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Clinical evidences of brain plasticity in stroke patients

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ABSTRACT

Emerging findings deriving from neuromodulation and neuroradiology are providing us new insights about plasticity and functional reorganization of the brain after stroke, but the direct clinical assessment of motor function should still be considered an indispensable tool for the evaluation of the effects of plasticity in stroke patients.

Recovery of motor function can be spontaneous or guided by training. Substantial functional recovery can occur spontaneously especially in the first month post-stroke. Instead, the guided recovery may take more time and may rely on a number of rehabilitation techniques which proved to be capable of stimulating cerebral plasticity. Even the time course of these processes is a decisive element. First, it is important to correlate the trends of plasticity after stroke, from the enhancement of earlier periods to the later stages, to the behavioral changes observed. Furthermore, it is crucial to distinguish recovery of function occurring through improvement of motor deficit from compensatory mechanisms, distinction that has also an effect on timing of recovery. Another relevant question is the maintenance over time of the improvements reached with the treatment, feature on which various clinical studies have been conducted in acute and chronic stroke patients.

Further studies are needed to allow us to get a more precise definition of the potentiality of functional recovery and of the mechanisms underlying the recovery depending on its levels and timing. Understanding the mechanisms, the effects and the limits of neural plasticity may eventually help enhancing the recovery process in stroke patients, significantly improving the quality of life of these patients. Then, a greater attention towards the clinical implications of the changes related to plasticity can be a crucial element to further improve the therapeutic options used in neurorehabilitation.

Key words

Stroke • Plasticity • Motor recovery • Neurorehabilitation • Clinical evaluations

Introduction

Stroke is one of the most important leading causes of chronic disability: one year after the acute event, approximately one-third of stroke survivors – regardless of whether it is ischemic or hemorrhagic stroke – has a high degree of disability, which makes them totally dependent (SPREAD Guidelines, 2012). Recovery of these deficits depends on several factors, among which a key factor is brain plasticity.

Brain plasticity is an intrinsic property of the nervous system to change its function and to reorganize after a lesion or environmental changes, which involves developing new neuronal interconnections and acquiring new functions in order to compensate the damage (Pascual-Leone et al., 2005). Plasticity is believed to be important in a wide range of neurological diseases: in addition to stroke, changes linked to plasticity have been found in disorders like Parkinson's Disease (Calabresi et al., 2007), Multiple Sclerosis (Mezzapesa et al., 2008) and dystonia (Quartarone et al., 2005). An important concept about plasticity is its homeostatic nature. Plasticity can be thought as the result of the balanced

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interaction between mechanisms driving to change and mechanisms promoting stability (Turrigiano, 1999). Recently, Guerra et al. (2014) described a case of unilateral change of cortical excitability in an ambidextrous and multilingual woman with congenital symmetrical hydrocephalous which may represent a mechanism of plasticity to preserve functionality of specific brain areas devoted to some special skills (such as multilingualism).

Plasticity is termed adaptive when leads to a behavioral gain. One of the most important mechanisms is the phenomenon of activity-dependent strengthening of synaptic transmission, known as long-term potentiation (LTP). It is also possible to highlight a weakening of synaptic connection, known as long-term depression (LTD).

Various forms of plasticity have been investigated extensively using various protocols of non-invasive brain stimulation (NIBS). For instance, transcranial magnetic stimulation (TMS) methods have been used to measure LTP-like and LTD-like mechanisms of cortical plasticity in the primary motor cortex (M1) but also in the supplementary motor areas (Dayan et al., 2013).

Even neuroradiology, with the spread in recent years of functional neuroimaging (Favre et al., 2014, Rehme et al., 2012), allowed us to investigate task-related activity patterns bringing to light new intriguing evidences about cortical reorganization.

In any case, despite the emerging technologies in the fields of neuromodulation and neuroradiology, a key role is still played by clinical evaluation, through which can be obtained a direct assessment of the effects of plasticity in stroke patients. In this review, our aim is to bring back attention to the clinical implications of the changes related to the plasticity, trying to understand how to further improve the therapeutic options actually used in neurorehabilitation. So, the main topics discussed in the following sections consist in the clinical evaluation of motor recovery, with its methods and timing, along with a look into the mechanisms underlying recovery in stroke survivors.

