Editorial

Motor system recovery: Evidence from animal experiments, human functional imaging and clinical studies

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1. Scientific perspective

As pointed out by Matthews et al. [13] functional restitution after brain damage might be based on brain repair, adaptive reorganisation, and/or compensatory strategies.

Function in the more restricted sense would include body functions such as the ability to move the body and its segments, to coordinate a movement, to integrate sensorimotor information, and to plan, conduct, and judge movements. Their recovery would affect activities, i.e. the ability to perform everyday activities such as purposefully handling objects [20]. Repair refers to the biological recovery of the damaged system itself, adaptive reorganisation to the recruitment of new systems that can activate the same final pathways, while compensation involves behavioural changes leading to an altered strategy for the completion of a task. Theoretically, rehabilitation could make use of either mechanism of functional recovery.

The promotion of motor system rehabilitation as a scientific medical discipline would have to address a variety of questions: the scientific description of functional deficits in the motor system both behaviourally as well as with regard to changes in brain activity, the observation of naturally occurring brain repair, adaptive reorganisation, and motor compensation, and finally the potential for enhancing motor recovery in terms of ei-

ther brain repair or adaptive reorganisation by medical interventions such as training therapy, technical stimulation, medication, or surgical procedures including cell or tissue transplants.

This special issue of RNN was meant to collate lab reviews from labs that made an important contribution to these scientific questions from either a basic or clinical science perspective. While a complete coverage of all relevant research would have been well beyond the scope of this special issue an attempt was made to collect information from different areas of research that contributed conceptually to the scientific issue of motor system recovery and might guide the reader to influential ideas and scientific "proof of concept".

2. Animal experiments

The lab review by Kaas and Qi [9] entertains several mechanisms of plasticity in the motor system of primates with long-standing amputation. Evidence is provided for more widespread connections of intrinsic M1 circuits and for a possible connection of alpha motoneurons (that would have been connected to amputated muscles) to remaining muscles. Further, the possibility is entertained that the corticispinal neurons that previously were connected to motorneurons of the amputated muscles form connections to motor neurons of

remaining muscles (for this aspect, no direct evidence exists). Thus, motor system reorganisation does occur at different levels in the nervous system.

Woodlee and Schallert [21] use a rat model with unilateral lesions of the forelimb area of the sensorimotor cortex to investigate the interplay between brain and behaviour and its consequences on lesion size, cortical plasticity, and functional recovery. Early excessive use of the affected limb may compromise weakened peri-lesion tissue that might have otherwise survived while immobilsation of the affected limb leads to mildly worse behavioural outcome. One consequence could be that graded motor rehabilitative therapy which starts out mildly may provide for optimal outcomes.

The negative results on brain lesions were obtained when excessive behavioural pressure was applied early after cortical damage, i.e. by casting the non-affected limb. The work presented by Johansson [8], however, sharpens our view for the notion that a stimulating environment that facilitates various sensorimotor activities and social interaction promotes motor recovery. Post-ischemic housing of rats in enriched environment, i.e. larger cages which allow for both social interaction and various activities, improves functional outcome, modifies gene activation, and increases dendritic branches and number of dendritic spines (in the contra-lesional cortex).

Taken together, these experiments provide "proof of principle" that motor behaviour after cortical damage has a clear influence on adaptive reorganisation and behavioural motor recovery and can be tailored to optimise motor system recovery.

Another clinically and scientifically relevant "proof of principle" has been provided by Feeney et al. [5] who showed that the interaction between medication and training can either slow or enhance motor recovery. Medication can transiently modulate neuronal (dys)function while a drug is biologically active ("facilitation"), or promote recovery leading to enduring effects ("learning"), slow down recovery or reinstall deficits after recovery has occurred. In cats with long-standing unilateral frontal lobe lesions, tactile placing could transiently be restored by single doses of either d-l or d amphetamine for up to 1 day (facilitation). The effect of amphetamine could be prolonged to 10 months when a continuous supply of catecholamines was provided by transplanting chromaffin cells from the animal's adrenal tissue into the cortical wound cavity. More important in the context of rehabilitation might be the fact that single doses of amphetamine and other drugs that increased noradre naline (but not

of dopamine agonists) combined with symptom relevant experience, e.g. motor training, enhanced recovery from hemiplegia in rats following sensorimotor cortex lesion. It was the combination of training and noradrenergic stimulation that had the potential to enhance recovery.

