Rational basis of rehabilitation following cerebral lesions: a review of the concept of cerebral plasticity

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Summary

Improvement and recovery of function after a cerebral lesion imply a reorganization of the central nervous system. This capacity of the nervous system to adapt its structural organization is referred to as cerebral plasticity. This paper summarizes the biochemical and histological basis of cerebral plasticity, reviews the modalities of brain reorganization following amputations and cerebral lesions, and concludes with a brief review of the most salient aspects of rehabilitation of memory, language, executive functions and dementia.

KEY WORDS: aphasia, cerebral plasticity, dementia, memory impairment, rehabilitation.

Introduction

Improvement and recovery of function after a cerebral lesion imply a reorganization of the central nervous system (CNS). The purpose of this presentation is to review some of the mechanisms underlying this reorganization, which, being defined as the capacity of the nervous system to adapt its structural organization, is generally referred to as cerebral plasticity. This capacity may be the result of development, of the environment and outside influences such as drugs and hormones, as well as of lesions. It is mainly the latter that will be discussed here.

It was thought for many years that, following development, brain structures were fixed and could not show regeneration or other forms of plasticity. These were the very words of Ramon y Cajal who shared the Nobel Prize with Camillo Golgi in 1906. In fairness, as pointed out by Kolb (1), Cajal later changed his mind and suggested that learning could produce prolonged morphological changes in neurons. In 1948, Jerzi Konorski thought that these morphological changes were activity-dependent. Donald O. Hebb, one of the lesser known fathers of modern neuropsychology proposed that the critical changes involved the synapses. However, it was only later that neurobiologists clearly recognized that some structures of the CNS have the potential capacity to modify themselves. Rosenthal and his colleagues at Berkeley were probably the first to demonstrate chemical and anatomical changes in correlation with behavioral changes (2). Actual regeneration phenomena have now been shown in humans (3-5) and in animals (6), demonstrating the possibility of functional recovery of the CNS following focal lesions and also degenerative diseases such as Parkinson (7), Huntington (8) and even Alzheimer’s disease (AD) (9).

A recent and very important development in our understanding of cerebral plasticity has been the advent of relatively non-invasive techniques such as functional magnetic resonance imaging (fMRI) (10) and transcranial magnetic stimulation (TMS) (11). These techniques now allow us to follow more closely and objectively the phenomena related to plasticity in the human brain.

Biochemical basis of cortical plasticity

In their review, Mark Hallett and his colleagues (12) state that several lines of evidence indicate that modulation of GABAergic inhibition plays a significant role in cerebral plasticity (13). It must be stressed, however, that this “evidence” is rather indirect. For instance, the application of a GABA antagonist, bicuculline, to the forelimb area of the motor cortex modifies cortical motor representation. Whether GABAergic changes play a role in, say, recovery from aphasia is a matter of speculation at the present time. GABAergic inhibition probably occurs in acute lesions, whether experimental or produced by nature. In degenerative diseases, even less is known. There has been mention of a “GABA deafferentation hypothesis” to account for the age- and AD-related degeneration in the forebrain (14) and this has led to therapeutic attempts, which for the moment are in the pre-clinical phase (15).

Other neurotransmitters play a role. The almost ubiquitous glutamatergic system is known to play a major role in neuronal plasticity and cellular resilience (16). A specific example is its role in long-term potentiation (LTP) in the encoding of certain types of memory (17). One needs also to mention the role attributed to Notch, a critical component of evolutionarily conserved signaling mechanisms that regulate development and may contribute to plasticity-related processes, including changes in neurite structure and maintenance of neural stem cells (18).
Neurotrophic factors have been shown to have a definite effect on cerebral plasticity in animals (19) and possible applications to rehabilitation are starting to appear. For instance it has been suggested that voluntary exercise may promote brain plasticity by upregulating trophic factors such as glial cell line-derived neurotrophic factor (GDNF), fibroblast growth factor-2 (FGF-2), and brain-derived neurotrophic factor (BDNF) (20).

Finally, it has been found that EGb 761 (Ginkgo biloba) shows beneficial effects both on brain glucose and energy metabolism and on behavior, hence its hypothesized role in facilitating functional recovery (21).

