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Neurophysiological markers of plastic brain reorganization following central and peripheral lesions

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ABSTRACT

There is increasing evidence supporting the concept that adult brain has the remarkable ability to plastically reorganize itself. Brain plasticity involves distinct functional and structural components and plays a crucial role in reorganizing central nervous system's networks after central and peripheral lesions in order to partly or totally restore lost and/or compromised functions. This plastic rearrangement occurs in fact not only after a central nervous system injury but also following a peripheral lesion. Interestingly, the existence of a certain type of maladaptive plasticity was clearly recognized in the last decade, which gives reason for example to poor outcome performances or aberrant phenomena. In this review we analyze stroke and amputees studies, as illustrative conditions of central and peripheral nervous system damage, and discuss the adaptive as well maladaptive plastic brain changes following these lesions. The emerging possibility, through neuro-imaging and neurophysiological advanced techniques, to clarify some crucial issues underlying brain plasticity will give the chance to modulate these mechanisms in a highly personalized therapy. This approach may have a tremendous impact in a variety of neuropsychiatric disorders opening a new era of restorative medicine.

Key words

Neuroplasticity • Brain plasticity • Maladaptive plasticity • Aberrant plasticity • Stroke • Amputee • Peripheral nervous system lesion • TMS, transcranial magnetic stimulation • MEG, magnetoencephalography

Introduction: basic notions and mechanisms of neuroplasticity

Neuroplasticity is the capability of the human central nervous system (CNS) to change its organization structurally and/or functionally throughout life, in order to cope with normal and abnormal experiences and inputs from the surrounding and internal environments. Accepting this definition can be easy nowadays, but the existence of some type of neuroplasticity was an idea rejected for the most part of the 20th Century. In fact only from late 1940's, through the studies of Donald Hebb, this concept received increasing consensus and popularity. In his theoretical model, Hebb suggested that plasticity relies mainly on an increase in synaptic efficacy due to repeated and persistent stimulation of presynaptic cell on the postsynaptic one (Hebb, 1949), a mechanism now known as "Hebbian learning". Some decades later the notion of neuroplasticity was enriched by Jacques Paillard, who introduced the idea that only those changes that are both structural and functional in nature can be defined "plastic" (Paillard, 1976; Will et al., 2008). More recently, Merzenich and Colleagues has clearly shown in experimental models that the central nervous system

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undergoes huge reorganization following "central" and "peripheral" lesions (Merzenich et al., 1984). Finally, we nowadays know that the structural elements of the central nervous system (synapses, neurons, neuronal circuits and networks in the brain) are in fact capable to perceive, adapt and respond to many different types of physiological or pathological stimuli, allowing short-term to long-lasting changes in their connections and behavior (Kandel and Schwartz, 1982; Pascual-Leone et al., 1998; Rossini et al., 2003; Pascual-Leone et al., 2005; Landi and Rossini, 2010).

From a mechanistic point of view, neuroplasticity can be distinguished in developmental plasticity (when neurons in the maturing brain sprout branches and form synapses mostly as a result of environmental experiences; Pascual-Leone et al., 1998), adaptive plasticity (that underlies the acquisition of new skills, learning, memory, adaptation to new contexts throughout the life span; Rossi et al., 1998a; Rossini et al., 2013) and restorative plasticity (when the brain attempts to compensate for lost activity after a central or a peripheral nervous system damage; Rossini et al., 1994; Rossini et al., 2010; Rossini et al., 2011; Rossini et al., 2012). In such a way the nervous system looks like a continuously changing structure of which plasticity is an inner property and the necessary result of each internal and external brain communication (Pascual-Leone et al., 2005).

Moreover, neuroplasticity can be also distinguished in functional plasticity (FP) and structural plasticity (SP). In FP synapses and synaptic strengths are considered as variable amplification factors within a hardwired network structure (Butz et al., 2009). FP can be expressed through synaptic and also non-synaptic changes. In the former case changes occur in synaptic transmission characteristics (Bliss and Collingridge, 1993; Malenka and Bear, 2004) while in the latter the neuronal intrinsic excitability homeostasis is affected by means of the modulation of the voltage-gated ion channels and passive "leak" channels, together hosted in neuronal membranes and determining the integrative and excitable properties of neurons (Hansel et al., 2001; Debanne, 2009). A large number of functional mechanisms subtending plasticity are known, including the unmasking, uncovering, or activating of structurally pre-existing but functionally silent synapses (Liao et al., 1995; Palop et al., 2006), many of which have been recently discovered (Kim and Linden, 2007; Sjöström et al., 2008).

Hebbian-like long-term synaptic potentiation (LTP) and depression (LTD) were the first described and are the most studied mechanisms of FP (for reviews see Malenka and Bear, 2004; Raymond, 2007; Massey and Bashir, 2007). LTP has been proposed to underlie use-dependent and temporal correlation dependent strengthening of sensory responses in young brains, reinforcement-dependent strengthening of responses in adult brains, and strengthening of spared inputs during deprivation-induced plasticity. LTD implements use-dependent, homosynaptic and heterosynaptic weakening and therefore may mediate response depression to deprived inputs. Multiple forms of LTD exist and may have different roles in plasticity (for review see Feldman, 2009). Other mechanisms of FP are: spike timing-dependent plasticity, in which the temporal sequence and interval between pre and postsynaptic spikes drive plasticity (Meliza and Dan, 2006; Jacob et al., 2007); plasticity of GABAergic inhibitory neurons and circuits, that play several important roles in sensory map plasticity (Feldman, 2009); metaplasticity, that is a sort of "plasticity of synaptic plasticity", a series of modifications that may lead to a persistent change in the direction or degree of synaptic plasticity themselves. Metaplasticity involves a wide range of mechanisms, many of which overlap with the mechanisms of conventional plasticity and appears to involve both NMDA and metabolic glutamate receptors (Abraham and Bear, 1996; Abraham, 2008). It is a form of homeostatic plasticity and it was hypothesized to counteract the inherently unstable, positive-feedback nature of Hebbian synaptic plasticity (Bear et al., 1987).

