BRAIN PLASTICITY MECHANISMS UNDERLYING STROKE RECOVERY

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ABSTRACT:

Spontaneous recovery represents the only hope of regaining autonomy, for the majority of stoke victims especially in developing countries like Morocco. This recovery is mainly based on the brain's reorganization capacities, referred to as "adaptive plasticity". Rehabilitation is one of the most powerful modulators of brain plasticity that, if well administered, can improve post-injury recovery.

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Introduction

Stroke, also known as cerebrovascular accident, is a disabling neurological condition caused by the interruption of blood supply to the brain [1]. This sharp decrease in the cerebral blood flow can be due to an occlusion (ischemic stroke) or rupture (hemorrhagic stroke) of a blood vessel transporting oxygenized blood to the brain cells, which threatens the affected brain areas' functioning [2].

Stroke is the third leading cause of mortality in developed countries after cardiovascular diseases and Cancer [3], and a major cause of long-term disability [4] with a considerable socioeconomic impact on patients, families, health services and societies [5]. In Morocco, Stroke prevalence rate is estimated at 284 cases per 100.000 of the population, with severe sequelae observed in more than 60% of the patients [6]. Thus, Stroke is now considered a serious public health problem in Morocco.

Until now, early-applied systemic thrombolysis has been the only approved curative and causal treatment of acute ischemic stroke [7]. Unfortunately, in developing countries with poor health systems like Morocco, thrombolysis cannot be offered to stroke patients on a large-scale basis, even in the absence of medical contraindications, but only to a minority of them (fast access to hospital, achieving a diagnosis within the first four hours after the symptoms had begun availability of thrombolytic drugs in the hospital…etc.). The majority of stroke victims are most likely to face severe mobility, sensorial and neuropsychological deficits. Their only chance of improvement greatly depends on spontaneous recovery that is closely inherent to the brain reorganization capacities, known as "plasticity" [8]. Therefore, it becomes imperative that every practitioner (medical doctor or therapist) dealing with stroke patients understands the spontaneous recovery mechanisms after stroke and the main factors promoting them, such as physical rehabilitation.

Spontaneous Recovery after a Stroke

Recovery after stroke has long been underestimated due to the formerly widespread idea that brain injuries cause permanent damage because nerve cells do not regenerate. However, this "natural" spontaneous recovery is, quite constant even if unpredictable both in terms of time and extent [9]. The post-stroke recovery process can last from a few days to several months, and can be quite complete sometimes, but the functional restitution is often only partial, leaving the patients with long-lasting impairments and disability [10].

Post-stroke motor recovery patterns were well identified through a large population-based-study, known as the "Copenhagen Stroke Cohort Study", in which 1,197 stroke survivors, treated in the stroke unit of a large hospital in Denmark were assessed on a regular basis [11]. This study results showed that most of the functional recovery occurs within 3 months after stroke in 95% of stroke survivors, then the recovery course reaches a plateau with a possible but slower further evolution over months or years[11-12].Many post-stroke recovery predictors have been identified such as age, cognitive impairment, sensory or motor evoked potentials, accompanying neurologic deficits, volume of injury, MRI spectroscopy, features and location of injury [13-16].However, it remains difficult to predict an accurate recovery prognosis for each individual, and to point out how efficiently brain plasticity would participate in the recovery process.

What is Brain Plasticity?

The 19th century witnessed a growth of interest in localizing brain functions, with early attempts to relate specific brain functions to particular brain regions, especially using electro-physiological studies in animals[17]. In 1950, Penfield and Rasmussen were the first to publish the human brain cortex cartography, and to describe the motor and somatosensory homunculus [18]. This functional cerebral organization was considered as permanent and unchangeable until the seventies, when several studies showed modification of cortical sensorimotor representations caused by peripheral lesions [19-23].