3. Human functional brain imaging

Brain imaging studies, especially motor activation studies, open a window to look into the functional organisation of the human motor system while being active and can thus elucidate mechanisms of recovery in human beings.

Rossini and Dal Forno [16] describe the various non-invasive brain imaging tools that are available as well as their strengths and limitations, i.e. Positron Emission Tomography (PET), functional Magnetic Resonance Tomography (fMRI), high resolution ElectroEncephaloGraphy (EEG), MagnetoEncephaloGraphy (MEG), and transcranial Magnetic Stimulation (TMS). They correctly point out that the integrated use of techniques has the potential to overcome limitations of individual techniques. The authors give a detailed account on cortical plasticity after stroke such as the within-pyramidal system reorganisation with a functional reorganisation of the motor output map and changes of intracortical and transcallosal inhibition (TMS), or the enlargement of the "hand extension" area in the somatosensory cortex (MEG). They further comment on the protracted time course of these changes that evolve over several months after stroke.

Seitz and co-workers [18] illustrate the evolution of ischemic brain lesions and functional recovery. They discuss the potential of brain tissue salvage by early reperfusion (MRI), behavioural recovery that can result from regression of perilesional and remote intra-cortical disinhibition (TMS), and the effect of training that can augment recovery by activation in the affected hemisphere (fMRI). The authors further point out that movement-related brain activation pattern are modified by stroke location, e.g. cortical vs. subcortical stroke, and time after stroke, i.e. early or late in the recovery process. In addition, movement-related brain activation of recovering stroke patients is likely to be influenced by specific sensorimotor and/or cognitive-motor demands such as more prominent reliance on visuo-motor, sensorimotor and/or cognitive control processes that most likely vary during the course of recovery and across patients.

Aside from these recovery-related determinants of brain activation variability (PET, fMRI) results of imaging studies vary also because of changes in blood flow post stroke, effects of task demands during activation studies, and movements of either right or left hand according to Cramer [3]. He further argues that in spite of this variability an important role of the primary sensorimotor cortex (SMC) for motor recovery can be substantiated across subjects.

Similarly, Nelles [14] summarises the results of three prospective imaging studies indicating that motor recovery after stroke as promoted by intensified motor training is associated with more ipsilesional SMC and less contralesional SMC activation.

Matthews and co-workers [13] provide further evidence that the motor system is capable of adaptive reorganisation (as compared to compensation only). An association between disease burden and reorganisation in MS patients that can be observed even without clinical deficit, the close association between reorganisation in active and passive movement conditions indicating that changes are independent of volitional activity and strategy, the training-induced behavioural recovery and enhancement of ispilesional SMC activation (fMRI), and the demonstration of the functional importance of the contralesional dorsal premotor cortex as assessed by reversible "virtual lesions" (repetitive TMS) are all in line with the assumption that cortical reorganisation in these circumstances was adaptive in nature.

Celnik and Cohen [2] comment on the relevance of somatosensory input, motor training, drugs, and cortical stimulation on motor function and motor cortex plasticity. Prolonged median nerve stimulation has been shown to improve grip strength in stroke patients and enhanced training-dependent encoding of an elementary motor memory in the primary motor cortex (TMS). Further, anesthesia of the proximal arm elicited transient motor improvements of the paretic hand and an increase in motor cortex excitability. It has further been shown that drugs with adrenergic or dopaminergic function, when used in combination with training, can enhance use-dependent cortical plasticity, while drugs that act as agonistic to the GABAergic function or antagonistic to NMDA and muscarinergic receptor function exert a deleterious effect on cortical plasticity. Most recently, it could be demonstrated that cortical stimulation (TMS) synchronously applied to a motor cortex engaged in a motor training task enhances use-dependent plasticity. Thus, a variety of strategies have been described that could represent an adjuvant to motor training enhancing adaptive brain reorganisation and motor recovery, i.e. peripheral sensory stimulation or anesthesia, pharmocological stimulation of brain receptor systems, and cortical stimulation.

Liepert and colleagues [11] note that post stroke changes of intracortical inhibition (ICI) and facilitation (ICF) in the motor cortex as assessed by TMS are influenced by lesion location. In patients with cortical or thalamic lesions decreased ICI was observed while patients with cerebellar infarcts showed the opposite pattern with increased ICI and reduced ICF. Functional changes of the motor cortex after brain lesions are thus likely to dependent on the alteration of influences that are exerted on this area by other functionally connected brain regions.