Functional recovery and its clinical assessment

Functional recovery could be defined as the restoration of function with resumption of the previous activity with characteristics comparable to those pre-stroke. This recovery can be appreciated at different levels: as improvement of motor deficit, as improvement of motor control, as improvement in functional activities of daily living (ADLs) and as improvement in participation in the community.

In general the most used scales for motor recovery evaluation could be divided between those assessing global aspects (i.e. the Barthel Index for ADLs) and those specifically assessing clinical function in one body part (i.e. Action Research Arm Test, ARAT, for upper limb).

The evaluation of ability in ADLs has been widely used as a main outcome measure after stroke (Kelly-Hayes et al., 1998) and reducing the degree of dependence in ADLs is one of the central aims of rehabilitation treatment in stroke patients. The prediction of ADL function at an early stage enables clinicians to select the best treatment programs and goals for these patients (Kwakkel et al., 1996).

Partial or complete motor recovery of upper limb, even after initial paralysis, represents an important example of the recovery potential of the brain (Hendricks et al., 2002). If we consider the upper limb recovery, the initial measures of upper limb impairment and function were found to be the most significant predictors of upper limb recovery (Coupar et al., 2011). In particular, the evaluation of active finger extension proved to be a strong and reliable early predictor of recovery of arm function in stroke patients (Smania et al., 2007). Moreover, initial shoulder shrug and initial presence of synergistic hand movement predict good hand movement and function (Katrak et al., 1998). Combining the early assessment of the movements of the hand and shoulder, the EPOS cohort study (Nijland et al., 2010) found that the evaluation of voluntary extension of the fingers and abduction of the hemiplegic shoulder within 72 hours after stroke predict upper limb function at 6 months (measured with the ARAT scale). Moreover, Stinear et al. (2012) outlined an algorithm, called PREP algorithm, to predict upper limb motor recovery including as a key factor the SAFE score, that is a measure of shoulder abduction and finger extension evaluated with MRC scale 72 hours after stroke onset. With this algorithm, they tried to stratify various levels of functional recovery according to clinical and neurophysiological evaluations and trying to define the goals of rehabilitation basing on that prediction.

Despite several scales have been used in different trials, this methodological heterogeneity makes quite difficult a results comparison across various studies and consequently the exhaustive understanding of the efficacy of rehabilitative intervention is lacking. In fact, the choice of a given outcome measure (rather than another one) can significantly influence the results of a study. A way to minimize or solve this problem might be the definition of feasible clinical guidelines, that are universally recognized and followed, with a smaller range of outcome measure basing on the type of patient and deficit. This would help in improving post-stroke clinical assessment in order to increase comparability between research articles.

Nevertheless, there is still a substantial unexplained inter-individual variability in the capacity for motor recovery that cannot be explained with clinical assessment. Prabhakaran et al. (2007) assessed motor recovery in 41 stroke patients with FMA Motor Score (administered between 24 and 72 hours after stroke onset and at 3 and 6 months follow-ups), finding that clinical variables could explain only 47% of the variance in recovery. Anyhow, they found that among the patients with the most severe initial impairment, there was a set of regression outliers who shows a very poor recovery. When these outliers were removed, clinical variables were good predictors of recovery among the remaining patients, showing a tight proportional relationship to initial impairment.

Recovery: spontaneous or guided?

Spontaneous recovery

"Spontaneous" recovery occurs without any specific training or intervention. Data from studies conducted on rodents and primates prove that they exhibit spontaneous recovery after stroke (Cramer, 2008); substantial functional recovery can occur spontaneously also in humans, especially in the first month post-stroke. Among the factors recognized to contribute to the extent of spontaneous recovery certainly have to be counted infarct size, infarct location, age and pre-stroke degree of disability.

In any case, it is not easy to define the "spontaneous" recovery in humans, also because to maintain a standard and uniform control group receiving "standard and usual care" is a critical aspect of clinical trials in rehabilitation (Nudo et al., 2011).

One of the mechanisms underlying spontaneous recovery is due to "diaschisis" reversal. "Diaschisis" is a phenomenon that follows focal injury to the brain (Feeney & Baron, 1986) and is represented by a reduction of metabolism and blood flow in intact brain regions outside of the ischemic core. It is thought that at least a part of the early functional recovery observed in both animal models and human stroke subjects must be attributable to the reversal, or resolution, of diaschisis, in those brain region that are anatomically distinguished but functionally connected with the injury core (Nudo et al., 2011).