In contrast to any forms of functional plasticity, SP changes anatomical connectivity among neurons, modifying synaptic connectivity patterns, synapse numbers and extension, axonal and dendritic branching patterns, axonal fiber densities and even neuronal numbers. Very rapid structural changes (hours to days) occur continuously at the level of spines and synapses; spine formation and retraction are associated with synapses formation and elimination (Kleim et al., 1996; Florence et al., 1998; Trachtenberg et al., 2002; Holtmaat et al., 2005). Thus, rapid changes in the synaptic knob as well as in new synapses formation and elimination may

contribute to rapid experience dependent plasticity. In contrast, large-scale structural changes involve macroscopic axonal projections including thalamocortical and horizontal, cross-columnar axons and, to a lesser extent, dendrites (Fox and Wong, 2005; Broser et al., 2008). These are considered to be slow, as they act in several days or weeks (Trachtenberg and Stryker, 2001). The more recently discovered – and maybe the most important mechanism of SP – is "synaptic rewiring". It occurs when a synapse is destroyed due to the loss of its pre- or postsynaptic element and involves at least three neurons (Feldman, 2009). Synaptic rewiring consists in joining the remaining synaptic counterpart with an unengaged synaptic element from another neuron (Butz et al., 2009). Thus, the formation of a synapse between two neurons by synaptic rewiring depends on the breaking of a synapse between another pair of neurons. Synaptic rewiring is particularly relevant in the context of adult neurogenesis (Butz et al., 2006) and it substantially contributes to the correct synaptic integration of new cells (Nudo, 2007; Butz et al., 2008).

In the last decade an additional notion to neuroplasticity was studied, that is the existence of a type of "aberrant" plasticity. In fact, besides the findings that brain plasticity acts in the acquisition of new skills and compensates for the loss of function (Hosp and Luft, 2011; Dayan and Cohen, 2011), it has been reported that injury and excessive training drive neural plasticity in a maladaptive direction (Flor et al 1999, 2008; Quartarone et al., 2006): in effect it was named "maladaptive plasticity". This neural plasticity contributes, among others, to the pathogenesis of phantom limb pain in amputees pain (Flor et al 1999; Flor, 2008), dystonia (Quartarone et al., 2006), and more recently was also associated to weaker motor functions and worse motor recovery after stroke (Murase et al., 2004; Duque et al., 2005; Takeuchi et al., 2007, 2012). The principal mechanisms underlying these maladaptive plastic changes are related to a loss of GABAergic inhibition, glutamate-mediated long-term potentiation-like changes and structural alterations such as axonal sprouting (Flor, 2008).

In modern neuroscience to shed light and deeply comprehend the main mechanisms of brain plasticity (both the adaptive and even more the maladaptive ones) is a crucial point. After a central as well as peripheral nervous system damage, the understanding of what happens in cortex can be extremely important in order to decide where, when and (mostly) how to intervene in a specific case to individualize therapies and/or rehabilitation strategies, providing the best possible treatment for that individual patient.

In this article we first will provide a brief description of the main neurophysiological techniques used to study neurophysiological markers of plastic brain reorganization following central and peripheral lesions (for a comprehensive review see Rossini and Ferreri, 2013). Then, we will describe stroke studies (as paradigmatic example of central nervous system damage) and studies conducted on amputee patients (as paradigmatic example of peripheral nervous system lesion).

Main neurophysiological techniques used to study brain plasticity

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a safe, noninvasive, and painless technique today widely employed in investigations of brain plasticity (Kobayashi and Pascual-Leone, 2003; Rossini and Rossi, 2007; Guerra et al., 2011). In TMS short current pulses are driven through a coil positioned on the scalp of the subject (Barker et al., 1985). The transient magnetic field generated in the brain produces an electrical current able to depolarize the cell membrane, resulting in opening of voltage-gated ion channels and consequently giving rise to the action potential. The classical assumption is that the activation of pyramidal neurons by TMS occurs predominantly via inter-neurons in superficial cortical layers (Di Lazzaro et al., 1999). The electric field induced by TMS depends on the position and orientation of the coil over the head of the subject and also by structural anatomical features and by the local conductivity of the scalp itself (Fox et al., 2004). TMS permits the non-invasive stimulation of underlying cortical representation areas (Basso et al., 2006) and when applied over the scalp regions corresponding to the motor strip, it triggers a transient and recordable electromyographic response in the connected "target" muscles, called motor evoked potential (MEP, Rossini et al., 1985). Different types of stimulation are possible: in this section we will

briefly discuss several different paradigms according to the hemisphere under examination.

Paradigms that permit to study the stimulated hemisphere's properties

– *Single pulse TMS*
When applied on the scalp overlying the M1, single-pulse TMS allows to assess the excitability and conductivity of corticospinal motor pathways. The amplitude, area under the curve, and latency of MEPs are all used in various ways to measure motor cortical excitability. The resting motor threshold (rMT) is defined as the minimum stimulator's output able to elicit reproducible MEPs (at least 50 μV in amplitude) in at least 50% of 10 to 20 consecutive stimuli at rest (Rossini et al., 1994a). rMT is predominantly influenced by mechanisms of neuronal membrane excitability, evidenced by its alteration in the presence of pharmacological modifiers of sodium and calcium channels and relative stability in the presence of modifiers of synaptic transmission (Ziemann et al., 1996; Chen et al., 1997; Ziemann, 2004).
– *Motor mapping*
By means of primary motor cortex (M1) mapping is possible to obtain several measures, including: the "hot spot" (the scalp position of maximum response), the map area (the sum of excitable scalp points) and the "centre of gravity" (an amplitude-weighted centre of the map, CoG; Rossini et al., 1994a). Changes in the CoG should indicate true changes in the topographical organization of motor cortex representations (Ferreri et al., 2003; Ferreri et al., 2011a; Guerra et al., 2014a).
– *Paired pulse - one location*
Paired pulse stimulation delivered through the same magnetic coil over M1 can be used to gain insight into the relative contribution of local inhibitory and excitatory inputs to M1 pyramidal tract cells. The most common parameters used to evaluate the intracortical inhibitory/facilitatory balance are the short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), that are likely to be mediated by GABA-A and glutamate, respectively (Kujirai et al., 1993; Ziemann, 2004; Ferreri et al., 2011b). These measures are fairly symmetrical in the two hemispheres of healthy subjects and are highly reproducible in a test-retest paradigm in the same subject, as well as across different subjects, being only partly influenced by the experimental conditions (Shimizu et al., 1999; Ferreri et al., 2006; Guerra et al., 2014b).
– *Contralateral cortical silent period*
When a single suprathreshold TMS pulse is applied during a constant muscle contraction there is an interruption of the electromyographic signal, which is called "cortical silent period" (CSP). When the drop in EMG activity is measured in a muscle contralateral to the stimulated hemisphere it can be defined "contralateral" CSP (cCSP) and it has been proposed to be a GABA-B receptor mediated cortical phenomenon (Ziemann, 2004).
– *Short-latency afferent inhibition (SAI)*
The phenomenon called "short-latency afferent inhibition" is thought to depend on neural interactions within the cerebral cortex (Tokimura et al., 2000; Di Lazzaro et al., 2004). It could involve either direct inhibition of motor cortex from fast conducting afferents, or withdrawal of tonic facilitation from other structures such as the thalamus and its generation seems to depend on central cholinergic activity (Di Lazzaro et al., 2000; Ferreri et al., 2012).

