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Neuronal post-stroke plasticity in the adult

Paolo M. Rossini and Gloria Dal Forno*
University Campus Bio-Medico, Roma, Italy

Abstract. Contrary to what previously believed, recent research advances have demonstrated that the adult brain has a certain capacity for plastic reorganization and self-repair after a lesion such as cerebrovascular accidents. The mechanisms subtending post-stroke recovery are probably complex and operating at different levels, from molecular to synaptic to anatomical reorganization. The integrated use of functional neuroimaging techniques, by overcoming the limitations of each specific methodology is likely to shed much light on plasticity mechanisms. In this review we discuss the neuroanatomy and neurophysiology possibly underlying reorganization of the central nervous system, as well as the experimental evidence of "*in vivo*" post-stroke plasticity. Better understanding of these mechanisms can provide neurorehabilitation with powerful tools in designing and implementing new therapeutic approaches to stroke patients both in the acute and the chronic stages after a brain tissue lesion has occurred and stabilized.

Keywords: Plasticity, post-stroke recovery, integrated functional neuroimaging, TMS, MEG

1. Introduction

Cerebrovascular accidents (CVA) are a major cause of morbidity and mortality in developed countries. The residual impairment in a number of functions fundamental for everyday activities, such as movement programming and execution, sensorimotor integration, language, and other cognitive functions have a chronic impact on overall level of functioning and quality of life. The long-term outcomes of strokes have been taught to be essentially irreversible, and it is common belief that the adult brain has no significant ability for self-repair or reorganization following injuries resulting in neuronal death, such as CVAs. However, it is not uncommon in clinical practice to see slow but consistent recovery over a period of weeks and months following lesions underlying seemingly stabilized neurological deficits [151]. Degrees of spontaneous recovery may range widely, even in light of very similar acute lesions and clinical pictures. Several explanations have been given for the recovery of lost function in stroke syndromes.

*Corresponding author: Gloria Dal Forno, MD, PhD, University Campus BioMedico, Via Emilio Longoni 83, Roma 00155, Italy. Tel.: +39 06 225411; Fax: +39 06 22541602; E-mail: g.dalforno@unicampus.it.

In the acute stages variability in clinical outcomes can be partly explained by phenomena such as reabsorption of perilesional edema and inter-individual variability in perfusion patterns as well as presence of collateral blood supply. It is known for example that the central necrotic core of acute stroke lesions is surrounded by an area of dysfunctional neurons defined *ischaemic penumbra* whose extension and potential for recovery contributes to the severity of the final clinical deficit. Survival of neurons of the *ischaemic penumbra*, if adequate perfusion is restored, can allow for a rapid, partial or total restoration of the lost functions. The induction of either post-ischemic or post-anoxic long-term potentiation (LTP) occurs few minutes after energy deprivation; ischemia may also impair physiological forms of synaptic plasticity such as activity-dependent LTP [24]. Finally, multiple representations of the same muscle function in separate cortical clusters in the primary motor cortex (MI), and the presence and amount of alternative neural routes (e.g., the *ipsilateral* corticospinal fibers) [108] are also factors implicated in the final clinical outcome.

A better understanding of the mechanisms underlying recovery (or deterioration) of function after a CNS lesion, as well as those leading to maladaptive or unfavorable outcomes, would be essential for directing

specific and effective rehabilitative strategies as well as avoiding potentially harmful interventions.

2. Plasticity in the central nervous system

The events that regulate the capacity of the CNS to change in response to injury or to physiological demands are described as *plasticity* phenomena. While usually used in describing pliancy and malleability, the term plasticity, when applied to brain function and behavior, indicates a *potential for change* [115]. This includes all mechanisms of reorganization of neural connections, even those involved in self-repair phenomena, such as the use of homologous but anatomically distinct alternative pathways, (e.g., non-pyramidal corticospinal pathways), synaptogenesis, dendritic arborization, and activity-dependent reinforcement of previous existing, but functionally silent synaptic connections [24]. Cortical representation areas indeed undergo transient changes throughout life under normal conditions, in response to external stimuli, motor patterns, and cognitive tasks [97]. Furthermore, cortical maps have been documented to be modified by sensory input, experience and learning [87,88,98,119,123,162]. The stability of such changes probably depends on the duration and intensity of a stimulus or motor pattern, (e.g. the permanent enlargement of the cortical representation area of the left fingers in string players) [43].