An important question is that behavioural changes that improve function may not correspond to the occurrence of true recovery (Krakauer et al., 2006). For example, a reduced time to execute a motor task, for example on an assessment like FMA, could be due to functional improvement but also to compensation with the proximal and axial muscles that contribute to the propulsion of the limb forward in attempting to reach an object. In this case, a global functional improvement on clinical evaluations may correspond to residual significant impairment in kinematics and kinetics of the affected limb.

Recovery guided by training

Another chapter is recovery guided by training. Intensive practice remains one of the most important methods to promote motor recovery in stroke patients (Kwakkel et al., 2006): together with other key features (early initiation after the event, task-oriented and context-specific treatment), it has been extensively demonstrated to enhance neural plasticity after stroke. In healthy subjects, motor training elicits cortical plasticity that encodes the kinematic details of the performed movements and is believed to be underlying the recovery of function after stroke. So the practice provokes use-dependent plasticity (UDP) and may result in encoding adaptive strategies for subsequent recall, making them available for the future behaviour (Pascual-Leone et al., 2005; Hummel & Cohen, 2005). In the last years, different forms of UDP have been studied in the literature in animals and humans. These practice-dependent changes of cortical plasticity can be modified by pharmacological interventions [suggesting that this form of plasticity relies on adrenergic (Sawaki et al., 2003a) and cholinergic neurotransmissions (Sawaki et al., 2002)], or enhanced by the combination of

Table I. - Main clinical scales used for basic and instrumented ADL ability and global motor recovery evaluation in stroke patients. Furthermore, clinical scales for trunk control and dysphagia assessment are mentioned.

Basic ADL ability	
Barthel Index (BI)	Assessment in 10 items of patient's ability to care for him/herself (Mahoney & Barthel, 1965).
Functional Independence Measure (FIM)	A measure of patient's disability with the indication of the level of assistance required for the patient to carry out ADL (Granger et al., 1993).
Instrumented ADL ability	
Frenchay Activities Index	Specific assessment for stroke patients of a wide range of activities of daily living (with items concerning domestic, leisure/work, and outdoor activities). The rating depends on self-reports by patients and caregivers (Schuling et al., 1993).
Philadelphia Geriatric Center (PGC) Instrumental ADL Scale	A simple measure of general functioning with questions on activities necessary for independent living (i.e. the telephone use, shopping, food preparation, walking etc.) (Lawton, 1988a; Lawton, 1988b).
Global motor evaluation	
Fugl-Meyer Assessment (FMA)	A feasible, well-designed and widely used scale for global clinical examination. The total score obtained can be divided in 5 different items: sensibility, pain, passive motion, active motion and balance (Fugl-Meyer et al., 1975; Gladstone et al., 2002).
Rivermead Motor Assessment (RMA)	An assessment that measures gross motor function, upper limb abilities, lower limb abilities and trunk control (Lincoln and Leadbitter, 1979).
Chedoke-McMaster Stroke Assessment	This scale measures the physical impairment and disability and the impact of the disease on the lives of stroke patients with the following purposes: to stage motor recovery in order to classify individuals in terms of clinical characteristics, to predict rehabilitation outcomes, and to measure clinically important change in physical function (Gowland et al., 1993).
Trunk control evaluation	
Trunk Control Test (TCT)	A test to examine some aspects of trunk movement in four different positions (rolling to weak side, rolling to strong side, sitting up from lying down and sitting in a balanced position on the edge of the bed, with the feet off the ground) (Collin & Wade, 1990).
Dysphagia evaluation	
Gugging Swallowing Screen	A quick and reliable method to identify stroke patients with dysphagia and aspiration risk (Michaela Trapl et al., 2007).

high-frequency repetitive TMS and motor training (Koganemaru et al., 2010). Other studies showed that UDP is reduced in healthy elder adults relative to younger individuals: the ability of the motor cortex to reorganize in response to training decreases with age (Sawaki et al., 2003b).

In recent years, a range of rehabilitation techniques have proved to be potentially capable of stimulating cerebral plasticity. Between these techniques, great interest was dedicated to new therapeutic approaches focused to improve motor function, like action observation therapy, motor imagery, mirror therapy, constraint-induced movement therapy, robotic-aided therapy and virtual reality.

Motor imitation is a complex cognitive function that includes several stages, among which action observation, motor imagery and motor execution.