Paradigms that permit to study the effects exerted by one hemisphere on the other one

– *Paired pulse - two locations*
A TMS suprathreshold pulse applied over the M1 of one hemisphere rapidly (6-50 ms later) followed by another magnetic stimulus delivered over the opposite hemisphere permits to study the "interhemispheric inhibition" phenomenon (IHI; Ferbert et al., 1992). IHI is likely mediated via transcallosal glutamatergic neurons from the conditioning M1 interacting with local GABA-B receptor mediated inhibitory interneurons within the target M1 (Daskalakis et al., 2002; Chen, 2004).
– *Ipsilateral cortical silent period*
When the CSP is measured in a muscle ipsilateral to the stimulated hemisphere it can be defined "ipsilateral" CSP (iCSP). It represent another form of measuring interhemispheric inhibition and it is produced at cortical level via a transcallosal route (Ferbert et al., 1992; Meyer et al.

1998), however being likely mediated by different subsets of transcallosal neurons and different interactions with local inhibitory circuits with respect to IHI (Chen et al., 2003; Trompetto et al., 2004).

EEG-TMS

EEG-TMS is a very promising tool that permits the co-registration of the EEG activity – which has a temporal resolution of a few milliseconds – during TMS. Thus, it allows measuring directly the local and early electrical response of cortical neurons to TMS, while bypassing subcortical, sensory, and motor pathways therefore enabling a non-invasive, finally direct, method to study brain's cortical excitability and time-resolved connectivity (Ilmoniemi et al., 1997; Virtanen et al., 1999; Ilmoniemi and Kičić, 2010). A network of neuronal connections is in fact engaged when TMS-evoked activation extends from a stimulation site to other parts of the brain and the summation of synaptic potentials produces deflections in scalp EEG signals, starting a few milliseconds after stimulus and lasting about 300 ms, first in the form of rapid oscillations and then as lower-frequency waves (Komssi et al., 2004; Bonato et al., 2006; Ilmoniemi and Karhu, 2008; Ferreri et al., 2011b; Ferreri et al., 2012, Ferreri et al., 2014b; for review see Ferreri and Rossini, 2013). The characteristics of these responses are thought to depend on the stimulation intensity and functional state of the stimulated cortex as well as the overall brain. Particularly, it has been suggested that the very first part of the TMS evoked EEG potentials (TEPs) reflects the excitability – that is the functional state – of the stimulated cortex while its spatio-temporal distribution over the scalp reflects the spread of activation to other cortical areas via intra and inter-hemispheric cortico-cortical connections as well as to subcortical structures and spinal cord via projection fibres – that is the effective connectivity of the stimulated area (Lee et al., 2003; Komssi and Kähkönen 2006). However, these components are not an constant pattern since in addition to interindividual differences, the responses depend on the exact coil location (Komssi et al., 2002) and orientation, on the state of the cortex (Nikulin et al., 2003; Ferreri et al., 2014a) and on the vigilance of the subject (Massimini et al., 2005).

Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive and very high time resolution technique able to detect the electromagnetic fields produced by active neurons. It can identify and provide a precise three-dimensional location of neurons that are synchronously firing, either spontaneously or in response to an external stimulus, in restricted cortical areas (Williamson and Kaufman, 1990). MEG follows the spatial and temporal evolution of a dipolar generator source, which is modeled as an Equivalent Current Dipole, able to explain 90% or more of the magnetic field distribution over the scalp. The strength of the dipoles roughly reflects the number of neurons firing synchronously 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, or to changes in the amount of sensory information (Rossini and Dal Forno, 2004).

Neurophysiological markers of plastic brain reorganization following a central nervous system damage: stroke studies

What happens in the affected hemisphere (AH) after the stroke?

In this section we will describe neurophysiological markers obtained from the affected hemisphere after the stroke, reviewing mainly TMS and MEG studies. We will discuss modifications of MEP and motor threshold, changes in intracortical inhibition and facilitation networks and plastic reorganization of motor and somatosensory cortices.

Evaluating MEPs amplitude obtained stimulating the AH is the easiest and immediate way to examine motor cortex excitability and it is also an useful tool for prognostic purposes. In fact during the acute stroke stage (hours or days) TMS even at maximum stimulation intensity often fails to elicit any MEPs and the absence of response is associated with a poor

functional outcome (Heald et al., 1993; Pennisi et al., 1999; Trompetto et al., 2000; Alagona et al., 2001; Rossini et al. 2003). Several studies demonstrated that MEP amplitude from AH had a positive correlation with the clinical presentation and with long term outcome, the higher the MEP amplitude, the better the outcome (Cicinelli et al., 1997; Traversa et al., 1997; Traversa et al., 2000). Moreover, Stinear and colleagues in 2007 showed that paretic limb MEP presence predicted meaningful gains in chronic stroke patients receiving motor rehabilitation; furthermore, within the subgroup of patients in whom MEPs could not be evoked in the paretic hand (theoretically predicting poor prognosis), functional outcome was poorer in patients with greater posterior internal capsule fiber disruption, as measured by MRI diffusion tensor imaging (Stinear et al., 2007). During the subacute-chronic stage of the disease MEPs may re-appear (Cicinelli et al., 1997) but this event has not sufficient predictive value for clinical recovery (Hendricks et al., 2002; Delvaux et al., 2003; Rossini et al., 2003). When MEPs are elicitable, the responses are generally smaller than those evoked from the UH or from normal subjects (Rossini et al., 2003; Rossini et al., 2007). In line with the data presented above, the rest (rMT) and active (aMT) motor thresholds on the AH tend to be higher than on the UH or in normal subjects, both in acute and post-acute stages (Heald et al., 1993; Catano et al. 1995; Turton et al., 1996; Liepert et al. 2000; Cicinelli et al., 2003) and they generally decrease gradually over time (Turton et al. 1996; Traversa et al., 1997). Another parameter which deserves to be considered, obviously only when the MEPs are present, is the central motor conduction time. It is usually a little bit delayed in the acute phase after stroke (Catano et al., 1995; Nardone and Tezzon, 2002) and it can be either prolonged or normal in the post-acute stage (at least in these cases when MEPs are firstly absent and after reappear; Pennisi et al., 1999). However, contradictory reports exist regarding the predictive value of normal acute and post-acute central motor conduction time (Rossini et al., 2007). Also the MEPs latency is altered stimulating the AH of stroke patients: longer MEP latencies are common compared to healthy subjects, and are more evident in the early stages after the injury (Cortes et al., 2012).