The "plastic" changes occuring in the CNS, probably include both cellular and anatomical phenomena including modifications of synaptic efficacy within neuronal networks [52], in relation to acquisition and recovery of sensorimotor function. The functional status and distribution of a network probably depends on the balance between excitation and inhibition and, probably, some cortical areas are kept 'masked' by active tonic GABAergic inhibition, thus allowing for a rapid change in size/distribution of the functional network, by simply removing or modifying this active inhibition [59]. Fast functional strengthening or weakening of synapses is also likely to occurr through processes akin to long term potentiation (LTP) and inhibition (LTI) [126] and these prototypic mechanisms of modified synaptic efficacy [17], can occurr through changes both at the pre- and post-synaptic level [22]. Animal studies have indeed demonstrated enhanced long-term potentiation in perilesional areas and in the contralateral hemisphere early after stroke [161], as well as fiber sprouting and formation of new synapses (see below) from surviving neurons [67].

Indeed brain ischaemia is known to induce LTP in specific subsets of neurons suggesting the existence of a form of synaptic plasticity operating in pathological conditions that may play a part in delayed neuronal death (e.g. in the hippocampus after global ischaemia) and in transformation of the ischaemic penumbra area into a necrotic infarct [24].

Neurotrasmitters from diffuse projection systems (e.g. noradrenalin from the locus ceruleus) are also likely to modulate synaptic efficacy [71,72]. Neuronal sprouting and formation of new synapses probably play a fundamental role in CNS plasticity over a longer time frame [145]. Indeed dendrites and dendritic spines, the main site for synaptic connections, undergo continuous remodelling [45] influenced possibly by local neurotransmitter and neurotrophic factor release, synaptic protein synthesis [73] as well as modification of gene expression in the brain [1,70,74,75]. Furthermore experimental stroke models, have demonstrated that placement of recovering animals in enriched laboratory environments results in improved recovery [61], suggesting that environmental manipulation may modify plasticity also in pathologic situations, a phenomenon similar to what is observed with experience-based or use-dependent plasticity.

In addition to cellular and synaptic mechanisms, the CNS functional anatomy seems to be organized, even through a certain degree of relative redundancy, so that damage can be, at least in part, functionally compensated for [115,152]. All damaging and restorative mechanisms are likely strongly influenced by the remote effects of the loss of excitatory or inhibitory modulation normally derived from a damaged area projecting to adjacent or distant brain centers, via cortico-cortical and transcallosal projections, a phenomenon called diaschisis. For instance, cortico-cortical inputs to the primary motor cortex (MI) are dominated by those from the supplementary motor area, premotor cortex and primary sensory cortices 1, 2 and 3, where spatiotemporal maps allow the integration of the proprioceptive, tactile and visual cues necessary for manual actions [118]. In addition interhemispheric interaction may be fundamental in the control of voluntary movements, as demonstrated in a recent fMRI study, by the functional hemispherical asymmetry in left and right supplementary motor area (SMA), with prevalence of the left SMA in right-handed subjects [8].

The converging cortico-cortical and subcortical-cortical inputs could thus interact, leading to the reshaping of cortical somatotopy both in normal and pathological conditions [6,39,104,105].

Voluntary motor activity requires sensory feedback from the moving limb [95,133]. Together with the output for movement, simultaneous discharges to the primary somatosensory cortex (SI) are fired by MI, probably providing the "efferent copy" of the motor program which the sensory feedback should be matched with [15,16,123]. An appropriate sensory feedback from a paretic limb, therefore, seems fundamental for long-term motor recovery and neuronal reorganization, even beyond the anatomical limits of the proper sensorimotor area [138]. Also, in healthy individuals, sensory deprivation from a limb district decreases the cortical motor output to the embedded muscles [119,123]. Furthermore, stroke patients who show little improvement of hand motor control indeed demonstrate severe metabolic depression in the thalamus [14,46].

In healthy humans the organization of the sensorimotor areas is rather symmetrical between the two hemispheres, and this has been demonstrated with different methods of functional brain imaging, particularly for hand control. When a hemispheric lesion occurs, functionally connected neuronal aggregates, whether adjacent or distant, can progressively take over for the lost neurons [33,155]. This type of reorganization is expected to modify neurophysiologic parameters of interhemispheric symmetry in terms of surface extension, number of "recruited" neurons, and spatial coordinates (see below). Symmetry can thus be used as an important parameter to study monohemispheric brain lesions.

The motor system has been studied more extensively than other systems as a model for basic plasticity phenomena, most likely because it controls readily evident human behaviors. At the same time, though, it is also complex enough to be representative of many other functional systems. Indeed, the understanding the neurophysiology of motor function, as well as the influence played by the sensory system on motor control is probably fundamental for understanding plasticity mechanisms [115].