Action observation can be used therapeutically through the observation (actual or by displaying a video) of another individual performing the trained motor task, by exploiting the existence of mirror-neuron system (Rizzolatti et al., 2004). Action observation therapy has been suggested as an important way to enhance training effects on UDP, being able to promote motor recovery, playing a role in memory formation (Celnik et al., 2008) and possibly in motor learning (Stefan et al., 2005) by engaging similar brain regions to action execution. The hallmarks of this kind of treatment may be especially useful in individuals with limited mobility.

Motor imagery is the mental execution of a movement without performing any overt movement or without muscle activation, while mental practice is the training method by which motor imagery is used with the aim of enhancing performance: the learning effects of mental practice may be explained by a top-down mechanism based on the activation of a central representation of the movement (Mulder et al., 2004; Mulder, 2007). It has been demonstrated that not only action observation but also motor imagery results in the activation of the same brain areas as real movement, realistically promoting the same plastic changes. Nevertheless, a review about the effects of a mental practice intervention on recovery in stroke patients (Braun et al., 2006) reported that clear definitions of the content of mental practice strategies and standardized measurement of outcome are needed, also because the mechanisms underlying are still not completely understood.

Mirror therapy was originally developed to reduce phantom limb pain in amputees: the reflection of the movements of non-amputated hand or arm in a vertical parasagittal mirror gave patients the sensation of having both moving arms, resulting in a decrease of pain (Ramachandran et al., 1995). At the end of Nineties, Altschuler et al. (1999) introduced mirror therapy for recovery of hemiparesis after stroke, showing that motor performance of chronic stroke patients improved. Later, randomized controlled trials have also reported the effectiveness of mirror therapy in improving motor function in subacute (Yavuzer et al., 2008) and acute (Dohle et al., 2009) stroke patients. More recently (Michielsen et al., 2011), 40 chronic stroke patients with moderate upper limb paresis underwent 6-week training program, 20 subjects with mirror therapy and 20 subjects with control treatment. After the treatment, the FMA improved more in the mirror than in the control group, but the improvement did not persist at 6 months follow-up. The results were associated with cortical reorganization: a shift in the balance of activation within the primary motor cortex toward the affected hemisphere was observed in the mirror group only.

Constraint-induced movement therapy (CIMT) involves the restriction of the use of the unimpaired upper limb to promote the increase of use of the contralesional limb. CIMT is a method initially used for upper limb rehabilitation, before a modified and extended version was also used for the rehabilitation of the lower limb and for the treatment of other diseases (Uswatte & Taub, 2012). A prospective, single-blind, randomized and multisite clinical trial (The Extremity Constraint Induced Therapy Evaluation, or EXCITE, trial) (Wolf et al., 2006) demonstrated that CIMT produced statistically significant and clinically relevant improvements in arm motor function of subacute and chronic stroke patients, as measured with Wolf Motor Function Test and Motor Activity Log. Moreover, studies in animals and humans provided the evidence that CIMT is able to produce structural and functional plastic changes in motor cortex (Liepert et al., 1998). An intriguing and promising approach to provide therapy to guide recovery is the use of robotic technology. Many studies investigated whether robotic-aided therapy can reduce motor impairment and enhance functional recovery.

For upper limb, Volpe et al. (2008) compared the robot-aided training with conventional treatment in chronic stroke patients, showing a substantial equivalence in functional outcome measured with scales like FMA, ARAT, Modified Ashworth Scale, Motor Power Scale for Shoulder/Elbow. Another trial (Housman et al., 2009) made a comparison between semiautonomous robotic training with an exoskeleton and conventional training using tabletop support, both of them in a gravity-supported environment. Even if patients' preferences and motivations were widely oriented toward robotic therapy, scores on FMA for upper limb at the end of the treatment were in practice equal to conventional training group scores, while in the 6-month follow-up emerged an improved benefit of about 2 points on FMA for robotic group scores (even though the global and functional clinical difference was meaningless). Liao et al. (Liao et al., 2011) tested a bilateral robotic-assisted treatment finding significant differences in functional outcome between robotic treatment and conventional therapy, differently from what assessed by Volpe et al. (2008) and Housman et al. (2009). Those differences were clearer in the improvement of ADL autonomy. The results are explained through the major treatment intensity and duration (90-105 minutes per session and 5 sessions a week, rather than 30-60 min per session 3 times a week, as seen in the other studies) and with the supplement of a functional rehabilitation training focusing on daily activities (for the duration of 15-20 min). Another arm robotic exoskeleton was also proposed by Frisoli et al. (2011) to design a training strategy in chronic stroke patients providing "assistance as needed", according to the force capability of

Table II. - Main clinical scales used for upper limb assessment in stroke patients.

