NEUROPLASTICITY: THE VEHICLE FOR MOTOR RECOVERY OF HEMIPLEGIC SUBJECTS

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INTRODUCTION

Stroke is the third leading cause of death in the developed countries and a major source of disability (Wolf, 1990; Domboy & Opek, 1997). Almost 75 percent of middle cerebral artery infarcts result in motor deficit particularly expressed in the arm (Wade et al., 1983). About 24 percent of hemiplegic patients have residual motor loss of the upper limb at three months post-stroke (Feys et al., 1998). Various longitudinal studies have investigated the long-term outcome following stroke (e.g., Kwakkel et al., 1999) estimated that between 30 and 60 percent of patients eventually regain functional arm movement; Wade (Wade et al., 1983) suggested that 50 percent of all acute hemiplegic patients starting rehabilitation will have a marked impairment of function of one arm, and only about 14 percent of these will regain useful upper limb function.

Figure 1: The Fugl-Meyer (FM) assessment of motor recovery in hemiplegic subjects during the first six months after stroke. Patients have been initially classified to minor, moderate, and major disability based on the FM score. All three groups improved their functioning due to the natural and therapy promoted recovery; they reached a plateau at about 6 months. The standard deviation shown with vertical lines at 0, 1, 3, and 6 months indicate an overlap between patients from the three groups at 6 months. Modified from Duncan et al. 2000.
Van der Lee et al. (Van der Lee et al., 2001) evaluated results of therapeutic treatment in hemiplegic subjects. She concluded "there are no sufficient evidences that would lead to definitive conclusions that the therapies have positive effect to the recovery of arm/hand function after CVA".. yet .. "the evidences suggest that therapies are beneficial!. Duncan and colleagues (Duncan et al., 2000) summarized that the recovery is leveling out below normal functioning approximately six months after stroke. This statement was based on the analysis of the Fugl-Meyer (FM) score (Figure 1) having the maximum of 66 points. Hemiplegic subjects were divided into three groups based on their FM score during their acute phase of hemiplegia: minor, moderate, and major disability. The recovery was the biggest during the first month, somewhat smaller during the second and third months, and slowly leveled out afterwards. The standard deviation, that is the variation of the FM score from the mean value, after six months was high: some subjects with the major disability at the time of stroke reached higher FM scores compared with some hemiplegics who had minor disability, yet improved only a little. In a study that followed up the hemiplegics for more than 18 months, it was suggested that the therapy in chronic subjects could lead to moderate improvement (Popovic et al., 2002). It was also shown that the functioning deteriorated at later times (after one year) for various reasons: non-use of the paretic arm, hemiplegia affecting the non-dominant arm/hand, aging process, and major life style changes leading to decreased activities (Chae, 2003).

Spontaneous and Training Events Contributing to Sensory Motor Recovery in Hemiplegic Patients

After a brain lesion, changes in other regions of the brain have been documented at different post-lesion times, from minutes to months (Nicolelis, 1997; Jones & Pons, 1998). Post-lesion events may be due to deafferentation, removal of inhibition, activity-dependent synaptic changes, changes in membrane excitability, growth of new connections, or unmasking of preexisting connections (Hallett, 1999). Unmasking has generally been proposed to be responsible for rapid changes in cortical maps (Jacobs & Donoghue 1991), and there is evidence that synaptic plasticity can be very rapid (Fischer et al., 1998).

Cortical mapping by intracellular recordings in primates has demonstrated that the tissue surrounding a small lesion in the hand representation area of the primary motor cortex in adult monkeys undergoes a further territorial loss in the functional representation of the affected body part, perhaps through non-use or disruption of local intrinsic cortical circuitry (Nudo & Milliken, 1996). This further tissue loss could be prevented and functional reorganization in the undamaged surrounding motor cortex stimulated by retraining of hand use, starting five days after induction of the lesion (Nudo et al., 1996). Similarly, reorganization of the primary
evaluated results of therapeutic therapies have positive effects yet. The evidence suggests that the hand representation area in the somatosensory cortex in the opposite intact (untrained) hemisphere (Xerri et al., 1998). Morphological studies in rats indicate that cortical lesions can induce an increase of dendritic branching in the contralateral hemisphere with a maximum two to three weeks after the lesion (Jones & Schallert, 1992; Jones & Schallert, 1994; Prusky & Whishaw, 1996; Jones et al., 1996).