The primary motor cortex (MI), is organized in multiple efferent micro- and macrozones often several millimeters apart, and separated by non-responsive districts, so that a particular movement can be elicited through stimulation of different MI regions [38,42,50, 57,78,99,128,134,139]. In addition, bi-directional projections interconnect motor cortex areas for different muscle districts [78,118]. Any movement, therefore, seems to be controlled by a network of neurons with the motor output from overlapping cortical territories converging onto single muscles, and the output from any given cortical site diverging onto multiple muscles, while horizontal intracortical projections interconnect subregions within the motor cortex [57]. This pattern is particularly evident for hand muscles [3,79] and is probably the anatomical substrate for the extraordinary repertoire of possible movement strategies initiated by the muscles at different joints, where the strict coordination of different muscle fields is essential for the successful execution of finger movements [78]. The primary sensory cortex (SI), on the other hand, is organized with a very orderly somatotopic arrangement, similarly to other cortical maps [68,103]. This possibly is due to the fact that while movements occur in a three-dimensional space, the body surface may be compared to a two-dimensional sheet, reproducible in a point-to-point correspondence in SI. The multiple representations of motor functions paired with the presence of distributed neural networks may thus cooperate and overlap spatially and temporally [69,127]. This offers flexibility in motor learning and it permits, to a certain degree, the functional substitution of a dysfunctional area with a related one. This mechanism is therefore more effective for recovery, flexibility and ultimately plasticity, than would one utilizing highly specialized and uniquely dedicated cell groups. Functional connections between SI and motor cortex are also fundamental for motor control. In addition to direct input to MI from the thalamus, SI is in fact a major source of input to the MI [64], being the only type of primary sensory cortex with direct access to the primary motor areas. Different areas within SI show a separate functional organization, and internal connections between the SI sub-areas are extensive [62–66].

Motor control involves large brain areas in addition to primary somatosensory cortex, such as visual, and motor cortices, as well as secondary sensory and motor areas. Basal ganglia and thalamic relays also significantly contribute to motor planning, sensory perception and sensorimotor integration. Supplementary motor and premotor cortices play a pivotal role in motor preparation and in the execution of movements carried out via corticospinal fibres under the parallel control of multiple descending systems, including those from cerebellar relays [8,115].

3. Non-invasive functional brain imaging

The biological basis of spontaneous post-stroke recovery of function, particularly that occuring over weeks and months after the acute insult, has long remained elusive. In spite of extensive animal re-

search [93,94], there is a lack of methodologies applicable to humans.

Functional imaging techniques to study the brain *in vivo* are nowadays available, though they all present both significant advantages and limitation. Some measure regional blood flow and metabolic changes linked with function-related changes in neuronal firing level such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) while others, namely high resolution ElectroEncephaloGraphy (EEG), MagnetoEncephaloGraphy (MEG) and Transcranial Magnetic Stimulation (TMS), analyze the electromagnetic properties of neuronal activation.

In particular, with PET, regional cerebral blood flow (rCBF) can be measured using various radioisotopes as markers of synaptic activity, demonstrating task induced preferential blood flow [92]. Furthermore, radioisotopes can be incorporated in specific receptor ligands [125]. Use of PET is unfortunately limited by high costs and relatively poor temporal resolution because of long signal acquisition time.

Functional MRI (fMRI) relies on the paramagnetic characteristics of deoxyhemoglobin, measuring its concentration changes in brain tissue, in response to task dependent neuronal activation. The MRI scanner can detect this concentration difference and the computed signal is called blood oxygen-level dependent (BOLD) signal [5,163]. The summation of all the BOLD signals acquired repeatedly over time, permits to detect the task dependent activation with good anatomical resolution within a relatively short period. Temporal resolution in fMRI, on the other hand, if compared to the rapidity of neuronal activity is limited by the timing of the hemodynamic response (neurovascular coupling) [53, 54,85].

Therefore, both PET and fMRI pose problems in discriminating the temporal sequence of a phenomenon and in differentiating neuronal firing decrease from increase (exciting vs inhibiting net effects). For example, in the case of motor studies it is impossible to distinguish activation due to motor programming and execution secondary to sensory feedback from moving parts, as well as the chronological activation of different areas firing in rapid succession [48,76].