Other characteristic features of the AH emerged from motor mapping studies. In fact an excessive asymmetry of the hand muscle motor maps between the AH and UH can be seen. Generally, the AH shows a restriction of the excitable area in acute/subacute stroke stages compared both to UH and to control patients, with a subsequent relative enlargement in the chronic stage (Cicinelli et al., 1997; Traversa et al., 1997; Chieffo et al., 2013). Interestingly, Thickbroom and colleagues in 2004 demonstrated that in patients with subcortical ischemic stroke a tendency for a larger map area positively correlate with motor recovery (Thickbroom et al., 2004). The other aspect highlighted in mapping studies is the migration of the excitable area (typically seen along the mediolateral axis) outside the usual boundaries, possibly due to a lesion affecting the brain district where the "hot spot" is. The "migration" may be apparent and due to the activation of a secondary hot-spot previously hidden by the predominant one, or in fact may be real and due to the progressive activation of new synaptic connections (Cicinelli et al., 1997; Traversa et al., 1997; Traversa et al., 1998; Byrnes et al., 1999). These changes tend to maximally occur within the first few months post-stroke, and become stable in the chronic stages of recovery. Some differences about these parameters in acute-subacute stage can be done according to the location of the stroke. In fact subcortical lesions show a greater number of abnormalities (such as a smaller motor map), 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 improve in chronic stage, overall, to the same degree in both cortical and sub-cortical strokes and acute lesion subtype does not influence clinical outcome (Cicinelli et al., 1997; Traversa et al., 1997; Rossini and Dal Forno, 2004).

Further insights in plasticity mechanisms after stroke came from the study of short intracortical inhibition (SICI) and facilitation (ICF). A decrease in SICI in AH have been consistently reported in the literature both in the acute and chronic stage (Liepert et al., 2000; Manganotti et al., 2002; Cicinelli et al., 2003; Wittenberg et al., 2007; Butefisch et al., 2008), although assessing changes longitudinally, it does

seem that acute disinhibition may normalize over time (Manganotti et al., 2008; Swayne et al., 2008; Dimyan and Cohen, 2010). On the contrary, ICF remains consistently normal both in acute both in chronic stages (Shimizu et al., 1999; Liepert et al., 2000; Shimizu et al., 2002; Cicinelli et al., 2003). This pattern (reduced SICI and normal ICF) suggests an unbalance of excitability in intracortical circuits towards excitation. This motor cortex disinhibition may be secondary to the remote effects of structurally intact areas (that is the diaschisis) and/or to the pre-existing organization of the motor areas (that is the amount of ipsilateral uncrossed corticospinal fibers) (Weiller, 1998; Rossini et al., 2003) and probably cause the rapid motor improvement seen in some patients. However, the correlation between the measures of intracortical inhibition (or also its changes) and function at any particular stage of the disease may be highly dependent on initial characteristics of the single patient (Butefisch et al., 2003; Manganotti et al., 2008; Swayne et al., 2008). In effect, Liepert and colleagues in 2005 found some kind of correlation between the lesion location and the pattern of motor excitability changes; in particular they suggested that motor cortex lesions exhibited deficient inhibitory properties and, in contrast, subcortical lesions displayed an enhancement of inhibition (Liepert et al., 2005).

In the years, other neurophysiological paradigms were used to investigate intracortical inhibition of AH. For example some researchers examined the contralateral cortical silent period and they found that it has a longer duration in the acute stroke phase and shortens during recovery (Kukowski and Haug, 1992; Classen et al., 1997; Liepert et al., 2000). Although there is some suggestion that the amount of shortening correlates with the recovery of hand function (Cicinelli et al., 1997; Traversa et al., 2000; Liepert et al., 2005) the exact relationship between silent period and motor function has not been exhaustively described in the literature (van Kuijk et al., 2005). A recent study also evaluated the short-latency afferent inhibition (SAI) in acute stroke: the authors found a reduction of SAI in the AH and highlighted a correlation between SAI and the modified Rankin Scale Score at six months. Thus they suggested that the reduced inhibitory function of the ipsilesional M1 in acute stroke patients could promote motor recovery (Di Lazzaro et al., 2012).

Another extremely useful technique adopted to study cortical plastic reorganization after a stroke is the MEG.

In effect several MEG studies demonstrated a functional rearrangement in the primary somatosensory cortex of the damaged hemisphere post-stroke and also provided very interesting insights about the prediction of clinical outcome. For example our group proved that in patients suffering from monohemispheric stroke of middle cerebral artery territory affecting the upper limb, the ipsilesional hand's sensory area shows a significantly larger cortical topography with respect the contralateral one; these findings suggest that brain areas outside the normal boundaries and usually not reached by a significant amount of sensory input from the opposite hand and fingers may act as somatosensory hand centers (Tecchio et al., 2000). Further insights to this view were provided one year later, when the same group demonstrated that some differences occurs according to the lesion topography (cortical *vs*. subcortical stroke; Rossini et al., 2001).

Regarding the correlation with prognosis, MEG findings in subacute and chronic stroke patients unable to reach a complete recovery showed a clear positive correlation between clinical outcome and amount of interhemispheric asymmetry of cortical neuronal sources recruited by a sensory stimulus from the hand (Rossini et al., 1998; Rossini et al., 2001; Rossini et al., 2003, Tecchio et al., 2006a). Furthermore, studying rest neuronal activity properties, frequency-selective alterations were found related to specific dysfunctions in subacute and chronic stroke phase. In fact, global clinical status was mostly impaired in patients with larger lesions and increased total and slow band activity powers, whereas hand functionality was mostly disrupted in patients with subcortical involvement and reduction of high frequency rhythms and spectral entropy (Tecchio et al., 2006b). A similar role of gamma band oscillatory activity was also found in the acute phase: in fact its reduction was direct linked with less severe clinical status (Tecchio et al., 2005). MEG, combined with brain source reconstruction algorithms and connectivity metrics, was also recently used to predict functional outcome in stroke (Westlake et al., 2012). Fourteen subjects affected by monohemisperic ischemic stroke in the territory of the middle cerebral artery with

prominent deficit of the hand were studied. Results showed a correlation between the improvement in motor recovery and changes in MEG-based alpha band functional connectivity, both in the perilesional area and contralesional cortex. In particular, a better motor recovery was found to be correlated with high functional connectivity value at baseline in ipsilesional primary motor and somatosensory cortex (Brodmann Areas 3 and 4) but also with reduced connectivity in contralesional sensorimotor regions.

