleted of neurons that no amount of Hebbian learning will ever allow reconnection (though potentially reversible inhibitory processes may also play a part—see Section B). Murre and Robertson (1995) and Murre et al. (1999) have demonstrated this phenomenon with a connectionist model of neural self-repair. Evidence for reconfigurable repair requiring a certain minimum proportion of cells and connections comes from several sources. In controlled crushes of the optic nerve in rats, for instance, leading to axonal injury and associated cortical changes, near-normal recovery in vision can be observed providing a minimum reserve of cells—in this case 10–15%—remain uninjured (Sabel, 1997; Sabel & Aschoff, 1993). A similar conclusion can be derived from PD, where patients only become symptomatic after about 80% loss of dopamine cells (Hornykiewicz & Kish, 1986), a result of additional dendritic sprouting between remaining cells (Anglade et al., 1996). In a quite different domain, following hemispheric strokes, it has been estimated that approximately 20% of cortico-spinal tract fibers must be spared to ensure restitution of fractionated fiber movements (Binkofski et al., 1996), and a similar estimate has been made for brain stem lesions (Jane, Yashon, Becker, Batty, & Sugar, 1968).

As argued earlier, compensatory approaches to rehabilitation are indicated for individuals whose impaired circuits fall below such a "minimal residual structure" (Sabel, 1997, p. 63) hypothetically required for plastic reconnection. This hypothesis is supported by Kolb (1996), who suggests that, whereas small lesions can result in restitution of function and of faithful replication of the original behavioral pattern, large lesions yield a recovery based on compensation and behavioral adaptation.

One example of such compensatory readjustment comes in a study of recovery from unilateral neglect, a relatively common disorder following damage to the right hemisphere of the brain, and in particular the right parietal lobe. It is associated with a failure to orient or respond to stimuli on the left side of space (Robertson & Marshall, 1993). Goodale and colleagues (Goodale, Milner, Jakobson, & Carey, 1990) studied a group of 9 participants who had suffered unilateral right hemisphere lesions approximately 5 months earlier. These patients had previously shown signs of unilateral neglect, but by the time they were tested by the authors, there was no clinically significant neglect. The experiment consisted of two tasks, one involving reaching out and touching one of a number of lighted targets presented on a vertical screen in front of the participants, and one involving requiring the participants to bisect the distance between two specified targets on the screen. The brain-damaged patients showed no difference from the controls on their accuracy of touching the targets. More interesting, however, were the trajectories of the hand as it reached to the targets. In both the target and bisection conditions, kinematic video analysis of the reaching movements was made. This revealed that the patients made a wide right arc into the final target, a pattern that was not apparent in the controls.

The above results suggest that, even after the apparent recovery of neglect, underlying distortions in spatial or attentional mecha-
a. Two small lesions

(b.1) [Diagram showing a circuit with a single large lesion, labeled as 'Single Large Lesion' and leading to 'Start Recovery' and 'Finish Recovery'.]

b. A single large lesion

![Diagram showing circuit recovery process for two small lesions and a single large lesion.]

Figure 3 Serial lesion effect: Two small lesions (Figure a) recovery better than a single equally large lesion (Figure b). Figures a.1 and a.2 are the same as Figures 2.a and 2.b, respectively. The lesioned circuit in a.2 recovers, resulting in the circuit of a.3. The recovery process itself is not shown, but is similar to that in Figures 2.c-e. A second lesion leads to the damaged circuit in a.4, followed by a second recovery phase, resulting in the recovered circuit of Figure a.5. Figure b.1 is the same as a.1 but now the circuit is subjected to a much larger lesion, as shown in b.2. Figures b.3 and b.4 show two stages of the recovery process. In b.4, some connections have been formed, but three of the neural groups do not have sufficient residual connectivity to the main circuit and become lost (at least, they will no longer take part in this particular circuit; they may still take part in other circuits that are not drawn here). Figure b.5 shows how the recovered circuit remains weaker after a single large lesion, compared with after two small lesions (Figure a.5).

nisms still exist, and the patients may have learned to compensate for their neglect by some additional undamaged, possibly visual, system. When the patients first executed the move toward the target, it appears that they did so on the basis of a distorted body-referenced spatial system. The rightward trajectory may then have been corrected by a compensatory visual feedback system that the participants had spontaneously learned to use to correct the spatial errors of which they may have been unaware. It is possible that a frontal-based system for the voluntary orientation of spatial attention may have compensated for a nonfunctioning parietal-
lobe-based system regulating the automatic orientation of attention (Ladavas, Carletti, & Gori, 1994).

In other words, it appears that, in some cases of unilateral neglect at least, the capacity for automatic orientation of attention to the left side of space has been permanently impaired, and this deficit can be unmasked by the appropriate experimental method. The apparent recovery appears to be mediated by a non-lesioned circuit, possibly in the frontal lobe, which achieves the behavioral goal in question and hence represents an example of appropriate compensatory reorganization in the context of nonrecovery of a particular lesioned neural circuit.

Although compensatory reorganization is a highly desirable mechanism for behavioral recovery following failure of Hebbian pattern completion in a neural circuit, there may at times be drawbacks if there is any possibility of restitutive completion in the damaged circuits. For instance, LeVere and LeVere (1982) found that visual decorticated rats would ignore visual cues and respond to nonvisual cues when attempting to avoid shock. Of particular interest in this study was that, if these nonvisual cues were made irrelevant to the task, it became clear that the rats could in fact still use the visual ones to escape the shock, albeit at a much lower level than prelesion, even though they were completely ignored beforehand. LeVere and LeVere conclude that residual spared functioning of the damaged visual system was "suppressed, masked or dominated" (p. 172) by the functioning of the nonvisual neural systems that remained intact, suggesting that not only can compensatory processes deter the usage of partially lesioned circuits, they may also actively inhibit such usage through inhibitory processes. These processes are discussed in some detail in Section B.

A human example of maladaptive compensation comes from the work of Beauvois (1982). In a case of optic aphasia, tactile recognition could be improved by tapping closed the lips of the patient to prevent implicit verbalization. Beauvois proposed that an intact tactile object recognition system was inhibited by the patient's attempts to use an impaired verbal system as a compensatory aid. Similarly, reports exist of congenitally blind individuals who regain their sight later in life and who show considerable problems in adjusting to, and using, the newly acquired sensory modality (Gregory & Wallace, 1963), partly because of a strongly learned reliance on other sensory modalities.

Restitution of function in damaged circuits may therefore be hindered by compensatory adjustments that improve function in the short term, while at the same time hindering reactivation of the damaged circuits themselves. It is the possibility of such reactivation that constitutes the main focus of the current article, which deals with the intermediate level of the recovery triage shown in Figure 1. Such circuits, we propose, are candidates for guided recovery.

There is therefore a theoretical possibility that restitution of function in damaged circuits may be hindered by compensatory adjustments that improve function in the short term, while at the same time hindering reactivation of the damaged circuits themselves. There is, however, also the possibility that overstimulation of lesioned circuits in an attempt to foster restitutive reconnection may actually hinder neurochemical and physiological repair within these circuits (see, e.g., Humm, Kozlowski, James, Gott, & Schallert, 1998). Hence, even where restitution is a viable long-term goal, compensatory adjustments may be a necessary short-term stepping stone facilitating achievement of that goal. Furthermore, compensatory adjustments should only have a detrimental effect on restitution of function if they inhibit activity in these circuits in the long term. We give examples of the latter below but would emphasize that compensatory processes are in many cases compatible with restitutive approaches. What may be critical is the timing of each of these interventions.

A central hypothesis of this article is that circuits that have lost an intermediate number of connections may be in a critical state where they could either lose connectivity completely, or alternatively recover patterns of connections subserving the impaired neuropsychological function. Rescue versus collapse may depend on such circuits receiving precisely targeted stimulation fostering Hebbian-based reconnection of the partially disconnected network. Certainly, this is exactly the prediction made by the mathematical model of reconnection described above. There is abundant evidence that, even in the undamaged brain, loss of stimulation or disuse results in declining connectivity in a circuit. For instance, immobilization of an ankle following injury causes the motor cortex area of the inactivated tibial anterior muscle to diminish compared with the unaffected leg without changes in spinal excitability or motor threshold. Furthermore, the area reduction was found to be correlated to how long the ankle had been immobilized (Liepert, Tegenthoff, & Malin, 1995). The same has been found for temporary partial anesthesia of the hand: the loss of sensory input causes a temporary reduction in the cortical motor representation of first dorsal interosseus muscle, supporting the notion that lack of input to a cortical circuit results in a shrinkage in the connectivity of that network (Rossini et al., 1996).

It is most unlikely that, in the lesioned brain, comparable losses of input cannot cause declining connectivity to lesioned circuits and to neighboring circuits also. Therefore, the viability of the notion of rescue versus collapse of lesioned circuits, depending on whether the appropriate input is given to the circuits or not, is strengthened. Now, we discuss the intermediate level of the recovery triage shown in Figure 1, namely, neural circuits that neither recover spontaneously nor fail to recover completely. Such circuits, we propose, are candidates for guided recovery.

Guided Recovery

In Figures 2 and 3 above, we saw schematic models of a possible way in which lesioned neural circuits may show spontaneous completion. There are, however, limits to these spontaneous completion processes (see Murre & Robertson, 1995, and Murre et al., 1999, for a more systematic exploration). Depending on the size of lesion and the size of the neural circuit, such Hebbian-learning-based reconnection may not be possible. In some such cases, however, providing additional input to such networks may facilitate a degree of completion that is not possible without such external, patterned input.

To give an example of this, Mayer, Brown, Dunnett, and Robbins (1992) showed that rats given striatal neural transplants only benefited from the transplants when they were given the opportunity for perceptuomotor learning: In the absence of such behavioral driving of the neural tissue, the necessary connectivity did not develop sufficiently to produce behavioral improvements. Another example of guided recovery comes from the work of Nudo, Wise, Sifuentes, and Milliken (1996), who showed that, following lesion
to the motor cortex of the squirrel monkey, hand movement representations adjacent to the area of infarct that were spared from direct injury underwent further loss of cortical territory. They went on (Nudo et al., 1996) to show that intensive behavioral training of skilled hand use resulted in a prevention of the loss of the hand territory adjacent to the infarct. In some instances, they found that the hand representations expanded into regions formerly occupied by representations of the elbow and shoulder. Furthermore, this functional reorganization of the undamaged motor cortex was accompanied by behavioral recovery of skilled hand function. The authors concluded that rehabilitative training can shape subsequent reorganization in the adjacent intact cortex.

In the following section, we review in more detail examples from further studies, mainly human lesion studies, to elucidate some principles of guided recovery. This review is followed by a section that reviews the most successful predictors of recovery. We conclude with a section in which we derive testable hypotheses from the theory developed in this article.

Section B—Principles of Guided Recovery

In this section, we consider a number of different approaches that can be derived from the model of recovery of function outlined above. In so doing, we draw on both empirical data as well as neural network models that have simulated these data. The five principles discussed below are nonspecific stimulation, bottom-up targeted stimulation, top-down targeted stimulation, manipulation of inhibitory processes, and manipulation of arousal mechanisms. Each of these is discussed in turn.

Before outlining these principles, it is important to raise the issue of the range of neuropsychological phenomena to which this approach is intended to apply. Much of the literature on adult cortical plasticity is based on reorganization of primary sensory and motor circuits in the cortex. This is understandable because of the well-understood and precise topographical maps that exist in these areas and that can reveal the reorganization that is now known to occur. The representations underpinning such systems as memory and language, for instance, are much less well articulated, and the question therefore arises as to whether our approach to rehabilitation applies only to relatively low-level, posterior sensory, perceptual and motor functions.