Histological basis of cortical plasticity

Much about plasticity has been learned through studies of cerebral development in rats (1,22). The attention of researchers has focused mainly on the following elements:

- genesis of neurons. In the rat, neurogenesis is possible for the cortex throughout life and is known to take place particularly in the olfactory bulb and in the dentate gyrus of the hippocampus;
- genesis of glial cells, particularly astrocytes. This is important because it is known that astrocytes produce chemical messengers such as neurotrophin that are known to facilitate plasticity (see above);
- production of synapses. This process likely requires dendritic changes;
- cell death and synaptic pruning. This provides a mechanism for fine-tuning the connectivity of the cerebral cortex.

Two main results of the work of Kolb deserve particular comment. First, as shown in figure 1, these cellular events take place mainly before, and shortly after, birth. However, they never stop and can be witnessed even in very old animals. Second, external stimulation during growth obtained through an enriched environment (Fig. 2) produces a dramatic increase in dendritic arborization (Fig. 3). Similar results have been obtained by others (23).

It is of course always a delicate matter to extrapolate rodent data to human reality. As pointed out by Rakic in a recent review (24), the rule is that there is no neural turnover or replacement of injured neurons in the adult human brain, despite the fact that astrocytes that can...
behave as neural stem cells are present in the walls of the lateral ventricle in the adult human brain. He attributes this to a resistance of the CNS to accept neural stem cells into a mature neuronal network. There is however some evidence that a limited amount of neurogenesis takes place in normal humans (25) and in the course of diseases such as AD (26).

On the other hand, the results of Kolb’s enriched environment studies may represent the basis of the well-known relation between education and incidence of dementia. This relation is illustrated by the results of the PAQUID (Personnes Agees Quid) study (27) and has been shown in many other studies performed in different countries including Italy and China. Of course, there are reasons to believe that it may not be education per se which is responsible for this effect. Whatever the reason, it is possible that greater stimulation during the early life of human subjects may provide the brain with greater “reserves”, thus delaying not the disease but only its clinical symptoms. The influence of early-life factors is also shown by results of the so-called Nuns’ study, which suggests that greater pre-morbid intelligence may be related to later incidence of AD (28).

**Brain plasticity and the body schema**

Ever since the demonstration by Cushing and others that the body has a rather precise somatotopic representation in the cortex (the so-called homunculus), the question has been raised as to whether body changes such as amputation might modify this representation. Human and animal studies following accidental or experimental amputation indicate that they do. TMS allows relatively easy in vivo studies and shows, for instance, that following facial palsy, there tends to be an extension of the hand area in the brain. In focal dystonia, in which overuse of the hand leads to a lack of motor control, receptive field size and columnar architecture are modified (29).

On the other hand, cerebral lesions may produce striking modifications of the body schema. This is particularly noticeable following lesions of the right hemisphere in right-handed persons with phenomena such as denial of illness (anosognosia), and failure to recognize as their own, dislike or even hatred of the paralyzed left hand (misoplegia). In order to account for the material existence of the limb, patients may resort to improbable rationalizations and confabulations (somatoparaphrenia). On one occasion, I remember showing a patient his paralyzed left hand and asking him what it was. He replied in a sepulchral voice “this is a dead hand, doctor”.

The body schema may extend to include inanimate objects. Figure 4 shows a patient described by Aglioti who denied ownership not only of her left hand, but also of the ring and watch worn on that hand, but promptly recognized them as her own when they were put on her right hand.

Dr Pascual-Leon and his colleagues studied early-blind subjects before and after they learned Braille. They showed (Fig. 5) that these subjects acquire a larger representation of the reading finger, as demonstrated by somatosensory evoked potentials and TMS. There is also recruitment of the occipital lobe (30) as shown by fMRI.

Another demonstration of structural changes in response to external demands is provided by positron emission tomography (PET) and fMRI studies that have shown a marked hippocampal development in migrating animals as well as in humans whose work involves considerable spatial demand, such as taxi drivers (31).

**Brain plasticity following lesions in humans**

More than half a century ago, Oliver Zangwill, another father of modern neuropsychology, proposed a theoretical framework which could be applied to rehabilitation and remains strikingly valid today (32). Zangwill men-
tioned three strategies for functional recovery: compensation, substitution and direct retraining. Compensation is defined as “a reorganization of psychological functions in order to minimize a given handicap”. Compensation occurs mainly spontaneously as, for instance, in the case of a right-handed patient with a right hemiplegia who learns how to use his left hand.