Studies using Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), transthoracic stimulation (TMS), and magnetoencephalography (MEG) support the concept of functional reorganization after stroke (Weiller et al., 1992; Weiller, 1998; Cramer et al., 1997; Rossini et al., 1998; Musso et al., 1999). PET studies on blood flow distribution during finger movements in a previously paretic hand have demonstrated complex patterns of activation, with increased activity with large individual variations (Weiller et al., 1992). Until now, there are few studies comparing the degree and pattern of activation in patients with good and less-than-good recovery and with specific therapeutic interventions, and the published data are sometimes contradictory. Because of large individual variations, careful longitudinal studies of individual patients with specific deficits and well-defined lesions are needed. Individuals may use different compensation strategies before and after training, and the activation pattern can change over time. It has been reported that changes in the activation pattern can be induced by forced training of the paretic arm for 10 years after stroke onset (Kopp et al., 1999). The knowledge that the degree of cortical lateralization and interhemispheric interaction varies for specific language components in the normal human brain may be relevant for the interpretation of data on aphasics (Pulvermüller & Mohr, 1996).

There is some evidence that forced use of the paretic arm may improve function in the chronic stage (Wolf et al., 1989; Taub et al., 1993; Kunkel et al., 1999). Clinical data are, thus, strongly in favor of early mobilization and training. On the other hand, there is some disturbing animal data indicating that over-training of the lesioned forelimb induced by immobilization of the intact forelimb can expand cortical lesions (Humm et al., 1998). Referring to those studies, Nudo et al., (1996) started training monkeys five days after the lesion. Housing animals in an enriched environment with the opportunity to perform various activities but no specific training significantly improves functional outcome without increasing tissue loss. However, if combined with more specific training from 24 hours after the insult, an increased tissue loss was observed. Despite the larger tissue loss in the early training group, these rats improved more than standard rats, confirming earlier data of poor correlation between infarct volume and functional outcome in rats housed in an enriched environment. The better outcome in the early training group than in
standard rats may be related to compensatory adaptation in the contralateral hemisphere, subcortical region, or cerebellum. It is important to define the window for a possible increased vulnerability and additional peri-infarct neuronal loss.

**Possible Mechanisms Behind Cortical Plasticity**

Hebb suggested that neuronal cortical connections could be remodeled by the new experiences (Hebb, 1947; Hebb, 1949). Many later studies have demonstrated chemical and anatomic plasticity in the cerebral cortex of adult animals (Bennett et al., 1964; Kolb, 1995; Klinissova & Greenough, 1999; Neuper et al., 1995). Animals reared or housed as adults in complex environments with access to various toys and activities develop more dendritic branching and more synapses per neuron and have higher gene expression for trophic factors than animals housed individually or in small groups in standard cages (Kolb, 1995; Klintsova & Greenough 1999). Similar changes can be induced during learning (Neuper et al., 1995). Merzenich (Merzenich et al., 1983; Merzenich et al., 1984) suggested another aspect of brain plasticity: they demonstrated that cortical representation areas (cortical maps shown in Figure 2) can be modified by sensory input, experience, and learning, as well as in response to brain lesions (Jenkins & Merzenich 1987; Jenkins et al., 1990; Liepert et al., 1995; Seitz et al., 1995; Schieber, 1995; Pascual-Leone et al., 1994; Elbert et al., 1995; Pascual-Leone & Torres, 1993; Pascual-Leone et al., 1995).