What happens in the unaffected hemisphere (UH) after the stroke?

In this section we will describe neurophysiological findings from the unaffected hemisphere after the stroke.

Generally, stimulating the UH is possible to find out within normal limits values of rMT, aMT, MEP amplitude, CMCT, motor map both in acute (Liepert et al., 1998; Pennisi et al., 1999; Alagona et al., 2001; Shimizu et al., 2002; Butefisch et al., 2003) and in chronic stages during motor recovery (Traversa et al., 1998; Shimizu et al., 2002; Fridman et al., 2004). Apart from these global considerations, some deviation from the "norm" could be highlighted. For example, sometimes, MEPs amplitude elicited from the UH may been enhanced in the hyperacute stage (the first 24 hours) after stroke (Rossini et al., 2007). Moreover, a recent study focused on subcortical stroke patients highlighted an acute increased excitability in the UH after stroke that normalizes at chronic stages; very interestingly the authors found that this hypexcitability has a negative prognostic value on recovery and negatively affects motor performance of the ipsilesional hand. They also suggested that the normalization of this parameter at follow-up indicate that the UH primary motor area does not contribute to recovery (Chieffo et al., 2013). A little, non significant difference between relaxed MEPs and active MEPs from the UH can be also described: in fact while the former remain normally stable over time, the others became smaller (although within normal limitis); on the contrary active MEPs from the AH increase over time (Cicinelli et al., 1997; Traversa et al., 1998). This pattern could reflect progressive interhemispheric balancing of excitability and is more prominent in patients with subcortical strokes. More interestingly, if no recovery occurs on the affected side, active MEPs from the UH become "giant" MEPs, leading to further interhemispheric excitability "unbalancing" (Rossini et al., 2007). Occasionally, also in UH motor map some differences occur from "normality": in fact, in patients with poor recovery persisting anomalous hot spots mirroring AH changes were reported (Cicinelli et al., 1997).

Also the study of intracortical inhibitory and facilitatory circuitry of the UH provided more interesting insights. Several authors reported a significant SICI reduction in UH in acute (Nardone and Tezzon, 2002; Manganotti et al., 2002; Butefisch et al., 2003; Manganotti et al., 2008) and subacute (Liepert et al., 2000) stoke patients, as compared to age matched controls. On the contrary ICF is generally normal, although could be a tendency for facilitation (Liepert et al., 2000; Shimizu et al., 2002), and measurements of cortical silent period after stimulation of the UH are consistently normal (Cicinelli et al., 1997; Liepert et al., 2000). These data clearly reflect the downregulation of GABA activity in UH, possibly due to damage of transcallosal fibers and loss of the physiological interhemispheric inhibitory modulation (Ferbert et al., 1992; Boroojerdi et al., 1996; Leocani et al., 2000; Liepert et al., 2001). Another alternative or also complementary mechanism to explain these findings could be the enhanced use of the unaffected arm in daily activities, since ICI is modified in a task and use-dependent manner (Liepert et al., 1998). Moreover, the UH disinhibition is probably the cause of the enlarging MEP amplitudes trend found by stimulating this hemisphere (Cicinelli et a., 1997; Traversa et al., 1998; Trompetto et al., 2000). Longitudinal studies demonstrated that UH acute disinhibition may normalize over time (Manganotti et al., 2008; Swayne et al., 2008). However, Shimizu and colleagues in 2002 showed that normalization of SICI in patients with longer disease duration and poor recovery does not support the functional significance of UH motor cortex hyperexcitability (Shimizu et al., 2002). Some interesting findings regarding the role of the UH came also from EEG and MEG studies. In fact, they demonstrated that UH delta band power could be considered a predictive factor for prognosis. In particular, a symmetry of spectral power between the two hemispheres is associated with mild neurological deficits (Sheorajpanday et al., 2011), on the contrary the presence of a large amount of delta

waves in the UH (Tecchio et al., 2007; Finnigan et al., 2008) or only an asymmetry across the hemispheres (Finnigan and van Putten, 2012) can reveal acute worsening with a poor recovery.

What is the effect exerted by one hemisphere to the other one?

In the last decade great attention to the study of functional interrelation between UH and AH was given by the scientific community. In effect brain connectivity is highly related to brain plasticity phenomena and cannot be overlooked. The main electrophysiological parameter used, at least in stroke studies, to evaluate transcallosal neurophysiology is the interhemispheric inhibition (IHI; see above).

IHI between the two M1s is likely altered after stroke, possibly in a lesion-location dependent manner (Boroojerdi et al., 1996).

IHI from the AH to the UH was not univocally described: in fact it was demonstrated to be reduced in patients with cortical and subcortical lesions in one study (Butefisch et al., 2008), but on the contrary it was similar to healthy controls in two other studies (Boroojerdi et al., 1996; Lewis and Perrault, 2007). However, Boroojerdi and colleagues demonstrated a more pronounced inhibition in patients with purely subcortical lesions compared to cortical-subcortical stroke patients. Differences in inhibitory networks were highlighted also by measurement of iCSP: in fact some studies demonstrated no iCSP in the unaffected hand after a single TMS pulse to the AH in cortical stroke patients and presence of some degree of iCSP in the subcortical ones (Boroojerdi et al., 1996; Shimizu et al., 2002; Perez and Cohen, 2009). In addition, a very recent study revealed an association between prolonged iCSP in the UH at acute stroke stage and more severe clinical impairments, but the absence of any type of prognosis prediction for this parameter at chronic phase (Takechi et al., 2014).

At rest, IHI from the UH to the AH was showed to be present and similar to healthy controls regardless of the infarct location (Murase et al., 2004; Butefisch et al., 2008). On the contrary, extremely interesting results arose by analyzing the pre-movement IHI: several studies demonstrated that in chronic and relatively well recovered stroke patients, initially normal IHI levels from the UH to the AH remain abnormally deep at the onset of paretic hand movement, in contrast to the facilitation that accompanies non-paretic hand movement (and also movement in age matched controls) during a simple reaction time task (Murase et al., 2004; Duque et al., 2005). So, these results could be interpreted with the existence of an abnormally high interhemispheric inhibitory drive from UH to AH in the process of generation of a voluntary movement by the paretic hand (Dimyan and Cohen, 2010).