The answer with respect to many high level functions is, firmly, no. There is evidence to suggest that the neural circuits underpinning high-level cognitive functions also are amenable to both restorative reorganization as well as compensatory adjustment, thus placing them squarely within the remit of the current framework. In studying recovery from Wernicke's aphasia, for instance, Weiller et al. (1995) showed that, as in the case of motor lesions studied by Seitz et al. (1995), remission from aphasia was associated with apparent plastic reorganization of the cortex revealed by functional neuroimaging. Phemonic discrimination improvements thought to be underpinned by training-induced changes in cortical reorganization have also been observed in children suffering from specific language impairment (SLI; Merzenich et al., 1996; Tallal et al., 1996).

The relevance of the approach to rehabilitation advanced here to the broad area usually described as executive functions is somewhat less straightforward, however. This domain of cognitive function is the least well understood in the brain, and the use of the terms executive and frontal interchangeably is not justified. For example, parietal lobe involvement is common in one putatively executive function—sustained attention (Coulh, Frith, Frackowiak, & Grasby, 1996; Pardo, Fox, & Raichle, 1991). Although efforts have been made to elaborate integrated subsystems of the executive processes in the brain, as yet there is no theoretical consensus about the nature of these subsystems, and hence as to the nature of the executive system of the brain (see, e.g., Allport, 1992; Stuss, Shallice, Alexander, & Picton, 1995).

In this context, it is impossible then to say whether or not our theory applies to the rehabilitation of executive functions in general. What we can do, however, is to confine ourselves to those aspects of control that have been somewhat more adequately described and examine to what extent the principles of guided recovery apply to these specified control processes. One such process has been broadly described as sustained attention, a system located frontoparietally in the right hemisphere of the brain and known to be involved in the maintenance of the alert state under conditions of monotony (Coulh et al., 1996; Pardo et al., 1991; Pau et al., 1997; Sturm, Willmes, Orgass, & Hartje, 1997). As we describe in more detail below, rehabilitation aimed at improving sustained attention not only results in improved sustained attention capacity but also in increased activity in the right frontoparietal network known to underpin this process (Longoni et al., 1999). This is similar to the type of experience-dependent restitution of function demonstrated in other domains. We can therefore extend the applicability of our model from sensory, motor, language, perceptual, and spatial attention domains to at least one higher level control system—sustained attention. Whether the model applies to other aspects of executive control remains to be seen.

This capacity to sustain attention has been shown to predict motor recovery following right hemisphere stroke over a 2-year period (Robertson, Ridgeway, Greenfield, & Parr, 1997, see below for more details), supporting the view that this aspect of control may be important for plastic reorganization to take place. Without anticipating the arguments advanced below overmuch, we argue that this is one type of top–down modulation from a particular control system in the brain, partly located in the right dorsolateral frontal lobe. We argue later that a second control system—one for selectively gating sensory and motor systems—also provides a type of top–down modulation of lesioned brain circuits. First, however, we turn to the five principles of guided recovery before returning to this anterior–posterior distinction at the conclusion of this section.

Nonspecific Stimulation

Earlier in this article, we alluded to an extensive literature showing that environmental and behavioral factors can have tangible effects on dendritic branching and synaptic connectivity in neural circuits. Environmental enrichment—nonspecific social and behavioral stimulation—has in animal research led to such changes in synaptic connectivity (Black, Sirevaag, & Greenough, 1987; Greenough, Hwang, & Gorman, 1985; Rose, Al-Khamees, Davey, & Attree, 1993; Will & Kelche, 1992; York, Breedlove, Diamond, & Greer, 1989).

A neural network model of recovery schematically illustrated in Figures 2 and 3 (Murre & Robertson, 1995; Murre et al., 1999) would predict such results. Pattern completion and reconnection in
a lesioned network will normally occur more fully if a greater number of coactivations of the to-be-connected nodes take place. Hence usually, nonspecific environmental stimulation can be expected to facilitate synaptic connectivity by increasing the probability of reconnection through Hebbian learning mechanisms.

Under some circumstances, however, such nonspecific stimulation may foster faulty or maladaptive connections. This would tend to occur if the stimulations tend to produce a greater coactivation of part of the lesioned circuit with some other neural circuit than with other parts of the partially disconnected lesioned circuit. Figure 4 shows this schematically.

There is also empirical evidence to support such a view. For instance, Wall and Kaas (1985) showed that humans with partial deafferentations of skin regions commonly showed hypersensitivity and increased tactile capacity on skin next to the denervated zones, suggesting the occurrence of plastic reorganization of cortical representations in response to changes in sensory input. However, mislocalizations of tactile stimuli were also commonly found following such reorganization, suggesting that the new representations were not entirely adaptive. To take another example, mislocalization of sensory tactile stimulation of the face in humans to the phantom limb resulting from an amputated arm (Ramachandran et al., 1992) may also be a result of maladaptive reorganization of somatosensory representations in the cortex, as Kaas (1995) has observed. As Kaas puts it "... 'arm' cortex may not respecify when activated by afferents from the face to help mediate face sensation but may persistently and incorrectly signal inputs from the missing arm" (1995, p. 52). The possibility also arises that similar types of reactivation without respecification may be responsible for the phenomena of phantom and thalamic pain (Melzack, 1990). Jastreboff (1990) has also suggested that tinnitus arising from acquired deafness arises from decreased input from the periphery that causes synaptic compensation through plastic changes in synaptic weights within the central auditory system, resulting in the false auditory sensations of tinnitus.

Not all such connections with other neural circuits need be maladaptive, however. For instance, the Nudo et al. (1996) study described above showed that, following cortical lesions, the cortical hand representations expanded into regions formerly occupied by representations of the elbow and shoulder.

In principle, the effects of nonspecific stimulation should not be different in anterior and posterior parts of the brain. Certainly, research on lesioned rats shows that the frontal cortex responds to nonspecific environmental enrichment by dendritic sprouting and linked behavioral recovery in the same way as more posterior regions do (Kolb & Gibb, 1990). And though the human frontal cortex is obviously vastly different from rat frontal cortex, the rat frontal cortex does share common functions with its human equivalent, including sustained attention (Granon, Hardouin, Courtiere, & Poucet, 1998) as well as divided and selective attention (Muir, Everitt, & Robbins, 1996). In short, then, one should expect that nonspecific stimulation should have comparable effects—benefits and potential costs—on recovery after lesions to the frontal cortex in humans.

**Bottom-Up Specific Stimulation**

The discussion above would suggest that, where possible, stimulation should be targeted such as to foster adaptive connections within the lesioned circuit. Such inputs can be considered in terms of bottom–up versus top–down types of guided, targeted stimulation; we consider the former type first.

By bottom–up processes, we refer to the provision of perceptual, motor, or other externally generated or cued inputs to the lesioned network designed to specifically foster connections within the lesioned network and to minimize the possibility of accidentally fostering faulty connections with other networks. Figure 5 shows schematically how such targeted input may facilitate pattern completion while at the same time minimizing the chance of faulty connections.

As described above, Nudo and colleagues showed that losses in the representational area of the hand that arose over and above those caused by the direct lesion are the result of a diminished use of the affected hand. Their finding that intensive behavioral training of skilled hand use resulted in a prevention of the loss of the hand territory adjacent to the infarct, with accompanying behavioral recovery of skilled hand function, is an example of the neural effects of bottom–up specific input in the completion of lesioned networks, as illustrated in Figure 5.

A human study of physiotherapy has given parallel results. This study of motor rehabilitation evaluated a therapy consisting of highly repetitive hand and finger movements in the impaired arm. This produced significantly greater improvement in hand and finger function than standard hand and finger exercises where a range of movements were used during training (Bütefisch et al., 1995). From the Hebbian learning framework illustrated in Figure 5, specific stimulation where the same movements are made repeatedly would result in a more rapid and complete pattern...
a. Spontaneous recovery

Random Stimulation

(b.1) (a.1) (b.2) (a.2) (b.3) (a.3) (b.4) (a.4)

b. Recovery through patterned input

Patterned Input

Figure 5. Schematic illustration of the effect of targeted input on pattern completion. In Figures a. 1–4 only random external stimulation is available, leading in this case to incomplete recovery (also cf. Figure 3.b). In Figures b. 1–4, pattern input is available that targets the circuit in more places, causing a fuller recovery of the circuit because fewer isolated neural groups remain.

completion because such repetitive training would consistently activate the same sets of neurons in a damaged network, allowing faster completion through Hebbian learning mechanisms. Such synaptic changes have been demonstrated in the form of long-term potentiation in the sensorimotor cortex contingent on activation of these pathways (Asanuma & Keller, 1991).

An extension of the approach by Bütefisch and colleagues was also effective in improving hand function among participants with a centrally paretic hand (Hummelsheim, Arnberger, & Mauritz, 1996). In this study, voluntary EMG activity in hand extensor and flexor muscles was used to trigger electrical stimulation of these muscles, resulting in improved movements. As voluntary force levels improved, the threshold of muscle activity required to trigger stimulation was gradually increased. This training produced enduring improvements in a number of hand and arm function measures, and it is likely that the specific bottom-up stimulation of the lesioned sensorimotor cortex facilitated long-term potentiation and hence synaptic reconnection in these circuits, as has been demonstrated in animals (Asanuma & Keller, 1991).

To give another example, Taub and colleagues have demonstrated the effects of specific motor stimulation on patients who have suffered unilateral strokes leading to partial hemiplegia of one upper limb (Taub et al., 1993). They showed that it was possible to improve function in the hemiparetic limb by (a) discouraging patients from using the limb on the unaffected side of the body and (b) encouraging use of the partially hemiparetic limb (the latter approach having been previously shown to be effective with chronic, putatively plateaued, stroke patients; Balliet, Levy, & Blood, 1986). With just a 2-week period of such training, a significant improvement in motor function lasting up to 2 years was observed in the hemiparetic limb. These were also patients who were long past the period where maximum motor recovery takes place. These positive effects were predicated on a specific pattern of stimulation—activation of one limb combined with deactivation of the other—that would likely not have occurred if the motor stimulation had been nonspecific and fostered activity in both limbs.

Though there were elements of top-down input in this training procedure, insofar as the movements of the hemiparetic limb were generated voluntarily, we conceive this as a largely bottom-up phenomenon, insofar as the restitutive effectiveness of this training is contingent on the repeated activation of the impaired sensorimotor circuits, leading, it is hypothesized, to plastic reorganization of the cortical sensorimotor circuits (Taub & Wolf, 1997). This is similar in principle to sensory stimulation methods used to improve functional sensation after nerve repair in the injured hand. As mentioned earlier in this article, the loss of cortical input that arises from peripheral nerve damage leads to cortical reorganization (Elbert et al., 1994; Knecht et al., 1995), and it seems likely that this reorganization may in part underpin impairment of sensory function. Peripheral stimulation and activation methods comparable to Taub's methods may therefore have their effects through producing further cortical reorganization sufficient to improve sensory discrimination. Rehabilitation following damage to
the median nerve of the hand that is based on such sensory
re-education principles has indeed been shown to be effective
(Parry & Salter, 1976) and may have its effects through such
cortical mechanisms (Byl et al., 1997).

Related evidence for the effectiveness of bottom-up stimulation
in fostering recovery of function comes from a study of gait
rehabilitation in nonambulatory hemiparetic stroke patients (Hesse
et al., 1995). Seven patients who could not walk were partially
supported with a modified parachute harness and were encouraged
to walk on a treadmill. Very significant improvements in walking
were found, with 3 participants walking independently after
the end of training and 3 more requiring only verbal supervision.

There is also some evidence to suggest that repeated stimulation
of blind visual field in hemianopic humans may result in some
enlargement of the measured visual fields (Kasten & Sabel, 1995).
Such effects would be highly compatible with the animal data on
reorganization and sprouting in the visual cortex (Darian-Smith &
Gilbert, 1994, 1995). Nevertheless, there are methodological is-
issues in the measurement of these effects (Balliet, Blood, & Bach-
y-Rita, 1985; Zihl & von Cramon, 1985), and the effectiveness of
such training, while promising, awaits further research.