Substitution consists of building up a new method of responses to replace others that have been irretrievably damaged by a cerebral lesion. Unlike compensation, substitution does not occur spontaneously, but normally requires the assistance of a therapist. Examples of substitution are lip reading in the case of impaired audition and Braille learning for the blind.

Finally, direct retraining requires a necessary substrate, corresponding to the function one wants to relearn. An example is the relearning of the multiplication tables by an aphasic subject. Zangwill indicated that there was no direct proof that such a mechanism exists, but at the same time expressed the hope that direct retraining might play a role in rehabilitation.

Using the analogy of a “Symphonia hemispherica”, Wilson has offered a metaphorical illustration of factors related to functional impairment and to remediation strategies. Tables 1a and b summarize her concept in modified form. The most important factors are the first two: the size of the lesion and its location. In addition, the table alludes to the phenomenon known as diaschisis, whereby a cerebral lesion may produce a functional impairment in a far removed, but connected region. This idea, originally proposed by von Monakow on the basis of clinical data (33), has received a new lease of life following confirmation, through neuroimaging techniques, that in some cases an undamaged area may function abnormally when it relies on interaction with a damaged region, but show normal responses when neural dynamics depend only upon integration with undamaged regions (34). One should add to these factors several others such as the age of the subjects, their handedness, the timing of the beginning of rehabilitation in relation to the time of the lesion (35), and even the etiology of the lesion, given that tumors tend to behave differently from, say, vascular lesions. The remedies mainly include teaching subjects new strategies to cope with their deficit. Current attempts to transplant embryonic cells in Parkinson disease patients reflect the other strategy (i.e., “recruit new musicians”) (36).

In proposing his theoretical model, Zangwill mainly had aphasia in mind, and, since WWII, aphasia has been the main area addressed by cognitive rehabilitation (37). Currently, cognitive rehabilitation techniques have been applied to deficits not only of communication, but also of attention and of judgment, and to neglect (38,39). The following sections will deal with rehabilitation of memory and aphasia and executive functions. Cognitive rehabilitation of dementia will also be briefly discussed.

Rehabilitation of memory and learning

Wilson (40) has provided guidelines for memory rehabilitation which actually apply to all learning processes. They are inspired by our current knowledge of the different systems that form what we call memory.

In order to facilitate encoding (getting the information in), it is important to simplify the information and to reduce it. It is better to present one name or instruction at a time, rather than several. It is important to check understanding, for example by asking subjects to repeat what they just heard. One should follow the principle of “little and often” or the distributed practice rule, and they should be encouraged to process or manipulate the information, for example by asking questions. They should be encouraged to make associations, linking what they heard to known facts or to images. A few years ago when I was working in the United States, I was impressed by the fact that patients always remembered the name of my colleague Dr Ratcliff. I then noticed that upon introducing himself, he would ask patients to remember the image of a rat running over a steep rock face. Making associations may well be the most important mechanism for learning and is mainly how mnemonists function, as vividly described by Luria (41) (see below).

Following encoding of the information, one must insure that it is properly stored. For this, one must encourage rehearsal and, when practical, testing. The two are combined in the method of spaced retrieval in which, following presentation of the information, a test is carried out immediately and repeated at intervals of increasing length.

Finally, it is useful to find ways to optimize retrieval and let me point out that retrieval difficulties represent a problem that all of us face from time to time. One way is to provide cues and some people, including patients, go systematically through the alphabet to find their own first letter cue. One should also teach patients to avoid context specificity, for example encouraging them to use a notebook not only in the context of the therapy sessions. The therapist will attempt to interact with the patient in different settings.

Another way to optimize retrieval of the information consists of encouraging the “ancient art of memory”, a technique practiced by orators of the classical age to

Table I - Symphonia Hemispherica, a metaphor of plasticity (modified), from a text originally proposed by Barbara Wilson.