Transcranial brain stimulation (TMS) [11], is increasingly utilized to study brain plasticity. TMS, through a brief and intense magnetic field, is applied directly to the scalp, and it permits, by recording the evoked responses, to map the cortical representation areas located under the coil [11,114,124]. For instance, when applied over scalp regions corresponding to the motor cortex, TMS elicits a recordable electromyographic response in the corresponding muscles, called Motor Evoked Potential (MEP) [116]. Therefore, the motor output from the cortex can be somatotopically mapped [154]. Through this method it is possible to demonstrate changes in cortical maps that are use-dependent or secondary to a lesion. For example, enlargement or restriction of a cortical excitable area can be recorded, without changes in the amplitude-weighted center of the motor output maps, an area called center of gravity (CoG). This phenomenon seems to be due to recruitment or inhibition of adjacent neurons. On the other hand, the area of maximal excitability or "hot spot" can be seen to migrate, for example after an ischemic lesion, outside the usual boundaries. Such "migration" may be due to the activation of a secondary hot spot previously hidden by the predominant one, or be due to the activation of new synaptic connections.

TMS is also very useful in studying mechanisms of intracortical inhibition and excitation [135,136], which is difficult with neuroimaging methods based on blood flow, such as PET and fMRI. Advanced EEG methods, through the use of mathematical analysis of the recorded signal, allow to eliminate the contribution of volume currents, in order to obtain reference free recordings. It is therefore possible to accurately distinguish the locoregional rhythmic or transient neuronal activities produced by both tangential and radially oriented generators from discrete brain regions underlying the exploring electrode [7,9].

Another promising computational EEG approach is the analysis of the coherence of the EEG rhythms (theta, alpha, and beta) generated in different cortical areas. Coherence analysis non-invasively studies with a high temporal resolution the connectivity of different brain regions, as well as task activation related changes. Coherence EEG methods, as well as the study of the coherence between EEG and EMG signals during voluntary motor activity, are very promising and they might permit a more in depth study of neuronal plastic changes secondary to physiological brain function or to disease [90,91,129].

Magnetoencephalography (MEG) represents a non-invasive technique able to spatially identify the synchronous firing of neurons from restricted cortical areas, in relation to either spontaneous cerebral activity or in response to external stimuli. Extracerebral tissue layers overlying brain do not influence the MEG signal. MEG follows the spatial and temporal evolution of a dipolar generator source, which is modelled

as an Equivalent Current Dipole (ECD), able to explain 90% or more of the magnetic field distribution over the scalp. It has a very high time resolution, in the order of one millisecond or less. Due to its physical properties, MEG allows a precise 3D-localisation of the firing neuronal pool [160]. Besides the spatial properties, the strength of ECDs (roughly reflecting the number of neurons firing synchronously), and their orientation can also be measured while response morphology provides indirect information on the underlying neural circuitries. Decrease or increase of dipole strength can be due to restriction or enlargement of the responsive area studied, possibly because of recruitment of a fringe of neurons surrounding those usually firing in response to incoming stimuli. These variations can be secondary to dynamic phenomena, such as use-dependent modulation of synaptic efficacy, to changes of excitatory/inhibitory input from adjacent or remote lesioned brain areas (diaschisis), or to changes in the amount of sensory information. The CoG of the responsive area, in this model, is not modified by "plastic" reorganization and the ECD baricenter remains stable. On the other hand, when a brain lesion affects the main afferents and/or their target relays in primary somatosensory cortex, recovery of lost function can be achieved if an alternative neural circuitry is progressively activated. In this case, the CoG, as well as the ECD baricenter of the responsive area, are shifted in space and the response morphology is modified.

It is probably only through the integration of different neuroimaging techniques that it will be possible to overcome the pitfalls of each methodology, in the study of both normal brain function [41] as well as post-stroke recovery [113,115]. Integrated methods of functional brain imaging have been employed, thus far only in a limited number of studies, some of which will be discussed below.

4. Stroke studies

Thus, there are various factors that influence post-stroke reorganization including site and extent of the lesion, diaschisis, interindividual variability in pre-stroke organization of the motor areas and perhaps presence and amount of ipsilateral uncrossed corticospinal fibers [159]. Conceivably, if damage to a functional system is partial, recovery is more likely to occur through potentiation and extension of residual areas, while complete lesions require vicarious substitution by functionally related systems [131]. According to experimental and clinical studies, 20% of the pyramidal fibers are probably enough to restore adequate finger movement after a lesion [21,36,122,142,146,147, 153]. This strategy, utilizing within-pyramidal system reorganization, is probably one of the most effective mechanisms for functional recovery and has been documented by functional imaging studies of stroke patients. Structures normally not involved in a specific task, such as sensory cortex and secondary motor areas, are activated along with the displacement of primary motor peak activation both in subcortical [25,102,165] and cortical infarcts [27,40,132].