Further evidence as to the possibility of bottom-up shaping the
connectivity of lesioned circuits comes from the problem of phan-
tom limb pain. Phantom limbs and associated phenomena are
known to be—in part at least—epiphenomena of cortical reorga-
nization arising from deafferentation of cortical circuits (Flor et al.,
1995; Knecht et al., 1995; Melzack, 1990). Not only can phantom
limbs be phenomenally compelling to the individuals, but they can
also ache, itch, and even clench painfully to the extent that nails
are perceived as biting into the phantom palm (Ramachandran &
Rogers-Ramachandran, 1996; Ramachandran et al., 1992).

In a series of such amputees who suffered from phantom limbs
that gave the sensation of being painfully paralyzed, Ramachan-
dran ingeniously tackled the problem of perceived paralysis—with
associated pain and discomfort—of phantom limbs. He did this by
presenting visual feedback that gave the illusion that the phantom
limb was in place. This was done using a simple box with a mirror,
in which the intact hand was placed, and the resulting reflection in
the mirror gave the illusion of two normal hands in normal position
placed in front of participants. Participants were then asked to
clench and unclench both hands, and as a result, several patients
experienced the phenomenal release from paralysis of their phantom
limbs—even to the extent of having the sensation of nails
biting into the palm in some cases (Ramachandran & Rogers-
Ramachandran, 1996). These positive therapeutic results can be
interpreted in terms of the provision of highly targeted input
(namely the visual correlates of movement of the phantom limb) to
the malfunctioning circuits subserving the representation of the
phantom.

Related findings have emerged in the study of rehabilitation of
unilateral left neglect—a visuospatial attentional disorder leading
to impaired perception of and responses to stimuli on the left side
of space. Robertson and North carried out a series of experiments
examining the therapeutic effects of left arm activation (Robertson
& North, 1992, 1993). This approach was based on part on the
work of Rizzolatti’s group (Rizzolatti & Berti, 1990; Rizzolatti &
Camarda, 1987), who have demonstrated the existence of multiple
representations of space in the brain, which interact together to
produce a coherent spatial reference system against which pur-
poseful motor movements are calibrated and organized. Figure 6
shows schematically this view. It is the parallel activity of these
different perceptuomotor neural maps that produces the represen-
tation of space, and, conversely, it is their breakdown that creates
distorted representations.

In the experiments by Robertson and North, the effects of left
hand finger movements on a visual scanning task were compared
with an instruction to visually scan to the left side of the task an
identical number of times as there were finger movements in the
finger-movement condition. This condition allowed the effects of
movements to be compared with a visual attention manipulation.
Only the finger movements significantly reduced neglect. Another
comparison was between out-of-sight finger movements of the left
hand in left and right hemispace, respectively. Only left-hemispace
blind finger movements significantly reduced neglect compared
with the standard condition. Third, blind left-finger movements in
left hemispace were compared with passive visual cueing (reading
a changing number), and again it was found that only the finger
movements reduced neglect. Finally, right-finger movements in
left hemispace were compared with left-finger movements in left
hemispace: Only the latter reduced neglect.

This suggests that the potent effect of moving the hemiplegic
side is not simply that of cueing attention to the neglected side, but
rather the fact of making movements by the left limb in left

Figure 6. Schematic representation of three semi-independent spatial
areas in the brain—personal, near extrapersonal, and far extrapersonal.
Research on both monkeys and humans shows that attention to these three
spatial domains can be partially dissociated and that unilateral neglect can
be found independently for each of these spatial areas across individuals.
hemispace. Applying this theory to the Robertson and North data, the participant may have been suffering neglect with respect to at least two independent but nevertheless integrated spatial systems—a personal space related in some way to some somatosensory representation of his body and a peripersonal or reaching space within which he manifested such deficits as neglecting the left in letter cancellation. These findings have been subsequently replicated (Ladavas, Berti, Ruozzi, & Barboni, 1997; Mattingley, Robertson, & Driver, 1998).

By inducing the participant to make voluntary movements with his left hand in left hemispace, it is possible that the left half of the somatosensory spatial sector was in some way activated or enhanced. Because of the integration of the somatosensory and peripersonal spatial sectors, this in turn produced enhanced activation of the impaired half of peripersonal space. Such is the interpretation that would follow from Rizzolatti’s work. But why did not left-hand movements in right hemispace similarly activate the left side of peripersonal space? After all, though left hemispace may not have been activated, the left side of the body was activated. One possibility is that reciprocal activation of more than one corresponding spatial sector of the closely linked neuronal maps in the brain must occur to overcome the deficit in representing the left side of space. In other words, cueing/recruitment of the hemispatial system was inadequate on its own. So also for the hemisporotal (personal) system. Only when both were activated simultaneously did some improvement of spatial perception of the left arise, possibly by reciprocal activation across the related neuronal systems.

The above studies led to a series of treatment evaluations (Robertson, Hogg, & McMillan, 1998; Robertson & North, 1992; Robertson et al., 1992), whose aim was to induce minimal movements of left limbs by using a neglect alert device that emitted random sounds that the patient had to prevent or terminate by pressing a switch with some movement of a left limb. The results of this training were positive and daily ratings of mobility difficulties arising from the neglect showed improvements in line with the onset of treatment. These ratings improved as the training commenced, and patients also showed improvements on standardized tests.

SLI in childhood has also responded to a bottom–up approach of targeted stimulation. Though largely a developmental disorder and not a consequence of specific brain lesions, studies by Tallal and Merzenich (Merzenich et al., 1996; Tallal et al., 1996) have shown that speech recognition—and in particular phoneme discrimination—could be improved in SLI children by repeated stimulation of a set of exercises designed to improve recognition of brief, successively presented auditory stimuli. Adaptive psychological methods were used to shape up this temporal discrimination ability, and in addition children were given training in discriminating consonant–vowel stimuli. Their discrimination was aided by acoustically modifying both the duration and the magnitude in decibels of the critical parts of the consonants that presented the greatest discrimination challenge. The authors of these studies imply that this training procedure may actually have caused plastic reorganization of the cortical basis for temporal segmentation in these children’s brains. If this indeed occurred, it happened because of thousands of targeted, bottom–up stimulation cycles, resulting in improvement not only in temporal discrimination and phonemic discrimination abilities, but also in more general language functions.

The concept of bottom–up stimulation is, at first sight, less straightforwardly applicable to problems of attentional control partly associated with frontal lobe lesions. This appears to be the case because of the fundamental architecture of the brain, whereby most sensory input is directed primarily to posterior brain regions. What, then, might constitute a bottom–up input for a lesioned prefrontal cortex?

Heilman has argued for the existence of neuroanatomical circuits that would correspond to two different mechanisms for modulating alertness in the brain (Heilman, Watson, Valenstein, & Goldberg, 1987). One mechanism increases arousal in a bottom–up way, through the mesencephalic reticular formation and the thalamic relay nuclei. According to Heilman, the cortical projections of this system are particularly strong in the frontal and parietal cortex and represent the ability of the brain to be aroused or alerted by novel, important, or emotionally arousing stimuli. Heilman and colleagues argue that the midbrain alerting system can also be activated in a top–down fashion, particularly from the right dorsolateral prefrontal cortex. This type of system would be needed in tasks where the external environment provides no intrinsically arousing stimulation but where nevertheless an alert readiness to respond must be maintained endogenously. These midbrain structures also seem to be closely involved in circadian fluctuations in arousal (Braun et al., 1997), as well as showing significant increases in activation from a relaxed state to one required for an attentionally demanding task (Kinomura, Larson, Gulyas, & Roland, 1996).

Exogenous alerting could, theoretically at least, act as a plausible example of bottom–up input to a lesioned frontal cortex, and recent studies have indeed found such effects. We have developed a laboratory paradigm of attentional failures that correlates with real-life problems of attentional control in traumatic brain-injured people (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). In this Sustained Attention to Response Test (SART), participants are asked to make a key-press response for every number they see appear on a computer screen. Because of the temporally predictable, rhythmic presentation of the digits every 1.15 s, this aspect of the task is trivially easy and vulnerable to rapid automation—that is, it requires little moment-to-moment attentional control. The catch is that periodically and unpredictably a target digit is presented to which no response should be given. Success in not pressing to these rare targets requires that attentive supervision of the response process is maintained. Most participants do this imperfectly and make a few errors. Patients with traumatic brain injuries in whom frontal damage is likely and patients with right hemisphere strokes and documented sustained attention deficits have significantly greater difficulty than matched controls on this task (Robertson, Manly, Andrade, et al., 1997).

When a phasically alerting exogenous auditory cue is periodically presented during the course of patients’ SART performance, however, errors are significantly reduced, indicating a possible bottom–up effect of an alerting cue on sustained attention (Robertson, Manly, & Heutink, 1998). Though these effects are temporary, they do show the possibility of modulating attentional control in a bottom–up way, using external, alerting stimuli. We are currently evaluating clinical methods based on this principle, where we will test the prediction that more enduring effects of this
type of bottom–up stimulation on attentional control may be
found.

**Top–Down Specific Stimulation**

There is abundant evidence that attention can gate the processing of information in primary as well as secondary sensory areas of the brain, and it is assumed that attentional circuits—argued to be based in part at least in the frontal lobes—are the source of such gating (Desimone & Duncan, 1995). This has been shown in vision (Moran & Desimone, 1985), audition (Knight, Scabini, & Woods, 1989; Woldorff et al., 1993), and in somatosensory perception (Drevets et al., 1995; Yamaguchi & Knight, 1990). Drevets et al. (1995) showed that bloodflow to the primary sensory cortex can be modified by attention–expectancy variables, such that bloodflow decreases in those somatic areas where stimulation is not expected. In another study, when participants paid attention to vibration on their fingertips, functional imaging showed 13% more activation in the equivalent sensory area of the brain than when they received the same stimulation but did not attend to it (E. Meyer et al., 1991).

Attention can modulate synaptic activity in posterior circuits of the brain (Büchel & Friston, 1997). Attention also influences synaptic connectivity in animals (Recanzone, Schreiner, & Merzenich, 1993) and direct evidence for this attention-mediated plasticity in humans comes from a study by Pascual-Leone and colleagues (Pascual-Leone et al., 1995). They showed that purely mental practice of fine motor skills enlarged the area of the motor cortex activated by the enactment of the learned skills. This enlargement of the neural circuits subserving the skilled behavior was measured by transcranial magnetic stimulation and was the first demonstration that purely mental rehearsal could influence synaptic connectivity in this way, though functional magnetic resonance imaging has also shown enlargement after physical practice of a fine motor skill (Karni et al., 1995).

Mental rehearsal can foster neural connectivity, and imagined movements are in part subserved by activations of the frontal cortex (Stephan et al., 1995). One of the principal functions of the frontal cortex is attentional control, and hence it is a plausible hypothesis that the mental rehearsal effects on synaptic connectivity demonstrated by Pascual-Leone and his group are attributable to top–down effects of anterior attentional systems on more posterior neural circuits of the brain. This hypothesis is strengthened by the evidence produced above showing that frontally based attentional circuits can gate processing in posterior sensory circuits of the brain. Support also comes from structural equation modeling of functional activations in the human brain during visual tasks where passive viewing was compared with active attention to the identical visual array. The observed attentionally gated changes in occipital and parietal cortex were found to have their modulatory source in the prefrontal cortex (Büchel & Friston, 1997), supporting the view that synaptic activity and hence plasticity can be modulated in a top–down way by attentional circuits partly based in the prefrontal cortex.

If this is true, then recovery of function in a wide range of neural circuits in the brain should be influenced by the integrity of the attentional systems of the brain. Put another way, the better the functioning of the attentional circuits of the brain (partly, but not exclusively, based in the prefrontal cortex), the greater should be the chance of recovery of more posterior cognitive, sensory, and motor functions in brain-lesioned patients, or conversely, an impaired frontal cortex will impair such recovery. (This is not to say that such attentional modulation is the primary determinant of recovery but rather that it is one of a number of factors that influence the likelihood of synaptic reconnection).