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<thead>
<tr>
<th>A. Factors that influence functional impairment</th>
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<tr>
<td>– Number of musicians who die</td>
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<tr>
<td>– Their position within the orchestra</td>
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<tr>
<td>– Effect of shock on the other musicians</td>
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<tr>
<td>– Their age</td>
</tr>
<tr>
<td>– Their handedness</td>
</tr>
<tr>
<td>– Timing of the event</td>
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<td>– Nature of the event</td>
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<th>B. Remedies</th>
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<tr>
<td>– Change the repertoire</td>
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<tr>
<td>– Ask other players to learn the violin</td>
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<tr>
<td>– Ask other instrumentalists to take over the music played by the violinists</td>
</tr>
<tr>
<td>– Recruit new musicians</td>
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learn the texts they had to deliver in public speeches. It consists of imagining a building or an image where one can locate the various portions of the material to be remembered (Fig. 6). An American neurologist, Bernard Patten, was probably the first to put back into practical use the “ancient art of memory” and to try it in patients with amnesia (42). Patten emphasized that the best results with this method were obtained in amnesic subjects still able to form strong and vivid visual images, who had not completely lost their recent memory, were aware of their deficit and were sufficiently motivated. Clearly, if any, of these criteria apply to AD even in its early stages. In fact one of his patients did have AD and drew no benefit from the technique. Carlesimo (43) has summarized the most commonly used cognitive rehabilitation strategies, dividing them into the following categories:

1. Use of tools as external memory aids. These tools may be passive, as when the environment is modified in order to improve orientation in time and space. This is the base of Reality Orientation Therapy (44). Alternatively, they may be active, such as handkerchief knots, shopping lists or notebooks, including the current Personal Data Assistants (PDAs). On the other hand, Wilson (45) points out that, unfortunately, many persons with a memory deficit have trouble using external aids, especially the most sophisticated ones, because they often forget to use them, are unable to program them, use them unpredictably or are embarrassed by their visibility to people around them.

2. Use of methods aimed at reinforcing residual learning abilities. These include methods centered on visual imagination such as the ancient art of memory discussed above. One can also use methods centered on verbal processing. For instance “deep encoding” of words centered on their semantic meaning has been shown to improve learning, as opposed to “superficial encoding” based on phonological aspects. This is the basis of one of the memory tests proposed by Buschke (46).

3. Rehabilitation methods based on teaching specific domains of knowledge. Glisky and his colleagues suggested that a set of limited and realistic goals be proposed, and developed a technique in which efforts are concentrated on teaching subjects computer use with the help of the “vanishing cues” technique in which initially the entire command is provided, after which the number of letters is progressively reduced (47). A different approach called “errorless learning” has been proposed by Wilson and Baddeley, based on concepts originally introduced in animals by Terrace (48). It has been shown that patients forced to guess an answer (errorful learning) showed less learning than when they were presented with the correct answer before guessing (40). These techniques have been used mainly in stroke and trauma patients. When talking about plasticity, memory and rehabilitation, everybody of course thinks in terms of improving or perhaps of preventing impairment of memory and learning. However, there is at least one famous example of the reverse situation. Alexander Romanovitch Luria, one of the leading figures in post WWII neuropsychology had the chance to examine for many years a man with an unusual characteristic (41): this man, whom Luria calls Veniamin, could remember without any apparent effort series of words, of digits and of meaningless syllables. He was able to reproduce them instantly, forwards and backwards, and was able to reproduce them again, usually without any mistakes, many years later. To me, one of the most striking events occurred when someone gave Veniamin the first 4 lines of Dante’s Divine Comedy. Even though they were read to him in Italian, a language he was entirely unfamiliar with and unable to understand, Veniamin was able to repeat them, word by word and with the correct prosody. To Luria’s astonishment, he was able to reproduce them again, naturally and exactly, 15 years later. It is practically certain that he had not heard them in between.

Veniamin had sufficient insight to provide details about how he accomplished these feats, which for him were not in the least extraordinary. His brain presented an unusual phenomenon: synesthesias; that is to say, external stimuli evoked sensation in several modalities. For example sounds had an odor and a tactile feeling and when he heard words, he was able to see them as if they were written on a blackboard. One of his problems, however, was an inability to forget and to erase images that had become useless. This caused a real problem because as a professional mnemonist who often gave several public performances in a row, he was always afraid that he might erroneously repeat the items he had seen and learned in a previous session. Veniamin learned to “erase the blackboard” and to cover it with an opaque curtain. Or he would “write” on a separate board the material to be forgotten. He tried...
Rehabilitation of aphasia

Aphasia is a frequent complication of cerebral lesions, particularly strokes. Much has been written concerning its rehabilitation (37, 49). Once it is established that aphasia produces a significant impairment, it is important to set goals based on the answers to the following questions (50):

– what difficulties does the subject encounter?
– what would he/she like to be able to do?
– what does he/she see as his/her main skills?