It is also possible to document long term plastic changes, and PET and fMRI studies have shown abnormal activation patterns during movement of paretic hands even after complete motor recovery [27,33,40, 156,157].

Peri-infarct activation is one of the potential mechanisms involved, and this has been described in experimental animal stroke models after partial damage of the primary motor cortex [93]. This feature is found in human CVA studies as well, after partial SI/MI infarction [27,40] along with ipsilesional premotor cortex activation [131] and posterior shift and inferior extension of M1 activation in both cortical and subcortical strokes. These findings suggest either disinhibition or unmasking of preexisting, yet functionally silent areas in the vicinity of the lesion, or the progressive activation of neural networks normally not devoted to the lost function [112].

Integration of TMS and MEG data has been used to document the functional reorganization of motor output that can follow a CVA [23,113,146,147]. Motor evoked potentials (MEPs) recorded over the affected hemisphere after a stroke are often abnormal compared to healthy controls [51]. Usually the changes consist of increased motor excitability thresholds, delayed response latencies and asymmetry of the motor maps between the Affected and the Unaffected Hemispheres (AH vs UH). The latter are mainly due to shifts of the Center of Gravity (CoG) of the response on the antero-posterior and medio-lateral axes. These changes tend to occur to a maximum degree within the first few months post-stroke, and become stable in the chronic stages of recovery [23,36,146,147].

The consistent finding of bilateral activation abnormalities suggests that both cerebral hemispheres play an important role in functional recovery and plastic rearrangement of neuronal networks [33,58,80]. The diaschisis-type of effects caused by acute neuronal failure at the site of a lesion may induce modulatory effects

on cortical excitability patterns of unaffected districts of both the same hemisphere (probably via cortico-cortical connections) and more remote effects on the contralateral unaffected hemisphere (via transcallosal fibres) at least for some stroke types [4,37]. Such mechanisms have been demonstrated in animal stroke models, as transient cortical hyperexcitability phenomena [19,20]. Early post-stroke cortical excitability in response to TMS has been studied as a possible prognostic tool [13,31,51,100]. Indeed MEPs from upper limb muscles seem to be consistently obtainable early on in those patients who will fully recover finger control [51,150].

It is not completely clear what role non-pyramidal fibers play in plastic recovery. Likely post-stroke reorganization of the motor cortex involving structures other than the physiological cortico-cortical connections, probably occurs over a longer time frame, requiring prolonged repetitive activation [138]. Recent fMRI studies [5,27,132] have actually shown post-stroke over-recruitment of both motor and non-motor cortical areas in either hemisphere, with displacement of the peak activation in the primary motor cortex. This acute phase bilateral hyperactivation pattern progressively decreases in time with repeated performance of a task, documenting dynamic changes in mode and degree of cortical activation which parallel clinical improvement. It must be noted, however, that enhanced activation during active motor tasks might just reflect a stronger effort to complete that performance. TMS studies have also shown increased excitability thresholds, and prolonged MEP latencies and central conduction time (CCT= conduction of the nervous impulse along the corticospinal pathways) when the AH is stimulated in the acute period after a stroke. Responses from the UH, on the other hand, have been shown to remain normal in different recording sessions, in the acute (4–72 hours), subacute (one week) and chronic stages (6 months) whenever progressive recovery takes place [110,111]. In general the differences between the AH and the UH were significant for all parameters. The responses obtained from the ipsilesional hemisphere show an evolution during follow-up, with most parameters demonstrating partial recovery. Though these remain overall abnormal at the time of final follow up, latencies of MEPs decreases and the amplitudes increase, with a tendency to return to normal. Of all neurophysiological parameters studied the interhemispheric differences between AH and UH, and particularly the excitability thresholds, are the most notable abnormalities that can be demonstrated.

MEP amplitudes recorded in the acute stage correlate significantly with the long-term clinical picture, the higher the MEP amplitude, the better the outcome. No long-term correlation can be found between type of the lesion (cortical vs subcortical) and neurophysiologic parameters.

In general, reduced TMS output is often seen after training and learning of a motor task in the healthy, or after reduction of the normal network devoted to a given function (such as a stroke). In this respect the discrepancy between the increased activation of fMRI in the studies reported above, and the decreased output during TMS is only apparent. In fact in the former the study subject is producing a voluntary movement (e.g. finger-tapping) which, because of the deficit, is quite complex and requires much effort and attention, in the latter mapping is obtained during full relaxation and representing a photograph of the remaining "hardware" still available for the function.