Upper limb assessment	
Wolf Motor Function Test (WMAT)	A time-based method to evaluate upper extremity function while providing insight into joint-specific and total limb movements (Wolf et al., 2001).
Action Research Arm Test (ARAT)	Assessment of upper limb function using observational methods (De Weerdt & Harrison, 1985).
Jebsen Taylor Hand Function Test (JTT)	A widely used and well validated test for functional motor assessment of a broad range of hand functions used in activities of daily living (Hummel et al., 2005).
Box and Block Test	Unilateral assessment of gross manual dexterity (Mathiowetz et al., 1985).
Nine Hole Peg Test	A simple and quick assessment for finger dexterity (Grice et al., 2003).
Motricity Index (MI) - arm scores	The arm scores of Motricity Index are used to measure strength in pinch grip, elbow flexion (from 90°) and shoulder abduction (Demeurisse et al., 1980).

the patient, together with an automatic measurement of movement parameters. The evaluations included a clinical evaluation (FMA, Modified Ashworth Scale, Bimanual Activity Test) conducted before and after the 6-weeks treatment, compared to the scores and the quantitative indices, such as task time, position/joint error and resistance torques, associated to the training exercises. The correlation of clinical and instrumental evaluations has proven an interesting way to increase the spectrum of evaluations.

An attempt to step forward and investigate the mechanisms related to the effects of robotic-aided training on motor control has been done recently in a case series study (Chisari et al., 2014) that tested the efficacy of Lokomat in gait retraining in 15 stroke patients, evaluating the effects using FMA score, Berg Balance Scale, 10 metres Walking Test, Timed Up and Go test and 6 Minute Walking Test, resulting in a significant improvement after the training in all scales (except 10 metres Walking Test). Strength and Motor Unit firing rate of Vastus Medialis were also recorded and analyzed: no increase of force was observed whereas a significant increase of firing rate of Vastus Medialis was recorded, suggesting an effect of training on motorneuronal firing rate that may contribute to the improvement of motor control. In any case large effect size and robust effects of robotic treatment have not yet been fully demonstrated.

Finally, therapies involving immersive or non-immersive virtual reality technologies have been proposed. The interest for these therapies is related to the possibility to add feedback during therapy (Kiper et al., 2014), to increase the motivation of patients towards the therapy and to modulate online the different difficulty of therapy (Lohse et al., 2014). The current evidence on the efficacy of using virtual reality in the rehabilitation of stroke patients is still not sufficient because the results of the published studies are practically conflicting (Henderson et al., 2007).

Recovery: main mechanisms and timing

Main mechanisms underlying motor recovery

Recovery of motor function can occur through improvement of motor deficit, improvement of motor control or compensatory mechanisms. The first two mechanisms are considered as the true recovery and they represent the regaining of the same (or close to the same) prestroke movement patterns (by the reduction of impairment). Instead, compensation means using alternative movements to perform the motor task (i.e. using different muscle groups, joints, or effectors) (Levin et al., 2009).

Neural plasticity is the means by which the brain compensates for the loss of motor function after stroke. In particular, adaptive plasticity underlies the acquisition of new skills, learning, memory, adaptation to new contexts throughout the life span (Rossi et al., 1998; Hosp and Luft, 2011). Moreover in the last decade it has been investigated a different type of neural plasticity linked to the injury and to excessive training (Quartarone et al., 2006; Flor, 2008), named “maladaptive plasticity”. Clinically, the importance of this phenomenon has been underlined in some relevant function like the vicariation of the distal upper limb movements with compensatory or substitutive movements and the delayed-onset involuntary abnormal movements (for a complete review see Takeuchi & Izumi, 2012). Nevertheless there is a lack of definitive evidence regarding the recognition of motor function-related maladaptive plasticity (Jang, 2013). An important issue is if maladaptive plasticity could be considered as a part of the functional recovery or, on the contrary, a harmful phenomenon that should be avoided and, if present, corrected by the clinicians. A contribution that would go in this direction comes from some studies that have shown the correlation between maladaptive plasticity and weaker motor functions and consequently between maladaptive plasticity and worse motor recovery after stroke (Murase et al., 2004; Duque et al., 2005; Takeuchi et al., 2007). Following that, for a successful stroke rehabilitation treatment, it would be important to recognize accurately the characteristics of maladaptive plasticity and for this purpose a thorough evaluation of neurological state using brain mapping techniques may be useful.