4. Clinical studies

While animal experiments and brain imaging studies elucidate the mechanisms that underly the evolution of brain lesions and brain recovery only careful and systematic clinical observations will determine the time course of human behavioural recovery and any clinical benefit of rehabilitation interventions.

Kwakkel [10] refers to a meta-analysis providing evidence that care by a specialised stroke team increases independency and more frequent discharges home among stroke victims. He further demonstrates for arm and leg strength and function as well as competence with basic activities of daily living similar non-linear pattern of (spontaneous) recovery evolving over approximately 6 months after stroke. The most powerful predictor of degree of independency at 6 months was the rate of recovery during the phase with fastest recovery (around 5 weeks post stroke). Intensified training accelerated recovery, but did not necessarily affect the final plateau. Reviewing mechanisms of brain and behavioural reorganisation he concludes that more detailed knowledge about motor control changes in patients could guide both future research on mechanisms of recovery and the development of rehabilitation strategies.

Platz [15] addresses this question and introduces the concept of Impairment-oriented Training (IOT). According to the concept, the control deficits for motor impairments such as paresis or apraxia need to be characterised specifically as a first step. Consequently, these detailed characterisations of control deficits form the basis to develop specifically targeting impairment-oriented training strategies. They aim to restore lost or impaired function. Two specific and comprehen-

sive training techniques have been developed for stroke patients with mild and severe arm paresis: (1.) The Arm Ability training for mild arm paresis trains different sensorimotor abilities such as dexterity, speed of isolated hand and finger movements, steadiness of the arm, aiming, or tracking under visual guidance. Improvement of these motor abilities leads to improved motor performance in every day life circumstances. (2.) The Arm BASIS training for severe arm paresis intends to restore more basic motor control, i.e. the full range of active non-segmented motion of all limb segments, the combination of both postural arm activities and dynamic motion control of the arm, and interjoint-coordination. Clinical trials with representative study populations supported both techniques' clinical efficacy.

Mark and Taub [12] introduce both concept and evidence related to the Constraint-Induced Movement Therapy (CIMT) for chronic stroke hemiparesis and other disabilities. After stroke and when spontaneous recovery has occurred, enduring non-use of an affected limb can be observed and may in part be behaviourally conditioned (by the experience of uselessness in the acute phase) and maintained, even though the affected limb's functional use would be possible. Because this functional deficit has been learned to a considerable extent, it can also be unlearned. CIMT, i.e. massed practice with the more-affected arm on functional activities, shaping tasks in the training exercises, and restraint of the less-affected arm has repeatedly been shown to be effective in reverting the learned non-use phenomenon and is accompanied by use-dependent brain reorganisation.

So far, the reviewed clinical intervention studies used training techniques mediated by a therapist to promote recovery and/or function. There might be instances where physical training can be supported by technical aids. Technical aids might help to focus patients' efforts to critical aspects of training, enhance motivation, provide objective progress measures and automated feedback, promote more extensive training schedules when therapist resources are limited, or might reduce the physical demand on therapists when treating severely disabled patients.

Cauraugh [1] presents data from his clinical studies with functional neuromuscular electrical stimulation (FES). He shows that active neuromuscular stimulation on the impaired upper extremity and coupled bilateral coordination training (i.e. mirrored movements of the less impaired limb combined with active stimulation of the impaired limb) can promote motor recovery in terms of muscle activation pattern and manual dexterity.

Hogan and Krebs [7] summarise their experience treating patients with novel upper-extremity robotic therapy modules. Their paper reflects a substantial body of experience (over 250 patients at the time of writing). The MIT-MANUS robot provides graded assistance: if the patient is unable to move, the robot moves the patient's hand towards the intended target; if the patient moves inappropriately, the robot continually guides the patient's hand; and as the patient gains ability to control the limb, the robot provided less assistance. In addition, the robot provides instruments for objective measurement and assessment of motor control and recovery. In their clinical studies the interactive robotic therapy significantly reduced motor impairment of the treated limbs. The authors also introduce a new, possibly more effective robot training concept, i.e. performance-based progressive therapy. Looking at motor recovery from a motor learning perspective the robot is designed to adjust both the amount of mechanical assistance (or resistance) and the challenge presented by the task as performance improves.

