The scientific basis of stroke rehabilitation

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Recovery after a focal brain lesion is in part driven by the brain’s ability to reorganise its circuitry, thereby enabling function by involving undamaged areas of the brain.

Evidence for this reorganisation, also referred to as recovery-related plasticity, comes from various sources. Functional imaging shows that rehabilitative motor training engages new areas of cortex and deep brain nuclei. Their activation correlates with functional gains in movement ability. Bilateral arm training over 6 weeks produced increased activation of premotor cortices in both hemispheres during paretic elbow movement consistent with recruitment of these areas to control paretic elbow movement [1]. Similarly, six months of treadmill exercise stimulated the activation of cerebellar and midbrain regions while the subject performed paretic knee flexion-extensions [2]. The reason for such changes in activation patterns may be modifications in existing cortico-cortical and cortico-subcortical circuits after cortical injury. In support of this hypothesis, Dancause et al. [3] showed that after primary motor cortex lesions in primates cortico-cortical connections sprout between premotor cortex and somatosensory cortex. Data from rodent models suggest additional structural reorganisation of the corticospinal tract [Starkey M, Schwab ME, personal communication]. Taken together, these findings demonstrate that intact cortical circuits are being reorganised either spontaneously or induced by training, i.e., activity, to improve functional deficits.

Whether recovery-related plasticity resembles the plasticity processes that enable implicit learning is unclear.

Implicit learning refers to the ability to learn from repetitive training without conscious remembering, e.g., when learning a novel movement. Implicit learning is associated with various functional and structural changes in neuronal networks. Among those are alterations in cortical activation patterns [4], motor cortex somatotopy [5] and dendritic trees [6] that resemble – at first sight – the recovery-related phenomena described above. However, learning and recovery are not identical, and may involve different pathways and cortical regions. That substantial differences exist is suggested by the divergent time profiles of learning and recovery. Rats that recover a motor skill after a cortical lesion do so in much slower fashion than rats learning the skill after injury for the first time (fig. 1). These different time profiles suggest that neuronal reorganisation enabling functional gains occur at a different pace, possibly because they involve different proteins to be expressed or different circuits to be modified. Hence, the commonly used term “re-learning after stroke” should be subjected to scrutiny.

Successful recovery interventions depend on treatment intensity.

Similarly to implicit learning, successful rehabilitative training depends on its intensity. The time spent on training and the complexity or demand that the repetitive activity imposes correlate with the treatment effect. Data from the EXCITE trial – comparing the efficacy of constraint-induced movement therapy to the standard of care in the US – confirms the correlation between training time and functional improvement for low-functioning individuals [8]. Thresholds have yet to be identified defining the minimum intensity required for a functional benefit. It is likely that different thresholds exist for different patient populations. Thresholds will depend on the timing of treatment and other factors such as comorbidity. The influence of training demands and complexity has not been systematically studied, but experience suggests that greater demand will yield greater improvement. Higher intensity and demand lead to greater functional gains independently of training modality, i.e., how and what the subject trains. Available training modalities differ widely; for example, training is conducted by a physiotherapist or a robot, is bilateral or constraint-induced focusing on the paretic side, or is assisted by functional electrical stimulation or mechanical assistive devices such as gloves with springs to facilitate hand opening. Controlled trials have failed to show differences between training modalities as long as the intensity was kept constant. But trials have shown a wide range of responsiveness among

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stroke survivors treated by a specific therapy. It therefore seems plausible that certain training modalities fit some but not other individuals, calling for a strongly individualised approach to rehabilitative training.

Successful recovery and learning depend on motivation and reward

Experience suggests that recovery depends on the motivation and the personality of the patient. Only patients that are not only compliant with training but are motivated to improve will do so. While this seems rather trivial it poses significant problems in clinical practice when patients drop out of rehabilitation programmes (mainly as outpatients) and do not continue to practice or use what has been trained at home. How motivation can be enhanced is currently a focus in therapy development; virtual reality, game environments and task-specific feedback are being investigated. The treatment of post-stroke depression is very important in this context, because depressed mood will affect the valuation of rewards. Accordingly, a controlled trial shows the benefit of the selective serotonin reuptake inhibitor (SSRI) fluoxetine for recovery of arm function [9]. Neuroscientific evidence suggests that reward-related brain activity may directly enhance the storage of motor programmes in primary motor cortex (M1). In the rat, dopaminergic fibres from the ventral tegmental area (VTA) of the midbrain to M1 are known to encode rewards. In motor rehabilitation, discrete rewards for single movements or training sessions could be used to enhance rehabilitative effects. Moreover, the VTA–M1 dopaminergic projection may explain why levodopa has a supportive effect on physiotherapy [11].

More translational research is urgently needed

The problems of the stroke survivor are complex and manifold. They demand a multimodal treatment approach consisting of various training and supportive measures (e.g., drugs, social and emotional support). Only a multimodal approach in which each component is individually selected and optimised is likely to yield greater benefits than those seen today. For each component the neurophysiological underpinnings need to be clarified before the therapy can be optimally adjusted to each individual patient. Currently, most clinical research investigating single treatment components makes a number of assumptions that are based on empiricism or experience, not neurophysiology – with constraint-induced movement therapy being one prominent exception. This needs to change.

Key words: learning; reward; motor cortex; plasticity

References