In another study of hemispheric motor output measured at 8 weeks (T1) to 18 weeks (T2) after a stroke, excitability thresholds are found to be significantly higher while the MEP amplitudes are smaller in the lesioned hemisphere, despite stimulation with a stronger TMS. In addition, the area of cortical output to the target muscle appears to be asymmetrically restricted, when compared both to controls and to the UH of the same patients [35]. The percentage of altered parameters is significantly higher in T1 than in T2. Furthermore, subcortical lesions show a greater number of abnormalities, possibly because of the large number of densely packed fibers affected in this type of lesion, coupled with a less efficient short-term "plastic" reorganization of subcortical structures. Cortical strokes, on the other hand, seem to be characterized by more frequent anomalous positioning of the "hot spot" sites. Despite these differences in the acute stages, neurophysiological parameters at T2 improve, overall, to the same degree in both cortical and sub-cortical strokes and acute lesion subtype does not influence clinical outcome. In 67% of cases the hand motor cortical area of the lesioned hemisphere is significantly larger in T2 compared with T1, a change that parallels clinical improvement, as measured by the Canadian Neurological Scale and the Barthel Index [35,113]. Though recovery appears to progress clinically for several months after a stroke, and various MEP parameters improved, the steepest part of the recovery slopes is concentrated in the 40 to 80 days after the acute event [148].

The contribution of ipsilateral corticospinal connections to recovery after hemispheric strokes is contro-

versial. Ipsilateral MEPs (iMEPs) have been elicited in some stroke series by TMS over the UH [28,29,56, 91,149,150] or the AH of stroke patients [2,47,149]. This is usually obtained by stimulating areas anterior and medial to MI, suggesting that the activation occurs through pathways originating in premotor areas. The relationship between clinical outcome and successful ipsilateral stimulation is variable and some authors note a positive correlation between iMEPs and motor recovery [28,29,149]. One study describes [2] an association between iMEPs produced by stimulation of the AH and bimanual dexterity 6 months after stroke, possibly reflecting hyperexcitability of the premotor areas of the lesioned hemisphere. Other authors report that presence of ipsilateral MEPs may be a negative prognostic sign [56,91,150]. It is uncertain if the iMEPs described in different studies are superimposable. In fact, while iMEPs described by some authors [28,149] have low excitability thresholds and large amplitudes, other studies using very high stimulation intensities produce only small iMEPs [150].

Paired conditioning-test TMS is a useful tool to study the mechanisms of intracortical inhibition (ICI) and facilitation (ICF) that might influence post-stroke recovery. Paired stimuli separated by programmable intervals can be delivered in fact in a conditioning/test stimulus paradigm where the 'conditioning' stimulus, depending on its timing, can depolarize or hyperpolarize a fringe of cortical neurons, causing the subsequent 'test' stimulus to impinge on them when they either are in a partial refractory state (as in ICI) or close to their firing state (as in ICF) [77]. The study of ICI/ICF in early stroke patients may indicate some mechanisms of brain plasticity.

Stroke location seems to play a role in motor cortex excitability as evidenced in a paired conditioning-test TMS paradigm (interstimulus intervals varying from 1 to 10 ms) applied to 12 patients with cortical and 9 patient with subcortical clinically stabilized strokes with resulting complete hand paralysis. Though patients in the subcortical group showed normal excitability curves, ICI was significantly reduced in the cortical stroke patients, the more recent the CVA, the greater the abnormality. In particular, the cortical group showed no transcallosal inhibition (TCI) in the active unaffected hand muscle when TMS was applied to the AH, whereas all the subcortical patients showed some degree of TCI, suggesting that the reduced ICI in cortical strokes group may be due to disruption of TCI. These findings do not seem to support the hypothesis of functional role for UH motor cortex hyperexcitability in cortical stroke recovery, at least in those patients with poor motor recovery [136].

An additional method in the assessment of post-stroke recovery is the study, via paired-pulse TMS, of the interhemispheric differences in ICI and ICF. The slopes of ICI/ICF, that have almost identical time courses in both hemispheres of normal individuals, in stroke patients, in fact were fond to be significantly different, showing a reduced ICI in the AH, and normal in the UH [34]. All these findings suggest that the relationship between ICI in the AH and UH could greatly modify post-stroke cortical plasticity and functional recovery.

Reorganization of hand and finger somatosensory areas has also been investigated via MEG methods.