The timing of recovery

The timing of recovery is strongly related to stroke severity at the onset: recovery is slower in those patients destined to have less successful outcomes (Cramer, 2008). Jørgensen et al. (1995) reported that functional recovery was completed within 12.5 weeks from stroke onset in 95% of the patients. However, best ADL function (assessed with BI) was reached within 8.5 weeks in patients with initially mild strokes, within 13 weeks in patients with moderate strokes, within 17 weeks in patients with severe strokes and within 20 weeks in patients with very severe strokes.

As we reported above, recovery of function can occur through restoration of function (by means of an improvement of motor deficit or an improvement of motor control) or compensatory mechanisms and the timing of recovery is clearly influenced by the mechanism involved.

Motor deficit recovers mainly within the first 3 months from the event, as a result of both spontaneous reorganization and increased responsiveness to enriched environments and training (Zeiler & Krakauer, 2013). Duncan et al. (1992) reported a clinical follow-up on stroke patients evaluated with FMA, concluding that most of the variability in motor recovery can be explained by 30 days after stroke.

Motor control was investigated by Van Kordelaar et al. (2014) in 44 ischaemic stroke patients performing 3-dimensional kinematic measurements to measure modifications in smoothness of upper limb movements in the first 6 months poststroke. They found the most significant contribution of progress of time during the first 5 weeks poststroke (reductions in movement duration and normalized jerk of hand transport and grasp opening).

Finally, it seems that the third mechanism (functional compensation) is developed for more time than the others: it can occur at any time after stroke, mainly beyond the sensitive period (Zeiler & Krakauer, 2013). In fact, in chronic stroke patients, Kitago et al. (2012) showed that functional improvement in the affected arm obtained with a constraint-induced movement therapy were mediated by compensatory strategies rather than a decrease in impairment or return to more normal motor control.

Persistence of improvements in acute and chronic stroke patients

Another relevant question is the maintenance over time of the improvements reached with the treatment.

Taking into account the patients with acute stroke, Masiero et al. (2007) performed a single-blind randomized controlled trial, with an 8-month follow-up, including 35 patients randomly assigned to two groups. Patients of both groups received the same dose and length per day of standard poststroke rehabilitation. The experimental group received additional early sensorimotor robotic training for upper limb (4 hours a week for 5 weeks). The control group was exposed to the same robotic device, 30 minutes a week, twice a week, but the exercises were performed with the unimpaired upper limb. Patients who received robotic therapy in addition to conventional therapy showed greater reductions in motor impairment and improvements in functional abilities, as measured by the MRC scores on deltoid and biceps, and by the FMA for the proximal upper arm; these gains were sustained at the 3- and 8-month follow-up.

Even in chronic stroke patients, Liepert et al. (2000) firstly demonstrated that the significant improvement in motor functions can be durable. They used a CIMT protocol, performing clinical evaluation with Motor Activity Log at 2 weeks and 1 day

Table III. - Main clinical scales used for balance, gait and lower limb evaluation in stroke patients.

Balance, gait and lower limb assessment	
Berg Balance Scale (BBS)	A scale to assess the ability to maintain balance, either statically or while performing functional movements, and to evaluate fall risk. It comprises 14 tasks common to everyday life (Bronstein & Pavlou, 2013).
Tinetti Falls Efficacy Scale	An evaluation of the perception of balance and stability during activities of daily living (Tinetti et al., 1990).
Six-minute walk test (6MWT)	Subjects are instructed to "walk as far as possible in six minutes", without encouragement (Eng et al., 2002)..
10-Meter Walking Test (10mWT)	Participants walk for 10 meters while being timed so that their walking speed may be calculated (Morganti et al., 2005).
Timed Up and Go Test (TUG)	In this test subjects are asked to stand up from a chair, walk for 3 meters, walk back and sit down again, while the time necessary to complete the exercise is recorded (Schoene, 2013).
Dynamic Gait Index (DGI)	DGI assesses individual's ability to modify balance while walking in the presence of external demands (Jonsdottir & Cattaneo, 2007).
Functional Ambulation Category (FAC)	Assessment of functional ambulation dividing walking ability in 5 broad categories (Mehrholz et al., 2007).
Motricity Index (MI) - leg scores	The leg scores of Motricity Index are used to evaluate strength in hip flexion, knee extension and ankle dorsiflexion (Demeurisse et al., 1980).

before treatment and at 1 day, 4 weeks and 6 months after treatment: the behavioural gains persisted in 6-months follow-up (as confirmed by electrophysiological data).