If, however, top–down input from attentional circuits can foster connectivity in the nondamaged brain, then such input should also be able to foster reconnection and repair in the damaged brain. Is there, however, any evidence from human clinical research to indicate that top–down attentional processes influence recovery of function following brain lesion?

In Section C, we review a large number of studies that show indeed that damage to the prefrontal cortex and/or deficits in attentional control systems are among the strongest predictors of recovery of function following brain damage. As already mentioned, however, the nature of these control systems and their relationship to the underlying anatomy of the brain is inadequately understood. Reasonably strong evidence does exist, however, to support the view that one can reliably distinguish anatomically separable circuits for sustained attention and selective attention respectively (Posner & Peterson, 1990). These factors clearly emerge from studies of attentional performance among normal individuals (Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996) and have been prospectively confirmed in a confirmatory factor analysis with children (Manly, Robertson, Anderson, & Nimmo-Smith, 1999). The sustained attention system appears to depend on both right frontal and parietal networks (Coull et al., 1996; Pardo et al., 1991; Rueckert & Grafman, 1996).

Sustained attention capacity has been shown to predict recovery of function following stroke (Ben-Yishay, Diller, Gerstman, & Haas, 1968; Blanc-Garin, 1994). Furthermore, as mentioned above, motor recovery following stroke over a 2-year period was significantly predicted by measures of sustained attention taken 2 months after right hemisphere stroke. Specifically, the ability to sustain attention to a tone-counting task (a validated measure of sustained attention related to right frontal function; Wilkins, Shallice, & McCarthy, 1987) at 2 months poststroke predicted not only everyday life function 2 years later but also the functional dexterity of the left hand in a pegboard task (Robertson, Ridgeway, et al., 1997).

These findings are strongly compatible with the animal evidence of experience-dependent plasticity. Several studies have shown that activity-dependent reorganization in sensory and motor maps requires active attention to the relevant stimuli: Passive stimulation of the relevant circuits while attention is deployed to some second task does not result in plastic reorganization of the stimulated circuits. For instance, in one study monkeys were trained in an auditory frequency discrimination task, resulting in plastic enlargement of the tonotopic mapping of the trained frequency range in the auditory cortex. Such plastic reorganization did not, however, occur when the same auditory stimuli were presented, but the monkeys were engaged in a separate tactile discrimination task (Recanzone et al., 1993).

Human functional imaging evidence confirms that the frontal cortex is activated when people attend to particular realms of experience. For instance, one study showed that, compared with when participants performed a well-practiced manual skill, being required to attend to that same overlearned skill activated the
frontal cortex, and in particular, the left dorsolateral prefrontal and right anterior cingular areas (Jueptner et al., 1997).

The fact that experience-dependent synaptic reorganization depends on attention being deployed to the relevant domains implies clearly that impaired ability to deploy attention in this way should hinder (though not necessarily prevent) top–down influences on plastic reorganization in the brain. Conversely, improvements in the ability to deploy attention in this way should benefit such effects on repair and reconnection. If attentional systems can act as one source of patterned input to lesioned circuits and hence contribute in some way to repair and reconnection in these circuits, are there any rehabilitative studies that demonstrate such an effect? There is relatively little data on this yet, and none show directly neural effects of top–down attentional modulation of neural repair. Nevertheless, there is some recent behavioral evidence that is supportive of this hypothesis.

In two single-case studies of rehabilitation of unilateral neglect, visuomotor imagery training was associated with improvements in unilateral neglect (albeit with inadequate controls for nonspecific effects of training; Smania, Bazoli, Piva, & Guidetti, 1997). Furthermore, in a study that did have appropriate controls, however, activation of a putatively right-frontal-parietal based sustained attention system resulted in significant improvements in unilateral neglect in eight patients. This study was based on Posner’s (1993) hypothesis that the posterior spatial orientation system—implanted in unilateral neglect—was modulated by a separate right hemisphere sustained attention system. His prediction was that changes in alertness should cause changes in the ability to orient attention in space. This hypothesis was bolstered by evidence that nonlateralized auditory sustained attention impairment is a marker of unilateral neglect (Robertson, Manly, Beschin, et al., 1997).

Consequently, eight patients were trained to periodically improve their level of alertness using a self-instructional procedure. This not only improved the ability to sustain attention but also had highly specific effects on spatial orientation with a consequent reduction in unilateral neglect (Robertson et al., 1995). Furthermore, these effects were confined to measures of sustained attention and unilateral neglect—no improvements on spatial orientation judgment were found. In a subsequent experimental study, it was shown that brief (300–1,100 ms prior to presentation of visual stimuli) nonlateralized auditory alerting stimuli could, on average, temporarily abolish the spatial bias in a group of people with unilateral neglect (Robertson, Mattingly, Rorden, & Driver, 1998). In short, although there is as yet relatively little evidence that attentional processes can be harnessed therapeutically to enhance plastic reorganization of more posterior circuits following brain damage, there are very strong grounds indeed to predict that this is the case.

What about these attentional processes themselves, are there any conceivable ways in which they could be subject to top–down rehabilitative influences? This is only possible, clearly, if a hierarchical structure of control is advanced, so that mechanisms higher in the structure can provide top–down input to ones lower in the hierarchy. Although our understanding of most aspects of these functions is insufficiently advanced to know whether or not this is possible, there is one aspect of attentional functioning that may indeed have such a hierarchical structure. This is right frontoparietal sustained attention mechanisms in relation to mesencephalic arousal systems, outlined by Heilman et al. (1987) and described in the previous section. Not only can the exogenous alerting system influence sustained attention in a bottom–up way, but the sustained attention system can activate the midbrain arousal systems in a top–down way (see also Paus et al., 1997, for a functional imaging study supporting the validity of Heilman’s proposed architecture). It is therefore likely that the sustained attention system can activate itself by giving top–down input to the midbrain arousal systems that in turn project back in a bottom–up way to the sustained attention system.

We have shown that this approach is indeed clinically tractable, in a rehabilitation study of eight right-brain-damaged patients suffering from, among other deficits including unilateral neglect, a severe problem in sustaining attention over time (Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995). We attempted directly to rehabilitate the sustained attention deficit using exactly this principle of top–down modulation of more basic arousal processes that in turn influence in a bottom–up way the higher level sustained attention processes. These eight patients were trained while doing a variety of tasks—for example, routine sorting tasks—requiring sustained attention. Periodically, attention to task was manipulated in a bottom–up way by a loud, alerting, external sound. Gradually, this sound was linked to external instructions to attend to the task in hand. Patients were then gradually taught to take over this alerting procedure using a self-generated verbal cue so that eventually it became a top–down, selfinstructional procedure. This resulted in significant improvements in the control of sustained attention in all eight patients. There were also improvements in a specific aspect of spatial attention in these patients, predicted on the basis of the interaction of two right-hemisphere attention systems, one spatial and one for nonlateralized sustained attention. There were no changes on other cognitive measures and so the clinical effects here were specific to the sustained and spatial attention systems.

In summary, with this example, we show that the principle of top–down, targeted stimulation to lesioned circuits may indeed be applicable to at least one of the control systems of the brain. As the theoretical understanding of attentional control processes develops, then to the extent that these have a hierarchical structure, other theoretically based clinical interventions of this type should emerge.

**Inhibitory Processes**

Transcranial magnetic stimulation (TMS) is the application of brief pulses of electromagnetic stimulation to specified areas of the brain. TMS can have facilitatory or inhibitory effects on the stimulated cortex, depending on the parameters of stimulation. Facilitatory TMS of the motor cortex of one hemisphere has been shown to produce temporary inhibition of the contralateral motor cortex and such inhibition has been shown to be reduced among patients with callosal agenesis, demonstrating that the inhibitory processes are effected through the commissures (B.-U. Meyer, Rörich, Einsiedel, Kruggel, & Weindl, 1995; Wasserman, Pascual-Leone, & Hallett, 1994). This supports the view that to some extent a competitive relationship exists between the hemispheres (Kinsbourne, 1993), and if this is the case, then damage to one hemisphere should reduce its inhibitory influence on the other.

Further support for the existence of competitive inhibition between the hemispheres comes from a study of TMS causing
inhibition of parietal cortex function. Such inhibitory stimulation caused an increase in sensitivity to ipsilateral cutaneous stimuli (Seyal, Ro, & Ralf, 1995). The authors argue that this is because the TMS transiently inhibits the parietal cortex, thus freeing the contralateral parietal cortex from competitive inhibition. As a result, ipsilateral cutaneous stimuli that are processed by this disinhibited contralateral parietal cortex are more strongly represented and hence have a lower threshold for perception.

Evidence indeed exists that damaged circuits in the brain suffer further loss of function because of inhibitory competition from undamaged circuits, particularly, but not uniquely, interhemispherically across the corpus callosum. Sprague (1966) for instance demonstrated that hemianopia in cats could be ameliorated by destroying the superior colliculus on the side opposite to initial visual input, thereby freeing the lesioned hemisphere from the collicular inhibition of the intact hemisphere and allowing ipsilateral circuits to operate; this effect was confirmed using electrophysiological measures in rats (Goodale, 1973).

Wallace, Rosaengquist, and Sprague (1990) demonstrated that cats with unilateral lesions of striate cortex show a severe contralateral neglect. They found substantial reductions in the neglect following a lesion of the substantia nigra in the opposite hemisphere, thereby reducing the competitive inhibition on the contralateral superior colliculus in the lesioned hemisphere. Monkeys with unilateral lesions of the posterior parietal cortex tend to make voluntary eye movements into the ipsilesional field when presented with bilateral stimuli. Lynch and McLaren (1989), however, showed that this bias is corrected when an additional lesion is subsequently made in the posterior parietal cortex of the opposite hemisphere. Again, the mechanism proposed to explain this is that the damaged hemisphere was freed from competitive inhibition from the undamaged hemisphere. That related phenomena occur in the human brain is shown by the fact that, compared with control participants, the undamaged hemisphere of the brain in a group of people having suffered unilateral stroke showed higher levels of regional blood flow (Weiller, Chollet, Friston, Wise, & Frackowiak, 1992).

On the basis of our core assumptions, we were able to model the Sprague effect using our connectionist framework (Murro & Robertson, 1995; Murro et al., 1999).

As we described above when discussing specific bottom-up stimulation of lesioned circuits, unilateral neglect may be ameliorated by left-sided limb movements made on the left side of the body (Robertson & North, 1992). In discussing this, we focused on the specific input to impaired circuits of the combined activation of circuits underpinning personal and extrapersonal space, respectively. But do inhibitory mechanisms play a part also? It seems likely that they do play a part, given that interstimulus competition causes extinction of the contralesional stimulus under bilateral but not unilateral stimulus presentation (Mattingley, Davis, & Driver, 1997; Rorden, Mattingley, Karnath, & Driver, 1997) following parietal lobe damage.

Human evidence for this type of mechanism in recovery of function comes from a single-case study of unilateral neglect following a right parietal lesion, which dramatically improved after a subsequent lesion to the frontal eye-field of the left hemisphere (Vuilleumier, Hester, Assal, & Regli, 1996). Kapur (1996) has reviewed evidence for paradoxical functional facilitation, including performance increments arising from additional lesions. The paradoxical increase in performance occurs because the new lesion reduces the activity of a network that was excessively inhibiting the functioning of the first, originally impaired, circuit.

A recently developed treatment for PD, for instance, involves stereotactic surgery of the globus pallidus, activity in which may disrupt motor output through its inhibitory effects on thalamocortical tracts. Improved functioning following pallidotomy has been shown to produce predicted increases in bloodflow in the supplementary motor area and prefrontal areas during performance of volitional movements following surgery, supporting the view that the surgery has its effects through reducing such inhibitory effects (Samuel et al., 1997).