![Figure 2: The area of somatosensory cortex (black) in a monkey before (A) and after (B) controlled tactile stimulation. Modified from Jenkins et al., 1990.](image_url)

In this paper we are suggesting potential relevance of the basic research for rehabilitation of hemiplegic patients after stroke. Transient alterations of the
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In the contralateral forearm, attempts to define the window of neuronal loss.

Several mechanisms should be remodeled by the brain and by training. Animal studies have demonstrated that the adult rat (Bennett et al., 1975; Neeper et al., 1995). Transplantation of embryos with access to various sensory inputs can support neural plasticity in the adult brain. More synapses per neuron can be formed in the adult than in the embryo (Bennett et al., 1975; Klintsova et al., 1992; Neeper et al., 1984). Cortical representation areas may be common in everyday life, as indicated by transcranial magnetic stimulation studies during learning tasks in human volunteers (Pascual-Leone et al., 1994). If we regularly perform a very skilled motor task, the cortical representation for the muscles involved will remain enlarged, as seen for the fingers of the left, but not the right hand in string players (Elbert et al., 1995). Similarly, the sensorimotor cortical representation of the reading finger is expanded in blind Braille readers (Pascual-Leone & Torres, 1995) and, furthermore, fluctuates with the reading activity pattern (Pascual-Leone et al., 1995).

Several mechanisms are likely to be involved in brain plasticity. Activity-dependent modification of synaptic connections and reorganization of adult cortical areas are thought to involve long-term potentiation (LTP) and long-term depression (LTD) mechanisms by which information is stored in the mammalian central nervous system (Buonomano & Merzenich, 1998). Synaptic plasticity in cortical horizontal connections has been proposed to underlie cortical map reorganization (Hess & Donoghue, 1994). There is evidence that mechanisms involved in synaptic plasticity vary between cortical regions (Kirkwood et al., 1999). Local neurotrophin actions, transmitter release, and synaptic protein synthesis are thought to promote synaptic remodeling and changes in receptor expression or activation.

As illustrated in Figure 3 (Appendix 1), dendritic spines, which receive the vast majority of excitatory synaptic contacts in the brain, are continuously being formed and modified (Johansson, 1999).

Methods to Promote Cortical Plasticity

Although there is overwhelming evidence now that patients treated in stroke units have a better outcome than those treated in general hospitals, there is no conclusive evidence that one conventional physical or occupational therapy is more effective than another, and there has been no conclusive evidence to support the effectiveness of conventional therapy in the treatment of upper limb impairment following stroke (Parker VM et al., 1986; Pomeroy & Tallis, 2002).

Electrical Stimulation (ES) of sensory-motor systems has been shown to lead to cortical re-organization (Rossini & Pauri, 2000; Ridding & Rothwell, 1999), yet there remains uncertainty about the best way to apply it and which individuals are most likely to benefit. Practice through repetition with positive feedback is fundamental to both motor learning and motor re-learning, and it is well understood that learning is more effective when repetition comprises random practice of slightly different repeated movements (Schmidt & Lee). ES provides cyclic repetition of movement. The typical exercise oriented ES does not allow for variation in the movement produced. This type of ES does not include voluntary initiation from the patient.
Factors that indirectly influence an individual's ability to regain motor control following stroke include spasticity, muscle weakness, and soft tissue changes that result in reduced range of joint movement. Each of these impairments can contribute to an individual's inability to perform an activity and, thus, prevent normal motor re-learning through practice. ES not only provides the opportunity for repetition of functional movements (Burridge & Ladouceur, 2001), but has also been shown to reduce spasticity and increase muscle strength (Burridge et al., 1997; Apkarian & Naumann, 1990). In recent small studies, an improvement in upper limb function has been measured following a period of stimulation using a variety of validated outcome measures (Francisco et al., 1998; Bowman et al., 1979; Sonde et al., 1998; Chae et al., 1998) with the greatest improvement being measured in the subjects who retained some upper limb function. From these studies it is not clear whether the improvement is simply caused by repeated movements or whether ES has a direct effect on the neural connectivity.