Recordings of the Somatosensory Evoked Fields (SEFs) were performed in CVA patients over the controlateral parietal regions, several weeks after a monohemispheric stroke, during bilateral electrical stimulation of the median nerve, thumb and fifth finger. The the Equivalent Current Dipole (ECD) characteristics (spatial co-ordinates and strength) were calculated at 1 msec intervals in the 15–50 msec post-stimulus epoch. The cortical sensory area for the hand ("hand extension") was calculated as the distance between the centers of the ECDs activated by stimulation of the fifth and first fingers. All results were superimposed on a MEG-brain MRI common reference system, defined on the basis of anatomical landmarks. Standard SEF parameters, including interhemispheric differences and abnormality thresholds, had been previously established by performing the same experiment in a group of normal control subjects [117,142,143]. Both subcortical and cortical lesions of areas normally receiving sensory input from the hand resulted in excessive asymmetry of the MEG spatial parameters. In addition the response morphology between the UH and the AH was different. In fact the "hand extension" area (cortical sensory area for the hand) was displaced on the lesioned hemisphere in 20% of cases of subcortical, and in 13% of cortical strokes, though because of the relatively small number of subjects studied for each group it is not possible to make definitive comparisons between the cortical vs subcortical stroke subtypes. Overall a 'migration' of the sensory hand area was represented by a significant enlargement of the whole hand area, displacement of the thumb area laterally and the fifth finger more medially, and a tendency of both finger representations to shift anteriorly. The time course of the cortical responses recorded over the AH were abnormal and excessively delayed in 20% ECDs. Strength of the

ECDs also differed between the two hemispheres, being greater than normal in 25% of cases after both types of lesions. The strength of the response was increased in the AH after all cortical strokes, and only in 24% of subcortical strokes [120]. In the hemisphere controlateral to the lesion abnormal parameters were rarely recorded. Greater interhemispheric asymmetry, reflective of cortical reorganization, correlated with worse clinical recovery. These findings, particularly the enlargement of the "hand extension" areas, suggest that cortical regions outside the normal boundaries usually not reached by a significant amount of sensory input from the opposite hand may "take over" and act as somatosensory hand centers, a mechanism likely linked with sensorimotor recovery. These findings are also in agreement with post-stroke longitudinal functional imaging studies of aphasic patients demonstrating that a better outcome was associated with return of perilesional activity in the left hemisphere language areas. On the other hand, persistent activation of homologous areas in the non-dominant hemisphere has been associated with poorer recovery, possibly representing maladaptive plasticity [27,55]. There is, however, experimental evidence demonstrating an important contribution of the controlateral hemisphere to positive recovery of language function [48,101,107,144]. These findings demonstrate that a bihemispheric network might be operating and that the site associated with language function recovery after stroke likely depends on lesion volume and individual distribution of the network.

Functional MRI has also been recently used to study interhemispheric differences, using a Laterality Index (LI), as an indicator of the shift of the activity of the motor network towards the hemisphere controlateral to a stroke, as well as spatial coordinates to localize the displacement of the motor cortex peak activation [26, 30,40,86]. In clinically stable strokes LI appeared more broadly distributed than in controls because of prominent activation of the unaffected hemisphere, with consequent loss of the normal interhemispheric balance. In one study correlation between LI changes over time and motion recovery was evaluated, documenting that degree of recovery was inversely correlated to greater activation shift towards the UH ($>$ LI value) [26].

It must be noted, however, that in order to compare hemispheric responsiveness and asymmetries, the motor paradigms used by most stroke fMRI and PET studies, based on finger tapping tasks, risk to introduce important biases linked to strategies of movement programming, execution, and feedback from the paretic hand with respect to the unaffected one. Therefore, objective and standardized types of activation methods (e.g. electric shocks) may be preferable in terms of accuracy, if not in terms of spatial resolution.

Integrated methods of functional brain imaging have been employed only in a limited number of case studies. In a paradigmatic case, fMRI, TMS and MEG all agreed in showing asymmetrical enlargement and posterior shift of the sensorimotor areas of the AH [113].

Integrated use of fMRI and MEG, as well as transcranial doppler (TCD) to study cerebral vasomotor reactivity (VMR) during CO2 inhalation, has recently been applied to study the relationship between neurophysiological and cerebrovascular-metabolic findings in patients affected stabilized strokes. MEG sensory evoked fields and BOLD fMRI responses to median nerve electric stimulation were recorded in 10 normal control subjects and 10 stroke patients. The two techniques elicited detectable responses consistently in the control group, while activation was variable in the patient sample. While all patients, in fact, showed clear MEG signals in both the AH and UH, over the primary sensorimotor cortex, some patients showed no fMRI activation in either the AH or the UH. Site of the lesion, presence of white matter hyperintensities, or anatomy of the large neck vessels did not correlate with this phenomenon of neuro-vascular uncoupling, while altered vasomotor reactivity to CO2 inhalation was strongly related. These findings suggests that the lack of BOLD contrast detection could secondary to small-vessel abnormalities, possibly fMRI being more more sensitive than TCD to chronic microvascular impairment [109].