In the behavioral realm, and following on from the studies of limb activation on unilateral neglect, a further study (Robertson & North, 1994) showed that the beneficial effects of single left limb activation in left hemispace could be eliminated if the right limb was simultaneously moved. This result was interpreted in terms of competition between the two hemispheres. Whereas a single left movement in left hemispace activated representations of both personal and peripersonal space, resulting in an improved ability to attend to contralesional stimuli because of this combined activation, bilateral movements activated competitor circuits in the undamaged left hemisphere. As a result of this competition, the activation in the right hemisphere was competitively extinguished, it was argued. This finding has been replicated in both single-case and group studies (Ladavas et al., 1997; Mattingley et al., 1998).

Figure 7 shows a simulation of this phenomenon by a neural network model. The model used in the simulation is described in detail in another article (Murre et al., 1999). It implements the principles introduced in this article, using, for example, Hebbian learning and neural groups that fire probabilistically and that can be stimulated and inhibited by other neural groups. These neural groups are represented as single nodes, and these in turn are organized into modules or areas, mimicking the overall organization of the brain. As is shown in Figure 7, these modules are sometimes connected in such a manner that they inhibit each other. To be able to implement a model, it is necessary to make a rather large number of specific assumptions (e.g., with respect to the activation and learning formulas used, how time is represented, how input patterns are represented, what connectivity patterns are used, what the exact parameter values are, what counts as a response, etc.). The details of the model are described elsewhere (Murre et al., 1999), and here are shown a few simulations as illustrations of this particular principle of recovery.

Figure 7 represents a simulation of this experimental scenario on the current network. In Figure 7a, in addition to the single input module on the left, there are four similar modules to those used in the previous figure. In this case, however, the bottom two modules refer to the personal–proprioceptive aspects of the spatial representation, for the left and right hemisphere, respectively, whereas the top two modules represent the extrapersonal aspects of the spatial representation. Figure 7f shows schematically the excitatory and inhibitory connections among the modules.

Figure 7c shows the consequences of lesioning 30% of connections in the top right module and all nodes in the right half of that module. As there is no motor activation (and hence no proprioceptive input) involved, the two lower modules are inactive. The consequence of the lesion is that, as in the previous example partial lesioning results in complete elimination of the representation because of the inhibitory connections with the left-sided module.
Figure 7. Simulation of motor (limb) activation to overcome hemineglect. (a) The intact network with all representations activated (normally the lower modules are only partially activated, see text). (b) Lower modules are silent: no motor activation. (c) Representations after a moderate lesion in the entire module (affecting only connections) and a severe lesion of the right half of module three (upper right; affecting all nodes in that area). (d) Motor stimulation to module three helps overcome inhibition from module two (upper middle). (e) Stimulation of both motor hemispheres causes a reduction of motor facilitation of module three. This is caused by competition between modules four and five (lower two modules).

Figure 7d, however, shows what happens when the personal– proprioceptive system is activated on the right side, by a conjectural limb movement, say. Because of the excitatory connections between the personal and extrapersonal modules, the combined activation is sufficient to overcome the inhibition from the left-sided module.

Figure 7e shows, however, what occurs when both the personal– proprioceptive modules are activated simultaneously—say, by simultaneous and bilateral limb movements. The partially recovered extrapersonal representation on the lesioned side is extinguished.

The above suggests that recovery of function may in part be determined by the extent to which the inhibition of damaged circuits can be reduced, either through activating circuits in the damaged hemisphere itself or through reducing activation in the undamaged hemisphere. Such effects may in part underlie the positive effects of forced use and rehabilitation outlined in Section A. We argue that inhibition from competitor circuits prevents the strengthening of representations in the damaged circuits because synaptic remodeling is inhibited. This conclusion is compatible with the evidence reviewed above showing competitive inhibition between hemispheres within the normal brain (B.-U. Meyer et al., 1995; Seyal et al., 1995; Wasserman, Pascual-Leone, & Hallett, 1994).

Further evidence that inhibited latent function may exist in the lesioned hemisphere comes from research showing through functional imaging that metabolic depression (and associated low levels of synaptic activity) can extend well beyond the area of cortical damage, sometimes known as diaschisis (von Monakow, 1914). For instance, in four cases of unilateral motor hemineglect (defined as lack of spontaneous and pain-induced activity in the absence of paresis, pyramidal signs, and sensory loss), depressed activity was found in a wide range of nonlesioned cortical and subcortical structures, including premotor, prefrontal, parietal, cingulate, and thalamic regions (vonGiesen et al., 1994). The primary motor cortex was structurally intact, yet motor output was disrupted by a disruption of a higher order network subserving motor function. Such spreading suppression within the lesioned hemisphere is similar to the effects of posterior lesions observed by Sprague, and transcallosal inhibition may play a part in this inhibition of activity in intact neural tissue. Other types of within-hemisphere inhibition
may also play a part, however, such as enhanced postexcitatory inhibition, which has been shown to underpin lack of motor activity in some cases (Classen et al., 1997). Whatever the origins of inhibition of activity in structurally intact neural networks, it is clear that they are, from the perspective of designing theoretically motivated guided recovery rehabilitation procedures, extremely important. In support of this, one study found that severe remote depression of thalamic metabolism was strongly correlated with poor restitution of hand function in hemiparetic stroke (Binkofski et al., 1996). The challenge for a theoretically based rehabilitation is to develop ways of unlocking latent function in inhibited but structurally intact tissue, and hence fostering its reactivation. The evidence reviewed above suggests that this is possible in some types of disorder, at least.

And it seems that this principle of inhibition may also apply to aspects of the brain’s attentional control systems. Two components of attention—sustained attention on the one hand, and selective attention on the other, are viewed as having a reciprocal, competitive relationship with each other (Posner & Petersen, 1990). As mentioned previously, the right frontal lobe is known to have a strong role in vigilance—sustained attention (Pardo et al., 1991) and the anterior cingulate in selective attention (Pardo, Pardo, Janer, & Raichle, 1990). According to Posner and Peterson, vigilance is a state of alert but nonselective readiness to detect external events. The nature of this state is such that it is antithetical to close, selective attention to some particular stimulus, and vice versa. In accordance with this hypothesis, a PET study that found the predicted increase in right frontal activation during an auditory sustained-attention task, found significant decreases in activity in the cingulate region of the brain (Cohen, Semple, Gross, King, & Nordahl, 1992).

Inhibitory relationships therefore do exist within the brain’s anterior regions, and therefore it is quite possible that recovery from some types of frontal lesions may be hindered by excessive inhibition from undamaged competitor circuits. We are optimistic that clinically relevant examples of this will soon be forthcoming, closely followed by appropriate treatments aimed at decreasing pathological inhibition and hence maximizing recovery of function.

Arousal

There is considerable evidence to suggest that noradrenergic and cholinergic neurotransmitter systems may have a permissive function in neuronal plasticity (Armstrong-James & Fox, 1983; Boyeson, Krobert, Grade, & Scherer, 1992; Feeney, 1997; Imamura & Kasamatsu, 1988; Kolb & Sutherland, 1992; McGaugh, 1990; P. M. Meyer, 1963; Whishaw, Sutherland, Kolb, & Becker, 1986; Will & Kelche, 1992). Animal research shows clearly the importance of the noradrenergic neurotransmitter systems in modulating recovery of function following brain lesions. Feeney (1997) argued that stimulant drugs should promote recovery from diaschisis (the temporary depression of activity in circuits functionally related to the lesioned area), if the latter were due to understimulation from neighboring cells. He indeed showed that amphetamine accelerated recovery and that haloperidol, which depresses these functions, impaired recovery. Sutton, Hovda, and Feeney (1989) also showed that amphetamine accelerates recovery of locomotor function following bilateral frontal cortex ablation in rats. Kasamatsu and Pettigrew (1976) showed that the adaptive neurophysiological consequences of monocular eye occlusion (e.g., eye dominance shift) in kittens were prevented by depletion of catecholamines and that this in turn was reversed by cortical perfusion with noradrenaline. Several other studies have shown the neuromodulatory and potentiation effects of noradrenaline (Armstrong-James & Fox, 1983; Bear & Singer, 1986; Feeney & Sutton, 1987; Feeney, Sutton, Boyeson, Hovda, & Dail, 1985; Imamura & Kasamatsu, 1988; P. M. Meyer, 1963; Singer, 1990; Watson & McElligot, 1984), and the considerable literature on noradrenaline and recovery of function in lesioned animals is reviewed by Will and Kelche (1992).

There is also some evidence that noradrenaline has a similar effect in humans, and Boyeson and Bach-y-Rita (1989) have argued that noradrenaline is the critical neurotransmitter in recovery from hemiplegia. A more recent study showed, in a double-blind placebo-crossover study using D-amphetamine in a head-injured patient, that there was improved cognitive performance and improved P300 results in the D-amphetamine condition. The improvement in cognition consisted of selective enhancement of divided attention and response inhibition (Starbuck, Bleiberg, & Kay, 1995). Clinical trials of amphetamine in motor rehabilitation have also been carried out. Walker-Batson et al. (1992), in an uncontrolled study, found what they assessed to be a faster than expected recovery from aphasia under amphetamine. In another study (Crisostomo, Duncan, & Propp, 1988), intensive physical therapy was combined with 3 hr of amphetamine administration, with a resultant improvement in motor function in the affected limbs the next day, in comparison to a control group who had received no amphetamine. Conversely, common clinically used drugs that depress noradrenergic activity have been shown to retard recovery from hemiplegia (Goldstein et al., 1995; Goldstein, Matchar, Mergandlander, & Davis, 1990).

But are such neuromodulatory effects at all related to arousal, as defined behaviorally? Arousal can be distinguished from the attentional functions reviewed above, in both its subcortical substrate (Paus et al., 1997) and its diffuse effects on the cortex (Heilman et al., 1987; Posner & Peterson, 1990). As we have just shown, arousal is mediated by a number of neurotransmitters, including norepinephrine (Harley, 1987), and many of these neurotransmitters are precisely those that have been shown to increase cortical plasticity and facilitate neural reorganization, as reviewed earlier.

Furthermore, as we showed above, midbrain arousal systems have particularly strong projections to the frontal cortex (Heilman et al., 1987) and can be a source of bottom–up stimulation to the frontal cortex. Conversely, frontal systems, in conjunction with parietal and other cortical areas, can modulate arousal in a top–down fashion and play a part in maintaining levels of arousal appropriate to the demands of the environment. This may well be one reason why integrity of the frontal lobes is a major factor in recovery of function (see below), possibly, one might speculate, by acting as a source of plasticity-enhancing arousal. Variations in arousal and alertness clearly have rather general effects on cognitive function and on synaptic plasticity. It is precisely for this reason that they are such important variables to be considered in the recovery of cortical deficits of any type. As already shown above, however, there are additional particular effects of increased arousal on frontal and parietal systems, par-
ticularly in the right hemisphere (see, e.g., Sturm et al., 1999). Thus, changes in a rather general arousal system can have specific effects on spatial attention (Clark, Geffen, & Geffen, 1989; Robertson, Mattingley, et al., 1998), as well as on partly frontal-lobe-based attentional control systems such as selective and sustained attention (Robbins & Everitt, 1995).

Clearly, these five proposed principles of guided recovery have only been tested to a limited extent in a clinical context. And though their validity has been supported where they have been tested (see, e.g., Robertson et al., 1992, 1995), long-lasting generalizable effects have not, in many cases, been demonstrated. The question of generalization of training effects, both over time and across situations, is perhaps the central question in rehabilitation. We return to this critical issue later in the article, but it is important to emphasize that when developing theoretically based rehabilitation methods, one must first demonstrate positive effects within a particular domain before one then goes on to demonstrate generalization to a different domain. Hence, many of the studies described above can be considered as a first stage preparation before embarking on the kinds of clinical trials that would allow us to fully determine the clinical use of this approach and the therapeutic methods it demonstrates.