There are several approaches to the therapy of aphasia (51). The most commonly used is the traditional language-oriented school. It is usually based on an assessment such as the Boston Diagnostic Aphasia Examination (52). It serves as a guide to treatment, which may then follow different approaches such as stimulation by various means. The same assessment is then used to estimate gains following treatment.

The functional/pragmatic/social school of aphasia therapy capitalizes on the patients’ particular strength(s) and trains patients to use compensatory strategies. It is practically always used in conjunction with language-based approaches.

The cognitive neuropsychology school aims to apply information-processing models to disorders of language, thus providing a more rational approach to treatment. The deficits most often targeted are word-retrieval, agrammatism and sentence comprehension.

These three approaches are not really so different from one another. The cognitive neuropsychology approach can be considered a branch of the language-oriented school as it uses cognitive and psycholinguistic theories to direct rehabilitation activities. In fact, the three approaches are often combined in the same patient.

Controversy over the effectiveness of aphasia therapy has not been resolved, but those who believe in it are comforted by an early study by Vignolo (53) (Fig. 7), which suggested that therapy can still produce positive changes 6 months after a stroke even in the absence of spontaneous recovery. Modern imaging techniques have contributed greatly to our understanding of such changes. For example Peck et al. (54) studied three aphasic patients who improved after therapy. They were able to show that latencies – in this case the fMRI-demonstrated differences in the time to peak (TTP) of hemodynamic responses between auditory and motor cortices – decreased after rehabilitation, becoming similar to the values found in controls. Most probably, Benson was right when he stated that “many aphasics benefit from aphasia therapy and almost every aphasic deserves consideration for therapy” (55).

Rehabilitation of executive function deficits

Executive function deficits, often, but not always, related to frontal lobe lesions, stand apart from other deficits. Perhaps because the “riddle of the frontal lobe” (56) is relatively new on the scene and remains intriguing, rehabilitation of these deficits has often been based on rational principles rooted in current findings of cognitive psychology. This has certainly not always been the case with the rehabilitation of other deficits.

In one of his major contributions to neuropsychology, Luria (57) proposed a specific treatment plan for some of the problems characteristic of dysexecutive syndrome: inertia of thinking, disorders of planning and sequencing, and the problem of motivation during task execution. His suggested intervention aimed at drastically reducing distractions and continually directing actions.

Later researchers have proposed interventions based on the characterization of the dyscontrol system that is one of the characteristics of the frontal lobe syndrome. Several strategies are envisioned:

– remove patient from circumstances in which he has to exercise behavior control;
– increase effectiveness of supervisory system;
– encourage patient to select previously existing behavioral routines.

The first two techniques seem unrealistic. The technique that best follows the third recommendation is the so-called response cost technique which consists of “punishing” undesired behavior by immediately provoking the loss of something.

Clearly, executive function deficits are very difficult to treat. A few years ago, a review concluded that “there is no cure for frontal lesions or for frontal syndromes” (58). This difficulty is probably related to the unique complexity of the frontal lobes in terms of anatomy and functional organization (59, 60). Rehabilitation of execu-

![Figure 7 - Evolution of aphasia with (R+) and without (R-) aphasia therapy. Interval in months. From: Vignolo L. Evolution of aphasia and language rehabilitation: a retrospective exploratory study. Cortex 1964;1:344-367. Reproduced by permission.](image)
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tive function deficits represents one of the biggest challenges for the future.

Rehabilitation of dementia

It is legitimate to wonder to what extent rehabilitation strategies such as the ones outlined above may apply to patients with AD and other degenerative disorders. It is true that these diseases tend to affect some cerebral areas more than others, but it is also true that, by definition, they are progressive in nature and therefore a terrain less than ideal for cognitive therapy. Some specific psychosocial interventions such as Reality Orientation Therapy (ROT) (44) can undoubtedly be of benefit, at least on a relatively short term basis (61). It is known that procedural memory is spared in AD (62), but the acts involved in this type of memory are difficult to apply to everyday life. Some improvement has been obtained by applying techniques based on memory learning strategies (63,64), and limited success has also been claimed in patients with primary progressive aphasia (65).

Concluding remarks

I have addressed several aspects of cerebral plasticity. I hope to have shown the extent to which basic research, cognitive psychology, neuropsychology and clinical neurology interact to provide a better understanding of brain functions and to help us help our patients and their families. Some of the techniques discussed above may actually be used in improving functions in normal persons, whatever their age. This will not prevent diseases from occurring but may well delay their clinical appearance and improve quality of life.

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