Michael Merzenich -one of the best-known researchers in this area- studied the changes in adult owl monkeys' cortical maps, after a digit amputation. He demonstrated that within two months, the sensory cortical territory formerly representing the amputated digit reacted to the peripheral stimulation of adjacent digits and palmar region [19]. In a different experiment, Merzenich and his team showed that cutaneous stimulation of distal phalanges resulted in the expansion of the corresponding representative surface in the somatosensory cortex, over the neighboring areas [24].

Similar observations have been made possible in humans with the advent of functional cerebral imaging, allowing the study of different brain areas activation during a specific task. Mapping human brain activity is based on measuring blood oxygenation levels (functional Magnetic Resonance Imaging), detecting changes in cerebral blood flow (Positron Emission Tomography), or recording the magnetic fields induced by brain activity (Magneto-encephalography).

In 1993, Ramachandran and his team showed that the somatosensory area representing the arm on the parietal cortex was invaded by the area representing the face within weeks after the arm amputation, which partially explained the weird sensations of the phantom limb, because stimulating the face was perceived as if it was on the amputated arm [21]. This is a typical example depicting the invasion of deafferented brain areas (that had lost somatosensory input) by neighboring cortical regions representing unimpaired body parts. On the other hand, it has been shown that the primary visual cortex was activated by tactile discrimination tasks among the blind and visually impaired patients [25], suggesting a functional reconversion of the primary visual cortex. Even without any injury, intensive use of a body part, in a learning process, can also induce cerebral reorganization or remapping. This has been particularly studied in professional violinists among whom the representative area of the fingers was larger than in control subjects [26].

Based on all these new findings, it has been clearly established and scientifically proven that the brain organization is changeable and can be influenced by learning and new experiences in adults. Useless neurons connections are undone or rarefied and more profitable ones are created or strengthened so that the subject can deal with new situations[27].This is referred to as "Brain plasticity" or "Neuroplasticity", reflecting the malleability of the brain, its flexibility and adaptability not only during child development periods but also throughout life [28].During the last twenty years, there has been an extensive body of research exploring the mechanisms of adaptive plasticity, which is considered as the substratum of functional recovery after brain injuries such as stroke.

Neuroplasticity Mechanisms Underlying Stroke Recovery

Stroke often results in the injury of a substantial part of the sensorimotor cortex causing contralateral hemiplegia. Even if we do nothing, spontaneous recovery of a variable extent is seen in a few days or weeks. Several studies were designed to help understand how the remaining unimpaired cortex could support the recovery of the impaired functions. Neuroplasticity mechanisms, underlying this recovery, have been described through numerous studies both in animals and humans, using electrophysiological techniques or functional imaging.

Increased Activation of Perilesional Areas

After brain injury, the motor system can recruit normally inactive brain areas. Cholet et al. showed in patients who had recovered from stroke, that performing a simple motor task (finger opposition) with the paretic limb induced the activation ,in the injured hemisphere, of a larger brain area, than the one activated in the uninjured hemisphere when performing the same movement with the healthy hand[29]. This implies a greater recruitment of associative motor areas (premotor cortex, supplementary motor area, parietal cortex and insula). A similar activation pattern (larger areas) can be seen in healthy subjects when performing complex motor tasks requiring several neural networks [29]. Consequently, after stroke recovery even the simplest motor action is performed as if it were more complex, which explains -at least partly- the increased fatigability accompanying the recovery process.

Animal studies have pointed out that perilesional reorganization does not occur spontaneously but is induced by rehabilitation. In two groups of monkeys who underwent ischemic vascular lesion, only the group that was enrolled in a rehabilitation program achieved substantial motor recovery with increased perilesional activation in the brain, whereas the group left to spontaneous recovery had worse functional results with a decreased brain activation area [23]. This perilesional reorganization can be explained by the removal of inhibitory input on pre-existing connections that are kept inactive in the normal state [13].