Before returning to the practical implications for rehabilitation of these methods, however, it is important to consider the framework of recovery we are proposing in the context of the known natural history of recovery from acquired brain damage. If the assumptions we make about the determinants of recovery are not compatible with what is known about predictors of recovery of function, then the model clearly will have little heuristic value. Before returning to the clinical implications, therefore, we review the assumptions made in this article and compare them with the empirical evidence about the natural history of recovery of function.

Section C—Predictors

In this section, we review the known predictors of more or less successful recovery from acquired brain damage in adults, in each case examining how compatible these findings are with the general framework proposed in this article. The predictors we consider are age, education/IQ, attentional control deficits, and awareness of deficits.

Age

We are only considering adult brain injury in this article, hence avoiding the complexities and controversies surrounding damage to the developing brain. Suffice it to say that the view that the so-called Kennard principle (Kennard, 1938) of earlier is better in terms of probability of recovery is not true in all cases. Kennard's original observation was made on monkeys, but the situation may well be a good deal more complex in the developing human being, as early lesions may impede various types of learning, resulting in delayed development of intellectual and other faculties (Taylor, 1984). In the adult brain, on the other hand, with a large repertoire of stored knowledge and skills already in place, an equivalent lesion could well have a less dramatic impact on the adult life than if experienced in childhood.

Although neuronal plasticity in the adult nervous system is clearly possible to a greater degree than was hitherto recognized, it is also the case that plasticity is almost certainly greater in the younger brain, and this has been shown even in young adulthood. Teuber (1975), for instance, found that in all domains of cognitive impairment, war-injured soldiers aged 17–20 made better recovery than 21–25-year-olds, who in turn had better recovery than those aged 26 and over. This association of recovery with age of injury held up when this sample of participants were followed up approximately 40 years later (Corkin, 1989).

In fact, there is evidence of considerable plasticity in the brain even in a teenager who was given a left hemispherectomy at age 16, 30 months after the onset of a severe epileptic illness (Patterson, Vargha-Khadem, & Polkey, 1989). This teenager showed speech that was much superior to that shown by global aphasics with large left hemisphere lesions, and the only possible source of this speech was the right hemisphere, given the completeness of the cortical and subcortical hemispherectomy. Given also that there is no known speech capacity in the normal right hemisphere, one can cautiously conclude from this study that some functional reorganization has taken place in the teenage years (Vargha-Khadem & Polkey, 1992), though of course the possibility that some preexisting reorganization took place prior to the onset of frank epilepsy cannot be excluded.

Another important aspect of the relationship between age and injury concerns the possibility that recovery of function following an injury may show a partial reversal as people grow older. Corkin (1989) followed up the Korean war veterans studied by Teuber who were mentioned above. Compared with age-matched veterans who had suffered nerve injury but no head injury, the head injured group showed a greater decline in performance relative to their early test performance 30 years previously. A comparable finding has also been obtained in rats, who have shown recovery of function following lesions early in life, but whose symptoms of brain injury begin to reemerge during old age (Schallert, 1983). These effects in adults of age of injury on recovery of function bring us to the question of cognitive reserve, which we turn to in the next section.

In our simulations of recovery and aging, we have implemented aging by both (a) decreasing the learning parameter, which directly decreases plasticity and slows down recovery, and (b) a global diffuse lesioning of connections. The latter has several indirect effects on recovery. First, it further slows down recovery as it takes longer for the system to reach states of stable activations during which Hebbian learning can take place in an effective manner. Second, it limits the degree to which recovery can occur. This effect has also been analyzed with the random graph theory mentioned above (Murre & Robertson, 1995; Murre et al., 1999). The conclusions of both the analyses and the simulations are that there is a sharp threshold of minimum connectivity, below which recovery becomes much less likely and the conditions of recovery become much more demanding (i.e., very precise input stimulation is necessary in this case). It should be remarked that the threshold itself is dependent on the size of the representation: Large representations have a higher recovery threshold; they will thus survive longer in the aging brain. Third, we observed in the simulations that lesions that had recovered successfully are uncovered when we age our models in the described manner. This is in full accordance with the empirical data mentioned above.
**Education/IQ**

The dendritic branching and (consequently synaptic connectivity) of the left hemisphere is correlated with the number of years of education that an individual has had in his or her life (Jacobs et al., 1993; Jacobs & Scheibel, 1993). These authors argue that this is evidence of activity-dependent changes in neural connectivity throughout the lifespan. It has also been argued that education and intelligence, both highly intercorrelated, endow the brain with a cognitive reserve (Alexander et al., 1997; Stern, Silva, Chaissen, & Evans, 1996), which serves partially to protect cognitive function from deterioration following disease, injury, or natural aging.

In accord with such a hypothesis, low levels of education have been identified as a risk factor for Alzheimer’s disease (Chun & Mayeux, 1994; Kondo, Nimo, & Shido, 1994). Furthermore, several studies have shown that preinjury intelligence/educational level is a significant predictor of degree of recovery of function following closed head injury (Brooks & McKinlay, 1987; Grafman, 1986; Gronwall, 1976). In fact, in his study of recovery after open head injuries in the Vietnam war, Grafman and colleagues found that preaccident intelligence was a better predictor of functional outcome than both lesion location and lesion size. Neural network simulations (Murre & Robertson, 1995; Murre et al., 1999; Powel, Zahnner, & Michelitzanakou, 1995) support this hypothesis, showing that the amount of impairment following a simulated lesion to the network correlates with the amount of prelesion learning that had taken place.

Whereas aging, in our modeling work, eats away at the cognitive reserve, the varied cognitive activities associated with education and high IQ have the effect of adding to the reserve in the form of increased connectivity. As is clear from our discussion in the previous section, higher connectivity implies faster recovery as well as more opportunity for recovery.

**Attentional Control Deficits**

The precise functions of the frontal lobes of the brain remain enigmatic. Executive functions are ascribed to this large brain area, but, as discussed earlier, the precise nature of these functions remains to be elucidated. As demonstrated earlier with respect to the sustained attention system, not all executive functions are entirely frontal lobe based, nor are all frontal lobe functions necessarily executive in nature. To give just one example, lesions to the frontal lobes can result in problems with motivational and emotional deficits as much as with more conventionally executive deficits such as planning and problem solving (Norman & Shallice, 1986; Shallice & Burgess, 1991; Stuss, 1991; Stuss & Benson, 1983). As argued earlier, however, two types of attention control that are partly frontally based—selective and sustained attention—are somewhat better characterized than other hypothetically frontal functions.

We discussed earlier in this article the role of these two attentional processes in modulating synaptic connectivity and cited some evidence to support the view that such top–down processes may facilitate repair and reconnection in damaged circuits. This hypothesis receives indirect support from three studies already cited showing that sustained attention deficits predict outcome following stroke (Ben-Yishay et al., 1968; Blanc-Garin, 1994; Robertson, Ridgeway, et al., 1997). A fourth study showed that motor impersistence—a measure of sustained attention—predicts functional outcome following stroke, and indeed this measure together with a verbal memory test was the strongest predictor of discharge outcome in 134 stroke patients (Novack, Haban, Graham, & Satterfield, 1987). Furthermore, Hier et al. (1983) found that frontal lobe lesions predicted functional recovery following stroke, providing anatomical evidence in support of this hypothesized link between these partly frontally based attentional control deficits and recovery of function proposed here.

Although there are many studies showing that recovery of function following brain damage is predicted in part by impairments on deficits loosely conceived of as executive, we are confining our hypotheses about top–down influences on recovery of lesioned circuits to the sustained attention and selective attention components of attentional control respectively. Although many, if not most, measures of executive function will make demands on these systems, few provide specific, well-validated measures of these components of attentional control. In this light, it is only with respect to the sustained attention system that reasonably strong evidence exists linking impairments in this system to more general recovery of function. Theoretically strong though the claims for involvement of the selective attention system in recovery are, there is as yet no direct evidence that pure measures of selection predict recovery after brain damage. The role of selective attention in providing top–down repairing input to lesioned circuits remains entirely hypothetical.

The demonstrated role of sustained attention in recovery, however, is compatible with the hypothesis that arousal is another important variable in recovery, given the evidence documented above about the close interconnections between the sustained attention and arousal systems.

**Awareness of Deficits**

Experience-dependent plastic reorganization of the brain requires attention to be paid to the activity or experience in question (Recanzone et al., 1993). People who suffer problems of awareness that they have deficits will therefore be less likely to attend to stimulation, experience, or activity that might aid repair and reconnection of lesioned circuits, it follows. As mentioned in the previous section, frontal lobe lesions often impair self-awareness (Stuss, 1991). From a rehabilitation perspective, awareness of deficits is critically important in recovery (Eslinger, Grattan, & Geder, 1995; Ezrachi, Ben-Yishay, Kay, Diller, & Rattock, 1991). Without such an appreciation of deficit, the patient is unlikely to make an effort to correct what is wrong. Anosognosia associated with unilateral neglect is, for instance, strongly predictive of motor recovery following stroke (Gianella & Mattioli, 1992), and efforts have been made specifically to train awareness of deficit in unilateral neglect, with some limited success (Söderback, Bengts-son, Ginsburg, & Ekholm, 1992). There is also evidence of poor awareness of speech output in jargon aphasia, and one study has produced evidence that this may in part at least have a basis in impaired attention (Shuren, Hammond, Maher, Rothi, & Heilman, 1995).

The important role of awareness of deficit in mediating recovery is again compatible with the principle of top–down patterned stimulation facilitating recovery in lesioned circuits. Without awareness of a deficit, attention will not be directed to inputs that
might play a role in facilitating plastic reorganization of the brain. Without attention, such plastic reorganization tends not to occur, as is shown above.

In short, there is no inconsistency between the empirical data on predictors of recovery on the one hand, and the framework presented in this article. That being said, we must add the caveat that our principles are general, as are the predictors, and this very generality reduces the chances of falsifying hypotheses. It is our intention here to develop a heuristically useful framework, and hence one must begin with general principles. But the ultimate test of the use of this framework is its usefulness in developing clinically effective rehabilitation methods. We therefore now turn to the last section of this article, namely, the heuristic value of the approach for developing clinical applications.

Section D—Implications for Clinical Rehabilitation

Some cautious but potentially important conclusions can be drawn from the review so far. They can be summarized in simple terms as follows. Following damage to the brain, a proportion of individuals will recover relatively normal function spontaneously through Hebbian-learning-based self-repair processes. In this autonomous recovery group, only significant extraneous factors may impede this self repair. One such factor could include abnormally low neuromodulator availability (e.g., caused by drug administration, which lowers levels of plasticity-enhancing neuromodulators in the brain). But in most cases, circumscribed lesions, which affect only a relatively small proportion of cells and connections in circuits subserving a particular function, should be restitutable through spontaneous self-repair processes. One caveat to this conclusion is that bottleneck lesions that destroy a pathway connecting two distinct processors may have a large effect, even though the lesion is small (see, e.g., Levine et al., 1998).

Very large lesions, on the other hand, which destroy significant proportions of such circuits, may not be restitutable in this way, and recovery of function, where it occurs, will take place in quite different ways among this group. Compensation and functional reorganization are likely to underpin improvement in this group, and the nature of rehabilitation needed for this category of individual may be different from that which is appropriate for the third category of the triage, namely, those whose lesions are potentially resalable and restitutable if the appropriate circumstances pertain. We suggest that such circumstances include the availability of sufficient general stimulation, as well as of appropriately patterned top–down and bottom–up stimulation to lesioned circuits. The absence of handicapping inhibition, adequate arousal levels, and capacity to unlearn faulty learning patterns are also factors that may be necessary for rescue within this group.

A number of important clinical questions arise from this approach to rehabilitation. These concern (a) implications for rehabilitation-oriented assessment, (b) general implications for a scientifically based rehabilitation, (c) the role of attention and arousal, (d) generalizability of therapeutic effects, and (e) possibilities for effective rehabilitation of attentional and memory deficits.