The study of the effect exerted by one hemisphere to the other one in stroke led to the formulation of the "interhemispheric competition" model, in which a damage to one hemisphere bring to a disruption in the balance of inhibition that exists in healthy subjects. In particular, according to this model, a stroke in one hemisphere causes a reduced inhibition of the UH by the AH, resulting in increased inhibition of the AH by the UH. So, the AH is thought to receive a double damage: the direct injury due to the stroke itself and the indirect damage due to the excessive inhibition from the UH. This model was also supported by many studies which proved that contralesional sensorimotor primary areas activation inversely correlates with the degree of motor performance recovery (Loubinoux et al., 2003; Fridman et al., 2004; Schaechter, 2004; Ward and Frackowiak, 2006). On this basis, the inter-hemispheric imbalance explained above could be regarded as an expression of "maladaptive plasticity" (Rossini and Dal Forno, 2004), more than of restorative plasticity, as interpreted several years ago by the "vicariation" model (according to which the activity in residual networks – included the UH areas – substitutes for those functions lost by damaged regions).

Anyway, a very recent article from our group focusing on the modulation of brain plasticity in stroke provided new interesting insights regarding the possible plastic mechanisms acting during and after a stroke (Di Pino et al., 2014). In particular, we proposed to move beyond the current models of plasticity (the old "vicariation" model and the more recent "interhemispheric competition" model) and suggested to focus the attention on a new parameter never considered before, the "structural reserve", that is the extent to which neural pathways and relays spared by the lesion contribute to recovery in an individual patient. So a bimodal balance-recovery model has been introduced, in which the amount of structural reserve determines whether interhemispheric imbalance dom-

inates over vicariation. In according to this model, if the structural reserve is high, the interhemispheric competition model can predict recovery better than vicariation model, which is more useful in predicting recovery in patients with little structural reserve (Di Pino et al., 2014).

Therefore, the key-point emerging from this modern model of post-stroke brain plasticity is the crucial role assumed by the inter-individual differences in stroke patients, regarding for example the lesion location, size and typology (haemorragic *vs*. ischemic) and the time elapsed after the stroke (acute *vs*. subacute *vs*. chronic). Only in this context is really simple to understand the not always homogeneous findings resulted from past neurophysiological studies.

To conclude, many evidences demonstrated that in stroke patients the affected hemisphere shows: hypoexcitability of M1 that in acute correlates with the clinical outcome, reduced inhibitory function of the primary motor cortex and functional rearrangement in the primary somatosensory and motor cortex (with asymmetry of the hand muscle motor maps and migration of the excitable area outside the usual boundaries); on the other hand the unaffected hemisphere exhibit normal or even increased excitability parameters of M1 (with some differences according to the stroke location) and acute disinhibition that may normalize over time. Moreover was clearly demonstrated the existence of an inter-hemispheric imbalance, that consists in an abnormally high interhemispheric inhibitory drive from UH to AH, which could worsen, at least in some kind and/or stages of the stroke, the recovery of function.

What happens during and after rehabilitation?

Several studies also focused on neurophysiological changes during and after post-stroke rehabilitation, providing insights in mechanisms underlying the beneficial effects of therapeutic interventions; in this section we will describe some of them briefly, only for demonstration purposes.

One of the first experiments in this regard consisted in neurophysiological monitoring before and after constraint-induced movement therapy (Liepert et al., 2000b). Authors demonstrated that the small motor output maps present at baseline in the AH increased in size after therapy by around 40%. On the contrary, the UH motor map was consistently, even if not significantly, decreased comparing with the baseline. Being these changes associated with significant clinical improvement, authors concluded that results were presumably due to increased use of the paretic arm and decreased use of the non-affected arm during training. Moreover, motor threshold (that was abnormally high in AH before therapy) was unaffected and, because motor threshold is determined at the centre of the cortical map, it was concluded that enlargements of the motor output map were caused by an increase in excitability at the borders of the map by GABA dependent modulation of horizontal intracortical inhibitory circuits (Liepert et al., 2000b). Few years later Hamzei and colleagues provided interesting insights in constraint-induced therapy beneficial effects, also regarding different stoke locations. In particular, using TMS measures of local inhibition and functional magnetic resonance imaging (fMRI) in chronic subcortical and cortical stroke patients, the authors demonstrated that functional improvement from constraint-induced therapy was accompanied by decreased fMRI activity and decreased SICI in the ipsilesional M1 only in the subcortical group, while opposite effects were found in patients with lesions in M1 or the corticospinal tract. So they concluded that the beneficial effects of this therapy might be mediated at least partially by modulation of intracortical inhibition within ipsilesional M1 (Hamzei et al., 2006).

Further insights came from Harris-Love and colleagues, which explored transcallosal inhibition by means of iCSP in moderately impaired chronic stroke patients after a single session of reaching practice. They found that benefits of this therapy is accompanied by decreased transcallosal inhibition only in the trained muscles, implying a specific and differential change in physiology that may contribute to the behavioral gains (Harris-Love et al., 2008). More recently, an interesting study was performed, that used MEG to evaluate plasticity in motor networks before and after 2 weeks of intensive task-oriented therapy (Wilson et al., 2011). MEG data were imaged using beamforming and the resulting event-related synchronizations and desynchronizations were subjected to region-of-interest analyses. Results demonstrated a reduction of in post-movement beta synchronization and during-movement gamma synchronization in the affected primary motor and supplementary motor cortices

after the therapy. So they discuss that these reduction in cortical synchronization may indicate that the intervention brings inhibitory function back toward more homeostatic levels, enhancing network efficiency in motor cortices.

Stroke and maladaptive plasticity

As discussed above in the other sections of this paragraph, some of the neurophysiological markers identified in the last two decades could be now interpreted as maladaptive plasticity stroke-related phenomena. In effect some factors influence maladaptive plasticity in motor-related areas after stroke, possibly interfering with the clinical recovery.

For example, in stroke patients with moderate-severe hemiparesis, compensatory/substitutive movements of the nonparetic limb and/or the use of trunk and proximal limb of the paretic side (the so called "compensatory movements") may induce maladaptive plasticity and limit genuine motor recovery after stroke, despite the improvement in daily activities performance (Takeuchi et al., 2012). In fact, dominant use of the nonparetic limb induces the phenomenon of learned nonuse of the paretic limb, which limits the capacity for subsequent gains in motor function of the paretic limb (Taub et al., 2006; Levin et al., 2009). These findings suggest that the AH becomes vulnerable to post-stroke experience with the nonparetic limb and that this nonparetic limb experience may drive neural plasticity in a direction that is maladaptive for functional outcome (Allred and Jones, 2008; Takeuchi et al., 2012).