Afterwards, in the already cited EXCITE trial (Wolf et al., 2006), a 2-weeks CIMT protocol was used including patients who had a stroke within the previous 3 to 9 months, resulting in substantial improvements in arm motor function that persisted in a 2-year follow-up (Wolf et al., 2008).

As mentioned above, Volpe et al. (2008) in a randomized controlled study administered an intensive robot-aided training to chronic stroke patients to understand if it was still possible to improve motor outcome in these subjects. Robotic training and an intensive conventional therapy improved the impairment measures of motor outcome significantly and comparably and motor gains were maintained at the 3-month follow-up after training.

Finally, a multicentric, randomized, controlled trial published by Lo et al. (2010) was conducted on 127 chronic stroke patients with moderate-to-severe upper limb impairment (49 assigned to intensive robot-assisted therapy, 50 to intensive comparison therapy, and 28 to usual care) who underwent an intensive therapy of 36 sessions of 1 hour over a period of 12 weeks. At the end of the treatment, the mean FMA score showed that robot-assisted therapy did not significantly improve motor function, as compared with usual care or intensive therapy, while, in a secondary analyses conducted over 36 weeks, robot-assisted therapy improved outcomes as compared with usual care but not with intensive therapy, showing in any case the persistence of the effects obtained for months.

These data provides evidence of the potential long-term benefits of intensive rehabilitation in patients with moderate-to-severe impairment even years after a stroke, contributing to the increasing awareness that persistent impairments in chronic stroke patients may not reflect exhausted capacity for improvement.

Conclusions

Despite the large number of studies in literature about brain plasticity, the mechanisms and biological basis for motor recovery are not yet entirely clear. Further studies are needed to allow us to get a more precise definition of the potentiality of functional recovery and of the mechanisms underlying the recovery depending on its levels and timing. It will also be important to understand more about the trend of plasticity after stroke: from the enhancement of earlier periods to the later stages, clinical changes are accompanied by modifications in plasticity.

Studies involving various rehabilitation techniques like action observation therapy, motor imagery, mirror therapy, constraint-induced movement therapy, robotic-aided therapy and virtual reality show that functional plastic changes may occur in motor cortex using the proper protocol in the appropriate kind of patients. A possible future perspective to improve the quality and the efficacy of the rehabilitative approaches is including some innovative neurophysiological or neuroradiological techniques that could help the clinicians to identify the best rehabilitative approach, at least for specific categories of patients. Some techniques recently introduced (for example the EEG-TMS co-registration) nowadays give the possibility to identify and monitor the effects of different rehabilitative techniques in order to choose the "optimal" one to induce the strongest and most long-lasting positive plastic brain changes. Applying this approach, it may be possible to individualize the rehabilitation protocol on every single patient, even if for now it has not yet been made.

On the other side, a greater attention towards the clinical implications of the changes related to plasticity proves to be a crucial element to further improve the therapeutic options used in neurorehabilitation. Behavioral changes allow to evaluate the characteristics of the recovery, its timing and its maintenance over time, enabling the clinician to correlate it to brain plasticity trend.

An important issue is that different clinical evaluations are used in different research articles. This methodological variability makes quite difficult a results comparison across studies. Since the choice of a given clinical scale (rather than another one) can significantly influence the results of a study, a better methodological uniformity is recommended. The definition of universally recognized clinical guidelines a means to solve this problem and to improve post-stroke clinical assessment but also to increase comparability between research trials.

In conclusion, the increase of such knowledge can be of vital importance in this field. To date studies comparing specific therapeutic interventions basing on modifications in plasticity are still not sufficient, so the optimal features of rehabilitation programs in order to have the highest impact on motor outcomes has not been precisely established. Certainly, stroke rehabilitation programs should include meaningful, repetitive, intensive, and task-specific movement training combined with an enriched environment to promote neural plasticity and motor recovery (Takeuchi & Izumi, 2013). Anyway, understanding the mechanisms, the effects and the limits of neural plasticity may help enhancing the recovery process in stroke patients, by eliciting and facilitating the spontaneous reparative potential of the brain.

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