- **Resolution of Diaschisis**

Diaschisis refers to reduced blood flow and metabolism in uninjured brain areas that are distant but anatomically connected with injured brain areas [13, 30-31]. Baron originally described it in the cerebellum after a contralateral cortical infarction, and called it "*Crossed cerebellar diaschisis*" [32] then it was found in different other brain regions. The progressive resolution of diaschisis, with restitution of brain activity in uninjured areas has been associated to post-stroke recovery in several studies [33-35]

- **Remapping:**

According to the topography of lesions, the brain function can be moved from an area to an adjacent one [36]. For example, when the motor cortical area representing the hand is injured, hand representation extends ventrally towards the face area [13]. This leads to a complete reorganization of cortical maps known as "Remapping"

Activation of the uninjured hemisphere

The degree of inter-hemispheric laterality rapidly decreases after brain injury [13]. A right hand motor task or a language activity, that would only activate the left hemisphere in healthy subjects, results in the activation of similar areas in both hemispheres after a left-sided stroke, sometimes with a greater activation of the uninjured hemisphere [34]. This shift of laterality toward the non-affected hemisphere tends to return to normal throughout the recovery process, with reduced activation in the non-stroke hemisphere and increased activation in the stroke-affected hemisphere [13].

This decrease in cerebral lateralization is more profitable to functions that are represented bilaterally on both hemispheres, such as gait [37], swallowing [38] and facial movements [39], which explain their faster and more complete recovery than highly lateralized functions such as distal extremity movements or language.

Modulation of brain plasticity:

Based on the studies mentioned above and more recent ones, it is now well established and scientifically proven that brain plasticity mechanisms represent the substratum of post-stroke functional recovery. Thus, identifying interventional means

tomodulate this plasticity would certainly help improve recovery and reduce disabling sequelae.

- **Rehabilitation and physical therapy:**

The importance of physical therapy and rehabilitation care, in the medical management of stroke victims, is widely recognized. However, in this era of "Evidence Based Medicine", the superiority of rehabilitation interventions over spontaneous evolution had to be proven. Animal studies were the first to demonstrate the highly modulating effect of rehabilitation interventions on the reorganization of peri-lesional areas after cerebral vascular injury[23]. Later studies on humans pointed out the positive effect of intensive rehabilitation on stimulating brain plasticity and promoting functional recovery [13, 26, 34].
Some motor rehabilitation techniques, such as constraint-induced movement therapy (CIMT),are based on neuroplasticity mechanisms and have proven their effectiveness and superiority to standard rehabilitation techniques [40-42]. Originally described by Edward Taub, CIMT requires an intensive use of the paretic limb, leading to the stimulation of adaptive plasticity in the stroke-affected hemisphere[13, 26].New experimental methods have been developed and are used in combination with rehabilitation to increase its efficiency, like repetitive Transcranial Magnetic Stimulation (rTMS). When associated with physical training, a high frequency rTMS (5Hz) of the injured motor cortex improves its excitability and the quality of functional recovery [43-44].

- **Drugs:**

The influence of drugs on functional recovery has been underlined especially through animal experiments. Antipsychotics and Benzodiazepines hinder post-stroke recovery [45], while D-amphetamines enhance it by promoting synaptogenesis and neuronal sprouting in perilesional regions [46]. In humans, experimental studies have controversial results. A randomized controlled double-blindedtrial, published in 2011 in *"Lancet Neurology"* [47], demonstrated the effectiveness of fluoxetine, a serotonin reuptake inhibitor, in enhancing motor recovery after stroke in the treated group. This result could be explained by the antidepressant effect of the molecule that might improve patients' implication in the rehabilitation programs. However, the authors argue a specific

action of fluoxetine on the modulation of brain plasticity [47].

Conclusion:

Brain plasticity is the neurobiological basis of post-stroke recovery. Several factors can influence functional recovery by modulating brain plasticity, and physical rehabilitation is one of the most efficient plasticity modulators.

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