Another crucial factor influencing maladaptive plasticity is the already cited interhemispheric "competitive interaction", resulting from the unbalanced changes that occur in both hemispheres after stroke. In fact, at least in some cases, hyperexcitability of the UH (possibly activated by the use of the nonparetic limb) inhibits the AH through abnormal interhemispheric inhibition and restricts motor recovery in stroke patients (Takeuchi et al., 2012).

Neurophysiological markers of plastic brain reorganization following a peripheral nervous system damage

The acute transient or permanent loss of nervous flow bidirectionally to and from a limb causes a deprivation-dependent neural reorganization involving both cortical and subcortical areas, mainly due to the consequent perturbed sensory experience. This reorganization involves both the topographical and functional representation of the missing limb in the nervous system. Thus, in the last two decades a large number of studies have clearly shown the existence of brain plasticity phenomena not only after a CNS damage but also following acute or chronic peripheral nervous system (PNS) lesions (Stavrinou et al., 2007; Rossini et al., 2011; Rossini et al., 2012; for review see Di Pino et al., 2009).

Studies from acute peripheral nervous system damages: ischemic limb deafferentation or similar

Studies that investigated neuroplasticity markers after an acute PNS damage are relatively few, obviously according to clinical priorities and the particular typology of such patients. Anyway, researchers avoided this problem by developing several experimental settings that reproduce this type of damage (e.g., transient ischemic nerve block, local anaesthesia or limb immobilization).

Brasil-Neto and colleagues were the first group in studying this experimental model: they investigated reorganization in motor cortex by using TMS before, during and after anesthetic block of the forearm and hand. A manifold increase of MEP amplitude in muscles proximal to deafferentation site that returned to baseline within 20 minutes was evident, suggesting a temporary increase in motor cortex excitability for those muscles adjacent to the anesthetized ones (Brasil-Neto et al., 1992). One year later they replicated this data by using a transient ischemic nerve block (INB) obtained by a pneumatic tourniquet: in fact results showed an increase in corticospinal excitability in muscles proximal to the INB within 7-8 minutes following application of the tourniquet. In that study Authors also proved the cortical origin of the phenomenon: in fact the amplitude of MEPs elicited by either transcranial electrical stimulation or spinal electrical stimulation, and of H-reflexes elicited by peripheral nerve stimulation, did not change in the presence of an INB (Brasil-Neto et al., 1993).

In the following years other groups confirmed these data (Ridding and Rothwell, 1995; Ridding and Rothwell, 1997; Ziemann et al., 1998; McNulty et al., 2002) and enriched them with other considerations. In particular researchers showed that muscles

proximal to an INB have steeper input/output curve slopes (Ridding and Rothwell, 1995) and larger motor representation maps (Ridding and Rothwell, 1995; Ridding and Rothwell, 1997). Moreover, no changes in SICI, ICF and LICI (at inter-stimulus interval of 80 ms) circuits was found (Ziemann et al., 1998; Vallence et al., 2012), providing evidences that none of these processes alone can explain the rapid plastic changes induced by INB.

Other studies documented short term plastic changes of cortical sensorimotor organization following manipulation of sensory input. For example it has been observed by means of MEG that cortical topography accompanying voluntary movements is strongly modified by deprivation of cutaneous feedback from the moving hand (Kristeva-Feige et al., 1996) and that fingers anaesthesia induces short-term enlargement and lateral or medial shifts of the parietal cortical representation of the unanesthetized finger (Rossini et al., 1994b). Another interesting MEG study come from Stavrinou and colleagues: they analyzed the temporal dynamics of plastic changes in primary somatosensory cortex following transient webbing of 4 fingers together for several hours and observed a decrease in the distance between cortical sources activated by electrical stimuli to the index and small finger 30 minutes after webbing, followed by an increase lasting for about 2 hours after webbing and then a return toward baseline values (Stavrinou et al., 2007). TMS studies conducted before and after an anaesthetic block of median and radial nerve (testing in effect a condition in which all the cutaneous and some of the proprioceptive inputs from a wide part of the hand are suppressed) documented a transient and rapid reduction in cortical motor maps of muscles surrounded by anaesthetised skin; on the contrary no modification or even a tendency of cortical topography enlargement was found in neural pools controlling muscles adjacent but outside the anaesthetized area (Rossini et al., 1996, Rossi et al., 1998b).

In conclusion, the prove of deafferentation-induced short-term plasticity in the human motor cortex was given. Due to the rapid nature of these changes, the underlying suggested mechanism involves the disinhibition of existing intracortical circuits (Cohen et al., 1993; Hallett et al., 1999), which produces an increase in the size of receptive field in the cortical map of the territories close to the cortical representation of the lost part (Calford and Tweedale, 1988; Chen et al., 1998). In fact, the reduction of GABA fast inhibition of excitatory synapses is considered to be the substrate of the main early mechanism of CNS reorganization after amputation, that is the unmasking of anatomically present but functionally inactive connections (Di Pino et al., 2009).

Studies from chronic peripheral nervous system lesions: post-amputation brain plasticity

The perfect model of a chronic PNS lesion is obviously the amputee patient. In effect is in this context that researchers can investigate late and stable brain plasticity changes in somatosensory and motor systems, as a result of the deafferentation and deefferentation.

Following an amputation, the primary sensory cortex deafferented areas become progressively responsive to inputs from the parts of the body adjacent to the missing one in the cortical somatotopic sensory map. In other words, body parts adjacent to the missing one in the Penfield “homunculus” shift their cortical representation toward that of the missing body part (Flor et al., 1995; Knecht et al., 1996; Elbert et al., 1997; Grusser et al., 2001; Karl et al., 2001). This phenomenon was proposed to be due to loss of input from the lost part combined and summed with increased use-dependent input from the contralateral extremity and from the stump (Elbert et al., 1997). Moreover, some authors described an expansion of receptive fields of thalamic neurons and nuclei, demonstrating also a subcortical involvement following the amputation (Lenz et al., 1998; Davis et al., 1998). Regarding the motor system it can be stated that a remarkable post-amputation plastic reorganization is evident in the deefferented primary motor cortex too. In 1991 Cohen and colleagues demonstrated that motor cortex stimulation via TMS in amputees evokes larger motor-evoked potentials and at a lower intensity of stimulation, and that stump muscles could be activated from a larger area than from the contralateral cortex controlling the intact limb, thus showing the enhancement of excitability in the motor cortex areas representing muscles contiguous to the amputation line (Cohen et al., 1991). The increase in size and excitability (reduction of rMT and increasing of MEP amplitude with respect the homologous muscles on the intact side) of the cortical map of stump muscles at the expense of the miss-