The most frequently used protocol for ES has been pre-programmed cyclic stimulation during which stimulation is applied for about 10 seconds to elicit a movement, followed by a rest period of a similar length. The individual has no need to be actively engaged in the exercise. More recent studies have investigated the use of stimulation under voluntary control. These studies have used the electromyographic signal (EMG) to activate the stimulation (Chae et al., 1998; Kraft et al., 1992; Cauraugh et al., 2000; Thorsen et al., 2001; Johansson et al., 2001) usually taking the signal from the same muscle that is to be stimulated. The advantage of this is that the delivery of stimulation is directly controlled by the individual's conscious desire to move, but there are two disadvantages.

The results from clinical studies in hemiplegic subjects where voluntarily controlled ES was applied, called Functional Electrical Therapy (FET) (Popovic et al., 2002; Popovic et al., 2002; Popovic et al., 2003), suggest better recovery of function compared with conventional ES. This difference is likely arising from the fact that FET provides intensive traffic of neural information towards the brain; thereby, promotes to a larger extent neural plasticity. The mechanisms through which this may happen are as yet poorly understood, but the following are possible explanations: 1) FET stimulates directly sensory nerves, 2) FET stimulates indirectly sensory nerves (e.g. when motor nerve is stimulated, it causes a contraction which then activates receptors and through that sensory nerves, 3) visual input of the actual movement is integrated into the control, 4) antidromic stimulation, and 5) other pathways. Electrical stimulation of a motor nerve generates both an orthodromic (towards the muscle) and an antidromic (towards the spinal cord) train of impulses. The antidromic impulses could play an important role. The detailed analysis of the F-wave supports the argument that the impulses have circumnavigated the anterior horn cell to return down the motor axon. The antidromic discharge may explain why FET facilitates motor learning. Hebb
indirectly influence an individual's ability to regain motor control include spasticity, muscle weakness, and soft tissue changes that limit range of joint movement. Each of these impairments can result from an individual's inability to perform an activity and, thus, prevent learning through practice. ES not only provides the opportunity for functional movements (Burridge & Ladouceur, 2001), but has also been used to reduce spasticity and increase muscle strength (Burridge et al., 1992; Naumann et al., 1990). In recent small studies, an improvement in motor function has been measured following a period of stimulation using a variety of dose and outcome measures (Francisco et al., 1998; Bowman et al., 1998; Chae et al., 1998) with the greatest improvement being observed in subjects who retained some upper limb function. From these studies, it is clear whether the improvement is simply caused by repeated ES has a direct effect on the neural connectivity.

A frequently used protocol for ES has been to pre-programmed cyclically elicit the stimulation for about 10 seconds to elicit a contraction followed by a rest period of a similar length. The individual has no control over the duration, which is typically engaged in the exercise. More recent studies have investigated the effects of ES under voluntary control. These studies have used the muscle signal (EMG) to activate the stimulation (Chae et al., 1998; Carraugh et al., 2000; Thorsen et al., 2001; Johansson et al., 1998), which is from the same muscle that is to be stimulated. The premise is that the delivery of stimulation is directly controlled by the brain, thereby allowing the individual to control the intensity, duration, and frequency of the stimulation. The results from these studies have shown that voluntary control of ES is more effective in improving motor function than passive ES.

Clinical applications of ES have been developed in stroke rehabilitation, called Functional Electrical Therapy (FET) (Popovic et al., 2002; Popovic et al., 2003), have suggested better recovery of motor function than conventional ES. This difference is likely arising from the increased access to the brain's motor cortex, which enhances the brain's ability to generate neural activity. The mechanisms through which ES works are not yet fully understood, but the following are possible: 1) ES stimulates directly sensory nerves, 2) FET stimulates parasympathetic nerves (e.g., when motor nerve is stimulated, it causes a reflex that activates receptors and through that sensory nerves, 3) the actual movement is integrated into the control, 4) antidromic, 5) orthodromic (towards the muscle) and antidromic (towards the brain) pathways. Electrical stimulation of a motor nerve can trigger afferent stimulation of the somatosensory cortex: 1) augmented sensory feedback - appropriately timed sensory stimulation to trigger voluntary motor activity and 2) proprioceptive afferent stimulation as a consequence of movement and muscle activation mediated by electrical stimulation. Motor learning therefore cannot be dissociated from sensory learning and, thus, may be better termed sensorimotor learning.