Hesse [5] reports about his group's work on treadmill training with partial body weight support, enabling wheelchair-bound subjects to repetitively practice gait, the electromechanical gait trainer GT I reducing the physical strain on the therapists as compared to the manually assisted locomotor therapy, and the future HapticWalker which will allow the additional practise of stair climbing up and down and of perturbations. Applying the concept of task-specific repetitive training these gait training applications promote more intensive task-specific practice, less strenuous effort for the therapists, and the possibility of an intelligent man-machine interaction. Both treadmill training with partial body weight support and gait trainer therapy have been positively evaluated clinically.

Deutsch and co-authors [4] describe the use of virtual reality technology for the rehabilitation of individuals post-stroke. Two virtual reality systems, one that focuses on upper extremity use (Rutgers Master) and the other on lower extremity use (Rutgers Ankle) are presented. Each has several simulations that were created as enriched environments, which engage the user in a task that requires problem-solving in order to acquire a skill. In addition, they address specific impairments such as range of motion, strength, and speed, promote intense repetitive practice, and provide sensory input using haptic cues and feedback in a variety of ways. Like the robotic device, the VR systems can monitor

patient's performance and progress. In a series of pilot experiments with chronic strokes patients positive training effects at the impairment and functional levels have been reported.

Both animal experiments and human cortical plasticity investigations provided "proof of principle" that the interaction between (especially noradrenergic) medication and training can promote use-dependent plasticity and motor recovery. Among drugs that have been tested clinically in stroke patients when given in parallel to training therapy are d-amphetamine (several studies) and L-Dopa. Medication can, however, also block these positive effects, slow down recovery or reinstall deficits after recovery has occurred (e.g. haloperidol, clonidine, prazosin, ketamine, diazepam, midazolam).

Walker-Batson and co-authors [19] report about a pilot study of motor recovery comparing d-amphetmine/ placebo conditions. Ten hemiparetic patients were entered between day 16 and day 30 post stroke and followed over 12 months. Administration of a 10 mg dose of d-amphetamine was scheduled every fourth day for 10 sessions paired with physical therapy. Intense impairment-focused interventions addressing both upper and lower extremity recovery were performed during each session. Motor recovery between baseline and 1 week after amphetamine/placebo sessions and between baseline and 12 months was higher in the amphetamine group.

Scheidtmann [17] summarises two studies of motor recovery with a total of 63 hemiparetic patients comparing L-dopa/placebo conditions. L-dopa or placebo was given in addition to daily physiotherapy over a course of three weeks. Motor recovery between baseline and the end of the L-Dopa/placebo treatment period was bigger in the L-dopa group, but comparable afterwards, i.e. group differences remained. The author concludes that the gain in motor functioning depended directly on the adjuvant drug application and remained stable afterwards.

While these reports have been positive it has to be kept in mind that several clinical trials with amphetamine post stroke failed to enhance motor recovery. Age of patients, time after stroke, lesion location, severity of paresis, timing between drug and training, and type of training are all candidates to modify effects of medication.

5. Concluding remarks

Brain repair, adaptive reorganisation, and compensatory strategies can all contribute to functional recovery of motor systems after brain damage.

Animal experiments and human functional imaging studies clearly show that the injured brain changes its function with a complex pattern and variability across subjects and time. It is capable of functional reorganisation that promotes functional recovery. The evolution of these processes occur on different time scales and may take many months after injury. Further, motor behaviour influences these processes considerably. There is, thus, a need to tailor rehabilitation environments to promote recovery. A stimulating environment with a variety of experiences and interactions and graded motor rehabilitative therapy which starts out mildly may provide for optimal outcomes. Higher intensity training schedules than frequently provided in clinical settings seem to accelerate recovery in the post acute phase and to improve function in the chronic phase after stroke. Therapeutic strategies need to vary across subjects and with time and are best designed to target impairment constellations specifically. Technical aids such as electric and magnetic stimulation, robot devices, or virtual reality applications provide therapists with adjuvant therapeutic means that can contribute to more intensive and effective training schedules. Drugs that affect central nervous system transmitter can both slow or promote recovery. Their systematic evaluation has a high chance to increase the efficacy of clinical rehabilitation efforts.

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