All the findings from PET, fMRI, TMS and MEG studies suggest that reorganization of motor output is ongoing for several months after a stroke. Mode and degree of motor recovery may largely depend on the extent of the damage to the previously described distributed motor network, since different motor areas operate in a parallel rather than in a hierarchical fashion and parallel descending pathways might be able to compensate functionally for each other [46]. The post-stroke interval of some studies was long enough to suggest that the observed modifications were due to corticospinal tract reorganization, rather than recovery from perilesional edema and 'early' cortical hypoexcitability. Recovery of sensory deficits can also play a significant role, since the modulation of the tonic sensory flow from the skin enveloping the target muscle significantly affects the amount of its cortical representation [119,121].

5. Conclusions

The study of neuroplasticity has rapidly expanded in the past decades, partly because of development and integration of functional neuroimaging techniques [115]. Recent studies have clearly demonstrated the ability of the adult brain not only to be shaped by environmental input in health but also to be able to a certain degree of recovery after a lesion [12]. Neuronal aggregates adjacent to a lesion seem to be able to progressively vicariate the function previously played by damaged neurons. Such reorganization significantly modifies interhemispheric differences of somatotopic organization of sensorimotor cortices and subtends clinical recovery of motor performance and sensorimotor integration. Functional brain imaging studies document that recovery from motor stroke is associated with a marked reorganization of activation patterns of specific brain structures. The recovery process, at least for hand areas, brings activation of bilateral motor networks toward a more normal intensity/extent ratio, while simultaneously over-recruiting some areas, perhaps to sustain this recovery. Considerable inter-subject variability has been found in changes of activation/overactivation patterns over time. Findings in stroke patients suggest that the AH often undergoes a significant "remodeling" of sensory and motor hand somatotopy outside the "normal" areas, and/or an enlargement of the hand representation. The UH also undergoes a reorganization process, even if to a lesser degree. Since absolute values of neurophysiological parameters fluctuate across subjects due to individual anatomical variability, while interhemispheric differences within subjects are rather limited, the study of interhemispheric functional asymmetry of the sensorimotor hand areas seems to be the parameter with the highest sensitivity in describing brain reorganization following strokes.

Mapping motor and somatosensory cortical areas through TMS, fMRI, PET, EEG and MEG is useful to investigate hand representation and to detect interhemispheric asymmetries in normal subjects and in patients. TMS and MEG allow the detection of sensorimotor area reshaping, either due to neuronal reorganization or to recovery of the previously damaged neural network. They have a high temporal resolution but suffer from limitations. TMS, in fact, only provides bi-dimensional scalp maps while MEG allows for three-dimensional identification of sources obtained by means of inverse procedures that rely on the choice of a mathematical model of the head and sources. Nonetheless, a multi-technological combined approach in which functional MRI and PET, despite their poor temporal resolution, are integrated with TMS and MEG, constitute at present, the best way to evaluate plasticity phenomena underlying partial or total recovery of hand function.

Dynamic patterns of recovery are progressively emerging from the relevant literature [112]. Firstly, enhanced recruitment of the affected MI cortex, be it spared periinfarct tissue in the case of a cortical stroke, or intact but de-afferented cortex in the case of subcortical stroke, appears to be the rule, and is especially marked in the early post-stroke stages. Transfer over time of preferential activation towards contralesional MI as observed in some cases, appears to reflect a less efficient or maladaptive type of plastic reorganization. Activation of the motor cotex in the UH MI likely reflects redistribution of activity within pre-existing bilateral motor networks, and the functional role of this phenomenon is unclear. Finally, numerous studies of post-stroke motor recovery seem to underline the importance of the premotor cortex, particularly of the UH in recovery, as well as a significant correlation between cerebellar activation and improvement in motor function [60,137]. In conclusion, since the potential for intervention in modifying the outcome and survival of most neurons after a stroke appears at the moment very limited, developing strategies to enhance plasticity and improve long-term outcome seems fundamental. Furthering our knowledge of the mechanisms regulating long-term recovery of post-stroke neurological sequelae is likely to prompt new therapeutic strategies for this invalidating human disease.

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