**Implications for Rehabilitation-Oriented Assessment**

A critical question for the framework proposed here is how one can avoid circularity in defining in advance which individuals belong to which category in the triage. Present clinical methods do not allow us easily and directly to measure the extent of remaining connectivity in lesioned circuits, though earlier in this article we did review considerable biological evidence that restitution of function often appears feasible if a rump of 10–20% of undamaged cells and connections remain (e.g., Sabel, 1997). However, the presence of residual behavioral function apparent under certain circumstances may represent a reasonable clinical basis for assessing which individuals may potentially fall into the resalable part of the triage, where guided recovery of primary functioning may be possible.

At least two studies have shown that, using transcranial magnetic stimulation, it is possible to assess the degree of residual motor function in the acute stages following unilateral stroke; such residual function detected early poststroke predicts long-term recovery of motor function (Heald, Bates, Cartlidge, French, & Miller, 1993a, 1993b; Turton, Wroe, Trepte, Fraser, & Lemon, 1996).

A further example of this principle comes from the work of Taub and colleagues (Taub et al., 1993) described above. They showed motor recovery in the hemiplegic limbs of chronically hemiparetic victims of stroke, using a combination of deactivation of the unimpaired limb with encouragement to move the affected limb. The individuals selected for this study had to have some degree of movement in the affected limb. Specifically, patients had to be able to extend at least 10 degrees at the metacarpophalangeal and interphalangeal joints and 20 degrees at the wrist.

As a clinical yardstick, therefore, it would seem appropriate to suggest that restitution-oriented attempts at guided recovery of intrinsic functions, as opposed to compensatory approaches, may be attempted where some residual capacity in the affected function can be detected. Residual function may, however, be masked because of low levels of alertness/arousal, poor awareness of deficits, inhibition by competitor circuits, or inadequate ability to deploy attention to the relevant behaviors, as discussed earlier in this article. The assessment as to whether residual functioning exists therefore requires these variables to be monitored, and where possible manipulated, to determine whether residual function can be unmasked. Developing methods to do this requires the active collaboration of basic cognitive scientists with rehabilitationists. If, however, no such function can be detected after attempts to ensure that such factors are not preventing unmasking of such function, then allocation to the triage requiring compensatory-oriented rehabilitation is advisable.

At the moment, standardized assessment measures in neuropsychology and rehabilitation do not tend to take into account such variables when assessing particular functions. Yet, to take the example of the arousal/sustained attention complex, dramatic changes in the manifestation of unilateral neglect can be induced by modifying levels of alertness (Robertson et al., 1995; Robertson, Mattingley, et al., 1998). Standard assessment procedures for unilateral neglect do not take such findings into account, and hence the assessment of the degree of residual function is difficult to carry out using existing methods.

To give another example from a study briefly mentioned above, Shuren et al. (1995) showed that an individual with jargon aphasia was totally unaware of his errors in speech production as he spoke but recognized these errors when he listened to a recording of his own voice speaking. These authors concluded that an attentional
limitation prevented him from both producing speech and monitoring its content simultaneously. In this case, using standard assessment procedures that did not manipulate this attentional variable may draw erroneous conclusions about the residual capacity of the speech production system of the brain.

Sterzi and colleagues (Sterzi et al., 1993) have found that there is significantly greater incidence of apparently primary visual field, tactile sensation, limb position sense difficulties, and motor problems in patients who have suffered right hemisphere strokes compared with carefully matched patients who have suffered left hemisphere strokes. The authors argue that this can only be attributable to a subtle bias of attention toward the right side of the body, leading to impaired performance on sensory, proprioceptive, and motor tasks on the left side, which masquerade as primary deficits in these areas. This has also been dramatically confirmed with vestibular stimulation approaches to unilateral neglect, where improvements in hemianesthesia, limb position sense, and distorted body image can be obtained purely by methods that activate the vestibular system of the impaired hemisphere (Cappa, Sterzi, Vallar, & Bisiach, 1987; Vallar, Bottini, Rusconi, & Sterzi, 1993). These findings show clearly that in these particular cases, the apparently primary sensory and motor problems were actually attentional in origin.

Again, the conclusion from these studies is that current methods of standardized assessment may not yield adequate measures of spared residual function unless they are combined with quasi-experimental methods that examine the extent to which spared function can be detected. This may require the development of extensions to current methods of assessment that without losing the rigor of standardized procedures attempt to maximize the possibility of detecting residual function, whether that be motor, sensory, cognitive, or praxic. Such procedures would have the virtue of locking assessment procedures more closely to the process of rehabilitation.

Although dynamic assessment methods of this type are not yet widely clinically available, the principles can still be applied by slightly adapting current procedures. For instance, as described earlier in this article, repetition of standard tests of unilateral neglect under different limb movement conditions can reveal latent residual capacity in the right hemisphere attentional system, with clear positive behavioral results (Robertson & North, 1992, 1994; Robertson et al., 1992).

**General Implications for a Scientifically Based Rehabilitation**

As was argued earlier in this review, the restitution of function in lesioned circuits, where it is feasible given the remaining connectivity of the circuit, may depend critically on the specificity of input to that circuit, if the appropriate patterns of connections are to be re-established. It follows that certain types of stimulation may foster a dysfunctional connectivity in a fragile representation (see Figures 4 and 5 above). Phantom limb pain and referred sensations (e.g., from phantom limb to face; Ramachandran et al., 1992), for instance, may be examples of such dysfunctional connectivity (Flor et al., 1995; Knecht et al., 1995). Though not necessarily caused by inappropriate planned rehabilitative input, such dysfunctional connections may have arisen either because inadvertent stimulation fostered these connections or because correctly targeted stimulation was not applied that would serve to rescue the appropriate mappings. We reviewed evidence above that appropriate visual input to these circuits could positively influence the dysfunctional effects of these faulty connections, as well as evidence from several other types of deficit, which could be significantly reduced if appropriately targeted input could be provided.

In clinical practice, it is possible that failure to take into account the functional architecture of interlinked circuits in the brain may result in lost opportunities for guided recovery. For instance, the overzealous application of motor rehabilitation strategies that emphasize the need for bilateral activation of limbs may hinder recovery of both motor (see Taub et al., 1993) and perceptual (see Robertson & North, 1994, and Figure 7) functions. In short, some people may be deprived of the opportunity for recovery if the rehabilitation inadvertently activates circuits that competitively inhibit the impaired networks. Furthermore, to the extent that inhibitory input and lack of coherent stimulation may reduce synaptic connectivity (Fitzsimonds et al., 1997) in a network, then there is a possibility that the wrong type of rehabilitative input may have negative neural circuits if pursued excessively.

Taking another example of jargon aphasia mentioned above (Shuren et al., 1995), the repeated production of nonsense speech which is not recognized as such may well foster faulty connections in the speech process if allowed to proceed unabated. If, as Shuren and colleagues suggested, this loss of error awareness was due to reduced attentional capacity, then it might be expected that constraining speech production to circumstances where attentional load is kept to a minimum may (a) improve error awareness and (b) as a result perhaps improve the likelihood of correct speech responses. Reducing attentional load could involve the use of cueing and shaping strategies based on the principles of learning theory, including errorless learning, as has for instance been used clinically with memory-impaired patients (Wilson, Baddeley, Evans, & Shiel, 1994). Such a therapeutic strategy may require rehabilitation staff to discourage any attempts at speech production outside of the controlled circumstances designed to minimize attentional demand and maximize the likelihood of a correct response.

The possibility of inadequately targeted stimulation fostering maladaptive connections must be treated with caution, however. This is a theoretically derived hypothesis, and there is not a large amount of clinical evidence showing that it is a widespread phenomenon. That being said, the fact that such evidence has not been collected, does not necessarily mean that the problem does not occur. It is one of the purposes of the article to stimulate research into this and related questions in rehabilitation.

The potential importance of top-down, attentionally mediated, targeted inputs to lesioned circuits has also been largely ignored in rehabilitation. There may be practical reasons for this—for instance, attentional limitations in some people—yet the possibility of using mental rehearsal and attentional tuning to improve performance of impaired functions deserves much more research effort. Although it has been shown that mental practice can increase synaptic connectivity in non-brain-damaged individuals (Pascual-Leone et al., 1995), there has been only a little research on its application (Smania et al., 1997). We return to the question as to whether it is possible to train the attentional processes that may underlie such capacities.
It follows from the framework proposed in this article that the
timing of rehabilitation may be critical. If networks can decay,
they may do so quickly following a lesion. The provision of
patterned input, along with the discouragement of responses that
might foster faulty connections, should be provided, theoretically
at least, as soon as medical stability is achieved. The work of Nudo
and colleagues (Nudo et al., 1996) reviewed earlier showed for
instance that a lesion may result—possibly through deafferentation
of neighboring regions—in additional loss of synaptic connectivity
and behavioral capacity over and above what is caused by the
lesion itself. Such additional loss of function could be prevented by
the timely input of behavioral stimulation to rescue the at-risk
networks. In other words, for certain circuits, there may conceivably
be a critical period within which the appropriate patterned
stimulation must be given if the networks are to survive. It seems
very likely that similar processes may occur in humans, and thus
the timing as well as the nature of rehabilitative input becomes
critical. A reasonable working principle would be that this input
should be provided as soon as it is medically feasible. Though the
timely and intensive application of patterned stimulation to acceler-
sate self-repair of networks may be of crucial importance, this
need not necessarily imply an increase in total rehabilitation time,
but rather the more timely deployment of the resources available;
this may require a flexibility of rehabilitation input, intensively for
short but carefully timed intervals of treatment. Again, however,
is this a hypothesis and not a fact. We hope that in advancing this
hypothesis, rehabilitation research can be oriented to this and other
related questions, thus helping to develop theoretically based
rehabilitation.

In the absence of clinically viable and noninvasive measures of
brain connectivity, it is likely that the key to inferring the state of
damaged systems will rest on sophisticated detailed behavioral
testing of the cognitive architecture of these systems. Current
standardized neuropsychological tests are usually not sensitive
enough to reveal the complex inhibitory and facilitatory relation-
ships between different networks, as discussed above. As cognitive
neuroscience develops, the latest behavioral experimental methods
will be adapted to probe the cognitive architecture. These assess-
ments can then serve as a basis for (a) determining whether
potentially restitutable residual function exists and (b) what opti-
mal inputs must be provided to this residual circuitry in order to
maximize the chance of restitution of function.

Attention and Arousal

A further limitation on the duration of treatment concerns the
attentional capacities of the individual. As we showed earlier in the
article, it is known that plastic neural reorganization does not occur
passively but instead requires that active attention be paid to the
relevant behaviors during stimulation. It follows, therefore, that if
attention can only effectively be deployed for periods of seconds
or minutes, then rehabilitation input should ideally be confined to
such attentional windows, with more frequent, brief sessions of
therapy offered, rather than bureaucratically determined sessions
lasting up to 1 hr.

The capacity to deploy attention over time, sustained attention,
has been shown to predict motor recovery after stroke (Robertson,
Ridgeway, et al., 1997), as outlined earlier in this article. Further-
more, there is some evidence that sustained attention may be
amenable itself to rehabilitation (Robertson et al., 1995; Sturm et
al., 1997). Hence, rehabilitationists may be able to do more than
modify therapy session duration to attention span—they may also
be able to extend that span so as to be able to provide a greater
input of effective therapy for other impaired functions.

The ability to attend selectively to particular stimuli in the
environment, body or mind is also important for the guided recov-
er of lesioned circuits, we have argued. Whether or not this can
be trained is not yet clear, though some interesting evidence that
this might be the case has been published (Sturm et al., 1997).
Clearly, this is a potentially important area for future clinical
research.