ing limb representation was subsequently described by most authors (Pascual-Leone et al., 1996; Chen et al., 1998; Dettmers et al., 1999; Karl et al., 2001), despite some different challenging views are present in literature (Gagnè et al., 2011). Other studies demonstrated the possibility to evoke movements or muscle contractions of parts of the body that are represented in the cortical somatotopic map adjacent to the missing body part stimulating the cortical area previously devoted to the missing limb (Fuhr et al., 1992; Kew et al., 1994; Ridding and Rothwell, 1995; Chen et al., 1998; Roricht et al., 1999; Irlbacher et al., 2002). However, the modality of the cortical "invasion" discussed here above is not univocally described; in fact while some studies found that the stump muscle representation invaded the hand representation resulting more lateral than the homologous muscle's representation (Dettmers et al., 1999; Schwenkreis et al., 2001; Irlbacher et al., 2002), others found it was more medial (Karl et al., 2001) or that there was no difference (Roricht et al., 1999). Anyway, some recent studies provided evidences that the motor representation of the missing hand can survive in the amputees' brain despite the absence of targeted muscles, maintaining in time a residual amount of responsiveness and retaining at least some "memories" of motor functions of the lost limb (Calford, 2002; Wall et al., 2002; Theoret et al., 2004). Furthermore, movement related activity in primary motor and sensory cortices may still be found years after amputation (Mercier et al., 2006; Reilly et al., 2006; Gagne et al., 2011).

Amputation and maladaptive plasticity: the phantom limb syndrome

Like for brain plastic reorganization following a CNS damage, even in amputees adaptive cortical changes (e.g. the enlarging of somatosensory representation of the stump which increases sensory discrimination attempting to partially compensate for the loss of the limb) can occur together with maladaptive plasticity phenomena. In fact in a variable percentage of 50-80% of amputees after amputation, a painful dysesthesic perception in the lost limb called phantom limb syndrome (PLS) is observed, which is a further cause of disability (Ephraim et al., 2005). The pathophysiological substrate of PLS has to be found in aberrant cortical reorganization's phenomena and nowadays this syndrome is widely considered as a maladaptive correlate of neuroplasticity (Flor et al., 1995; Flor et al., 2006). In particular, after an amputation a discrete number of fibers survives and redundant connections (moreover with multiple parallel pathways) appear, so relays between CNS and peripheral nerves are not completely canceled but unfortunately they are involved in this aberrant reorganization (Flor et al., 1995). Authors demonstrated a strong association between sensory and motor cortices changes and PLS, but not with non-painful phantom sensation (so called "phantom awareness" or "phantom sensation"; Flor et al., 1995; Flor et al., 1998; Grusser et al., 2001, Hunter et al., 2003; Karl et al., 2004). More recently other authors hypothesized that activation of the hand movement representations (survived in primary motor cortex of amputees) is necessary for the experience of phantom movement (Mercier et al., 2006).

Very interesting insights on maladaptive plasticity in amputees recently came from studies regarding the use of innovative nerve-interfaced hand prosthesis (Carrozza et al., 2004; Carrozza et al., 2006; Rossini et al., 2010; Raspopovic et al., 2014). In fact, after the implant of cybernetic hand and 4 weeks of training, a clear restriction of the cortical excitable area of representation of muscles adjacent to the stump was demonstrated by means of TMS mapping, that was in parallel with decrement of PLS symptoms (Rossini et al., 2010). Moreover, a normal modulation of background rhythms for movement preparation (α/β band desynchronization) in the sensorimotor area contralateral to the missing limb was regained, the α band synchronization of Rolandic area with frontal and parietal ipsilateral regions was restored (Tombini et al., 2012) and a normalization of functional balance of the directly-connected control areas within the bi-hemispheric system necessary for motor control was found (Di Pino et al., 2012).

Finally, a very recent EEG-TMS study from our group (Ferreri et al., 2014b) demonstrated, for the first time in a direct manner, the cortical plastic aberrant changes induced by the amputation itself (with evidence of partial disruption of the rearranged hemisphere N46 wave's dipole, probably representing M1 functionality, and abnormal anterior displacement of its positive pole) and clear redirection toward restorative neuroplasticity after training with the hand prosthesis (with regaining of the N46 posi-

tive pole's normal location and reduction of cortical M1 excitability).

Concluding, as happens after a CNS lesion, also after a PNS lesion plastic brain changes and rearrangement phenomena can be clearly highlighted. In fact, after a peripheral acute damage, studies demonstrated an increased corticospinal excitability in proximal muscles, short and long term plastic changes of cortical sensorimotor organization, with larger motor representation maps, and no clear changes in intracortical inhibitory or facilitatory circuits.

Particularly in amputees the deafferentation and deefferentation with loss of sensory inputs and of muscle target motor control deprivation cause a remarkable somatosensory (with body parts adjacent to the missing one in the homunculus that shift their cortical representation toward that of the missing body part) and motor (with an increase in size and excitability of the cortical map of stump muscles at the expense of the missing limb representation) cortices rearrangement.

Summary

Providing a brief overview on neurophysiological studies in stroke and amputation we wanted here to outline that brain plasticity can occur not only after a CNS damage but also following a PNS lesion, not only in subacute or chronic stage but also in the acute or hyperacute phase of diseases. There is increasing evidence to support the concept that brain plasticity involves distinct functional and structural components, each requiring multiple cellular mechanisms working at distinct synaptic loci, timescales and developmental stages within an extremely complex framework (Feldman and Brecht, 2005; Feldman, 2009). In the past ten years these concepts have also been introduced in clinical settings by means of techniques that have revealed a continuous plasticity/connectivity modulation driven by many physiological and pathological conditions, as well as many similarities and differences across cortical areas (Ferreri and Rossini, 2013). An improved knowledge of neuroplasticity basic mechanisms and the awareness of their constrains would strengthen the possibility to guide the plastic potential of the brain, opening a broader field of new therapeutic and research perspectives (Platz and Rothwell, 2010). This may have a tremendous impact on future research efforts in a variety of neurological disorders even though much methodological work is still needed in order to fully unfold its potentiality in providing substantial new insights in the mechanisms underlying human brain physiological and pathological neuro-plasticity (Siebner et al., 2009).

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