Reduction of motor impairment to maximize physical activity remains an important strategy in stroke rehabilitation and in other neurological injuries and diseases (Popovic et al., 2002; Popovic et al., 2003). Therapeutic use of FET aims to reduce motor impairment primarily through motor re-learning. However, other physiological effects such as muscle strengthening and modulation of spasticity can also influence the motor learning process. For instance, spasticity, reduced range of movement, or selective muscle
weakness may influence an individual's capability for movement. Through modulation of spasticity or increased strength of a particular muscle group, both of which have been demonstrated as effects of FET, a movement may become easier to perform. The subsequent performance or practice of that movement may influence the motor re-learning.

An Example: Functional Electrical Therapy in Acute and Chronic Hemiplegic Subjects (Popovic et al., 2002; Popovic et al., 2002; Popovic et al., 2003).

Subjects. The following three patient groups were evaluated: 1) 16 acute hemiplegic subjects (more than two weeks and less than three months following first stroke ever) assigned to functional electrical therapy, 2a) 14 acute hemiplegic subjects assigned to the control group, and 2b) the same 14 subjects in their chronic phase of hemiplegia (more than one year post stroke) when assigned to FET. The mean age±SD for all 30 subjects was 61.5±7.5. The acute subjects were accepted in the study at an average of 6±2 weeks after the onset of stroke, while the chronic subjects were accepted after 56±9 weeks. Patients from the group (1) were evaluated at the 52 and 78 weeks, but no treatment was given to them in their chronic phase of hemiplegia.

The inclusion criteria into the study were: stroke of ischemic or hemorrhagic origin confirmed by MRI or CT scan, age over 18, able to give informed consent, and cognitive status sufficient for learning how to use FET. The exclusion criteria were: dependent on care prior to stroke for activities of daily living, severe medical condition in any arm which precludes participation in the study, previous injury or disease or contracture affecting hemiplegic or non-hemiplegic arm or hand, and pre-existent neurological disease or injury. All subjects were able to extend their paretic wrist for more than 20 degrees against gravity, and they could extend all fingers for more than 10 degrees against gravity at the entry to the study (three weeks after stroke). The average spasticity in the acute hemiplegic subjects was 2-3 (modified Ashworth scale), and it was 2 in chronic subjects at the beginning of the treatment. All study subjects signed informed consent approved by the local ethics committee before entering the study.

Treatment. All subjects received conventional physical therapy. Acute subjects were randomly assigned to control (2a) or FET (1) groups. FET is a procedure of voluntary activation of all preserved sensory-motor mechanisms of the paretic arm in synchrony with a neural prosthesis that applies four channels of surface stimulation in order to assist opening and closing of the hand, holding objects, and releasing of objects in a fashion similar to the one seen in able-bodied subjects. The FET was applied in acute (1) and chronic (2c) hemiplegic subjects on a daily basis for three consecutive weeks. The FET sessions lasted for 30 minutes. During the FET session the assignment given to patients was to functionally use various objects used for typical daily activities (e.g., can, telephone receiver, comb,
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A functional use of an object comprised the following phases: reach, grasp, manipulate the object, bring object back to the original post, and release it. Details on the procedure are explained elsewhere. Hemiplegic subjects from the control group (2a) were required to exercise daily for 30 minutes trying to accomplish the same tasks as the FET group, yet without a neural prosthesis.