Arousal—the generalized state of alertness which is linked to
diurnal variations in wakefulness—may also have to be at optimal
levels for successful guided recovery and plastic reorganization to
take place. This is also supported by our connectionist model
(Murre & Robertson, 1995; Murre et al., 1999), where arousal
must be at a certain minimum level for representations to recover,
and hence patterned input may not be indicated until appropriate
levels of arousal are achieved. This may require the combination of
pharmacological interventions with behavioral training in some
cases, and preliminary studies using such an approach have pro-
duced promising results as we outlined earlier in the article.
Conversely, the importance of neuromodulator levels in the brain
means that much more attention should be used as to the choice of
drugs given to patients during recovery from brain damage. Many
commonly used drugs reduce plasticity and hinder plastic reorga-
nization of the brain (Goldstein et al., 1990; Goldstein et al., 1995),
thereby hindering functional recovery.

There is, furthermore, evidence that REM sleep may be neces-
sary for the consolidation of learning, perhaps through facilitating
the strengthening of synaptic weights in the networks underpin-
ing learning (Kami, Tanne, Rubenstein, Askenasy, & Sagi,
1994). It follows that the use of drugs in therapy that interfere with
REM sleep may also adversely affect cerebral plasticity. Certainly
there is evidence that diazepam for instance can impair plastic
reorganization in animals (Schallert & Lindner, 1990; Stein,
Braiwowsky, & Will, 1995), and it may be necessary to minimize
use of drugs of this type during rehabilitation, to maximize the
chances of learning-based reorganization and recovery taking place.

Generalizability of Therapeutic Effects

We have argued that rehabilitation draws on the same underly-
ing brain mechanisms as do the various types of learning that we
know to exist. The failure of learning to generalize from one
setting to another is not necessarily a mark of failure of the process
of learning. There are circumstances where learning is context
dependent, and hence if one wishes to see learning generalize to
other settings, then one must repeat the training within that con-
text. This is often true for compensatory scanning in unilateral
ger, for instance. In one study, patients with unilateral left
neglect were trained to scan to their left for obstacles that were
marked by bright colored markers. Even when these markers were
removed, the patients successfully learned to avoid the previously
marked obstacles. When these patients returned home, however,
there was no generalization of the leftward scanning strategies they
had learned in hospital, and the scanning habit had to be retrained in the home setting (Lennon, 1994).

Learning, however, need not always be so closely tied to context. In limb activation treatments for the high level attentional deficit, unilateral neglect, for instance, relatively enduring effects of this training have been found without the need for training to be repeated in every different context within which the patient operates (Robertson et al., 1992; Robertson, Hogg, et al., 1998). Here, it is argued, latent attentional and perceptual function in the damaged right hemisphere is being inhibited by competitor activity from the undamaged left hemisphere. Activating the left limb can temporarily overcome that inhibition, as we showed earlier in this article. But how is this temporary activation translated into enduring improvements in everyday life? Our hypothesis is that there the hemiparetic limb is underused because of lack of attention to that side of the body caused by the left neglect. This lack of use contributes to the underactivation of the damaged right hemisphere. With repeated activation of the left limb (as opposed to short-term activation for experimental purposes), attention to the left side of the body is improved because of the revived latent activation in the right hemisphere. And because attention to the left side of the body is improved, the patient is more likely to move that side of the body, resulting of course in further activation in the damaged right hemisphere. This, we argue, causes Hebbian learning reinforcing the activation pattern and making it easier to reproduce it with repeated activation. Thus we have, hypothetically at least, a virtuous, self-strengthening circle of induced activation, leading to improved attention, leading to more activation, leading to greater attention, and so on. This type of learning, with associated reduction in inhibition, is of course married to a context, but this is a context that patients carry with them—their own bodies.

These two examples are just that—extreme examples taken from a single, cognitive disorder to allow comparison. But the principle may, if our framework has use, hold for a vast range of other cognitive disorders. Context can be internal as well as external, and so rehabilitation can embed new learning both within particular external environments as well as within existing well-learned cognitive routines.

This being said, the essential test of generalization must be clinical trials. Some of the methods described under the five principles of guided recovery above have been subjected to clinical testing. For example, the study by Taub and colleagues (1993) showed that improved arm use in everyday life was maintained for 2 years after the end of a training period. Furthermore, limb activation training for unilateral neglect (Robertson et al., 1992) showed effects that lasted up to 3 weeks after the end of training. In a recently completed but as yet unpublished study, we have carried out a randomized controlled study of this treatment, and found positive rehabilitation effects lasting at least 6 months beyond the end of training.

Generalization effects are not, however, confined to cognitive disorders such as unilateral neglect, or motor disorders such as hemiplegia. In a study of rehabilitation of disorganized behavior following traumatic brain injury (Levine et al., in press) that is described in more detail below, a single-case study of the effects of a rehabilitation method known as goal management training showed enduring benefits of performance in a real-life situation 3 months after the end of training.

Rehabilitation of Memory Deficits

Episodic memory has proved resistant in general to the types of stimulation-based treatments that appear to have been successful in the rehabilitation of motor, sensory, and some cognitive functions as outlined above (Baddeley, Wilson, & Watts, 1995). In general, episodic memory has benefited from compensatory strategies, such as the use of external cues, structure, or the learning of mnemonic or other compensatory strategies (Wilson, 1998).

There is an important theoretical reason why episodic memory should be considered a special case as far as the principles of rehabilitation outlined in this article are concerned. We have recently modeled amnesia, both retrograde and anterograde, as well as the recovery from amnesia, in a connectionist model called TraceLink (Murre, 1996, 1997). The trace system of TraceLink has been used in the recovery simulations described in this article. The more complete version, however, also includes a link system (hippocampus and adjacent areas) and a modulatory system (includes certain basal forebrain nuclei). Without these systems, episodic learning is impossible (i.e., the system exhibits anterograde amnesia). Moreover, lesioning of the link system causes a severe retrograde amnesia that is graded in time: Recent memories are less accessible than remote memories.

In patients, the time period of lost memories typically shrinks after the trauma. Shrinkage of retrograde amnesia is modelled by resurrecting a certain percentage of the lost cells in the link system (one could argue that they were depressed temporarily). This type of recovery of the link system may also be accompanied by a decrease of anterograde amnesia in the model. In addition, we see a small effect of additional Hebbian repair of the type outlined in this article and used in our brain repair simulations (which occur in the trace system). The effect is small, because one of the basic assumptions of our model is that the connectivity between trace system and link system is just sufficient for the two to interact and accomplish initial storage of an episodic memory. Memory representations are only preserved in the long run when they are consolidated. Similar assumptions have been made by other models of hippocampus and amnesia (Alvarez & Squire, 1994; McClelland, McNaughton, & O'Reilly, 1995). The minimal connectivity between the link system (hippocampus) and trace system (cortex) precludes a significant cognitive reserve, which may be why recovery of retrograde amnesia has benefited so little from rehabilitation therapies. We predict some effect of guided recovery (i.e., visiting places that represent lost memories), but primarily in speeding up the process of shrinkage. Memories that are on the verge of re-emergence will benefit from such specific stimulation. Compensation in the case of recovery from retrograde amnesia, in the form of relearning of past memories, is often difficult because patients typically also suffer from anterograde amnesia. Relearned memories, moreover, do not have the same phenomenological quality as the original memories (i.e., remembering an experience is very different from remembering that someone told you that you had the experience).

In conclusion, we argue that recovery from amnesia is difficult because the memories lost in retrograde amnesia are mainly those that have not built up a significant cognitive reserve at a trace level. In case of hippocampal damage, recovery of amnesia is strongly constrained by percentage of remaining tissue and is not subject to the five general principles of recovery outlined in this
Rehabilitation of Sustained and Selective Attention Deficits

To our knowledge, there is only a single study showing restorative rehabilitation effects on either of these two systems. This study, however, clearly justifies our claims that the principles of guided recovery proposed in this article extend to at least some of the highest level cognitive systems of the brain and not just to lower-level perceptual and motor circuits. Sturm and his colleagues in Aachen (Longoni et al., 1999) used a computerized training procedure to train sustained attention capacity in a variety of simulated tasks. The training was administered for 14 sessions of 45 min each and before and after the training a comprehensive neuropsychological test battery as well as functional imaging of cortical activity was carried out. One patient showed a significant improvement in sustained attention after the training and the other did not. After the training, the former showed an at least partial restitution of the right hemisphere sustained attention network especially in the frontal cortex—superior frontal gyrus Brodmann’s area (BA) 8, middle frontal gyrus BA 6, inferior frontal gyrus BA 47, middle temporal gyrus BA 38—whereas before the training a considerable left hemisphere activation (postcentral gyrus BA 40) with only small RH foci was present. The patient who failed to improve with the training showed no increases in right hemisphere bloodflow.

So far, there is no evidence to show that selective attention can be restituted in this way, and so the applicability of the principles of guided recovery to that control system remain hypothetical. The complexity of other control functions partly subserved by the frontal lobes means that it is practically rather difficult to distinguish between compensatory and restitutive processes underlying recovery of function. It may be that, with the possible exception of sustained and selective attention, rehabilitation of such systems may call on a combination of compensatory and restitutive mechanisms that can never be satisfactorily disentangled. Certainly it is possible to rehabilitate some of the types of complex behavioral deficits that tend to be considered under the rubric of executive problems (Levine et al., in press; von Cramon & Matthes-von Crumon, 1992, 1994; von Cramon, Matthes-von Crumon, & Mai, 1991). Clarification of the role of compensatory versus restitutive processes in recovery from attentional control deficits must await more well-described models of executive function.

Conclusions

Recent progress in neuroscience provides us with an opportunity to try to place the rehabilitation of brain damage on a scientific basis. New evidence about experience-dependent plasticity of the adult brain allows us cautious optimism about the possibility of restitution of brain function following damage, given that such a basis is realized. This endeavor, however, will require strong interactions between basic and clinical research: Basic cognitive scientists must become intimately involved in supplying the necessary information to help make decisions about (a) whether potentially restitutable residual capacity exists in specified lesioned circuits and (b) what the inputs should be to maximize this restitution. This is central to the development of what must inevitably become a properly scientifically based approach to rehabilitation. Caution must however be exercised in overextrapolating two complex clinical settings from the findings of this more basic research. Nevertheless, progress has been made in evaluating the methods that have been derived from these principles, and there are grounds for suggesting that in some areas at least the theoretical framework proposed in this article provides a useful starting point for developing more theoretically based rehabilitation methods. But this framework is just that, a framework designed to stimulate more theoretically based research into the rehabilitation of acquired brain damage.

In this article, we use connectionist modeling for its heuristic and illustrative value, and also as one form of quality check on our theoretical framework and its derivations. Current modeling work is increasing rapidly in sophistication and scope, with biological models increasingly capturing details of cortical functioning and reorganization. Quantitative modeling of patient behavioral recovery data has proven to be a difficult undertaking, because of heterogeneity, small size of populations and lack of standardized testing limiting the extent to which results can be combined to increase the power of the models. Although the absence of such well-defined models might suggest little need for such data, in fact they are likely to be heuristically useful in hypothesis generation and testing.

In particular, connectionist models of recovery may afford some crosstalk between the cognitive and biological level of analysis. Although we are convinced that cognitive neuroscience and the behavioral data it provides are a cornerstone for developing theoretically based rehabilitation, cognitive models must operate within plausible biological constraints. Connectionist modeling of recovery and rehabilitation processes offers one possible way of
implementing these constraints on cognitive models in a nonarbitrary way.

Rehabilitation research has for too long been the Cinderella of both biological and cognitive research. In fact, in studying the processes of recovery and guided recovery, we are presented with the opportunity for a fruitful rapprochement between these two different levels of analysis in the study of the CNS. In challenging cognitive theorists to implement their theories in the context of the dynamically recovering brain, cognitive theory and rehabilitation simultaneously benefit. Through illustrating the ways in which cognitive and behavioral processes alter biology during the process of rehabilitation, we constrain biologists to assimilate into their theorizing the cognitive and behavioral processes that partly determine brain structure and function. If we do both of these things well, neuroscience and millions of brain damaged people throughout the world will be the beneficiaries.

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