**Figure 4:** The Upper Extremity Function Test (UEFT) is a measure that shows how many times during a two-minute period can a patient functionally use an object (fork, toothbrush, VCR tape). The results are the average ± S.D. (vertical lines) over all 11 tasks and all patients. The graph includes results from two studies: 1) FET vs. control group in the acute phase of hemiplegia (0 to 26 weeks), and 2) FET in chronic phase of hemiplegia (52 to 78 weeks). FET was in both cases applied for three weeks (marked as treatment), and the follow up was in both cases continued for the following 23 weeks. Most of the patients that participated in the first randomized clinical trial in acute phase of hemiplegia also participated in the second study (52 to 78 weeks). Group (1) – FET applied in acute phase of hemiplegia, group (2a) – control group in acute phase of hemiplegia, group (2b) – FET applied in chronic phase of hemiplegia.

**Outcome measures:** Upper Extremity Functioning Test (UEFT), and Drawing Test (DT). The subjects were assessed at the point of entry to the trial, after the treatment (three weeks), and at six, 13, 26 weeks after the beginning of the study. The statistical analysis used repeated ANOVA to compare the gains in outcome scores of each group and differences between the groups.
Results and discussion. Figure 4 shows the results of the UEFIT for acute (A) and chronic FET (C) groups and the acute control group (B). The slopes of the trend lines were different between the control and FET acute hemiplegic subjects. The UEFIT gains were the biggest for the acute FET. There was a statistically significant difference in the UEFIT gains in acute FET subjects ($p<0.01$, $F=8.5$) over time. There was a statistically significant difference between the UEFIT gains in FET acute subjects compared with the two other groups ($p<0.01$, $F=21.2$).

Figure 5: The Drawing Test (DT) shows the ability to draw the perimeter of a square with the side 20 cm long. The DT was performed on a digitizing board; each patient drew three times in clock and three times in counter-clock directions. The area surrounded in each trial was calculated, and all data averaged. Vertical axis shows scores in percent of the ratio between the averaged area and the area of the target square (400 cm$^2$). Horizontal axis is the time in weeks. The vertical lines are standard deviations. The graph includes results from two studies: 1) FET vs. control group in the acute phase of hemiplegia (0 to 26 weeks), and 2) FET in chronic phase of hemiplegia (52 to 78 weeks). FET was in both cases applied for three weeks (marked as treatment), and the follow up was in both cases continued for the continuing 23 weeks. Most of the patients that participated in the first randomized clinical trial in acute phase of hemiplegia also participated in the second study (52 to 78 weeks). Group (1) – FET applied in acute phase of hemiplegia, group (2a) – control group in acute phase of hemiplegia, group (2b) – FET applied in chronic phase of hemiplegia.
The results of the UEFT for acute (A) control group (B). The slopes of the I and FET acute hemiplegic subjects. acute FET. There was a statistically acute FET subjects (p<0.01, F=8.5) difference between the UEFT gains other groups (p<0.01, F=21.2).

**Figure 5** shows the results of the DT for all three groups. The trend lines demonstrate the changes in the slopes over time. The maximal slope of the trend lines was the one calculated for the acute FET hemiplegic subjects. There was a statistically significant difference in DT gains in acute FET subjects (p<0.01, F=1.3). There was a statistically significant difference between the DT gains in FET acute subjects compared with the DT gains in two other groups (p<0.01, F=9.6). The UEFT and DT scores for the control acute subjects remained below the scores of the chronic subjects throughout the evaluation.

**MESSAGE TO TAKE HOME**

Cortical maps i.e., neuronal connections are continuously remodeled by experience. Knowledge of the potentials of the brain to compensate for lesions is a requirement for optimal stroke rehabilitation strategies. Reorganization is likely the key process responsible for recovery of function after stroke, but what are the limits, and to what extent can post-ischemic intervention facilitate such changes? Improved knowledge of post-ischemic neurophysiological events and close interaction between basic and applied research is needed for optimal rehabilitation strategies.

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