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## Program of the symposium

### Stroke Recovery – Pharmacological Treatment Concepts in the acute and sub-acute phase

Sunday, 25 June 2017, 18:30–20:00 (Room: Forum)

Chairmen: Dafin Muresanu, Romania & Andreas Bender, Germany

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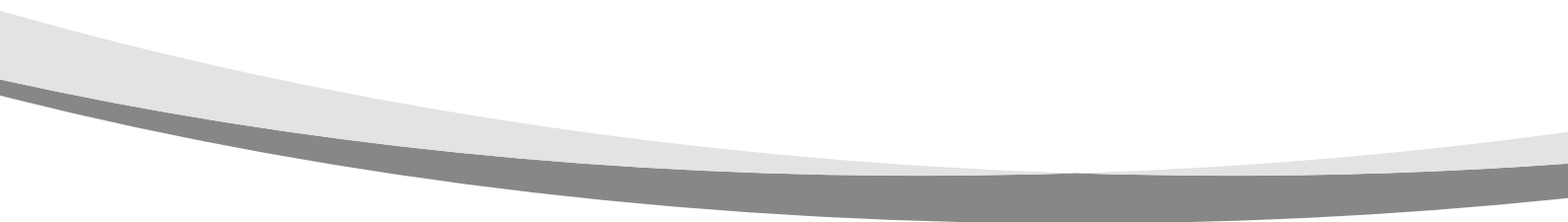
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# Timing, Training, & Tinctures – Reorganization & Recovery After Stroke



**Steven R. Zeiler**

Johns Hopkins, Baltimore, MD, USA

## ABSTRACT:

Studies in humans and nonhuman animal models show that most recovery from impairment occurs in the first 1–3 months after stroke as a result of both spontaneous reorganization and increased responsiveness to enriched environments and training. Improvement from impairment is attributable to a short-lived sensitive period of postischemic plasticity defined by unique genetic, molecular, physiological, and structural events. Data suggests that there are three important variables that determine the degree of motor recovery from impairment all else being equal: (i) the timing, intensity, and approach to training with respect to stroke onset, (ii) the unique post-ischemic plasticity milieu, and (iii) the extent of cortical reorganization. I will present data regarding both the biology of the brain's post-stroke sensitive period and the difficult question of what kind of interventions best exploit this period. I will describe limitations of current post-stroke rehabilitation methods and suggest novel interventions, which incorporate robotics, video-gaming, and pharmacological interventions including SSRIs and Cerebrolysin.

Dr. Zeiler discussed the research data coming from his lab, at Johns Hopkins University, as well as other labs within the context of the motor rehabilitation after stroke. He began by pointing to the fact that in the USA about 80 billions USD are spent every year for stroke treatment but, interestingly, only third of this sum is used for acute phase therapies. It means, that with advances in acute stroke management, higher proportion of stroke patients is able to survive and then has to cope with disabilities characteristic of chronic stroke. Up to 65% of stroke survivors have some motor deficits. Important for understanding the stroke recovery are concepts used to describe and define this complex process. The term “motor recovery” means improved success at a motor task, either by reduction of impairment or by compensation. The goal should be a true functional recovery rather than compensation. To this end, we understand that the plasticity processes are driving the functional recovery. How good are our current gold standard interventions in



the post-stroke rehabilitation in stimulating the brain plasticity after stroke? asked Dr. Zeiler. Regarding the upper extremity functional recovery, we have the situation that our interventions are not working (**Fig. 1**).

Dr. Zeiler went on to introduce the audience to the model of stroke which is used at his lab to investigate and better understand the nature of the functional recovery post-stroke. His team has noticed, that after stroke there is a short period of time during which the functional recovery occurs. After this sensitive recovery period, we can continue the rehabilitation with compensation, but true functional recovery is no longer possible (Fig. 2). In humans, it was found that the speed of recovery in the initial 4 weeks was maximum and the functional motor recovery stopped at 3 months post-stroke (Jorgenson et al., 1999). Interestingly, the authors from JHH (Johns Hopkins Hospital) found that the clinical picture at 72 hours post-stroke predicts very accurately the patient's clinical condition at 3 months. This means that whatever happens to the patients between 3rd and 90th day post-stroke has very little or no impact on their functional recovery (**Fig. 2**).

The conclusion is that the patients recover spontaneously, but current rehabilitation approaches have no impact on this process. The patients get better because of some kind of endogenous repair mechanisms. In order to improve our interventions we should better understand three important variables: the rehabilitation input, how it interacts with the sensitive recovery period, and to what kind of functional effects it leads. Dr. Zeiler went on to describe technicalities of the experimental setup used in his lab for studying motor function recovery with the mouse stroke model. The animals are trained in upper limb prehension and then subject to focal stroke affecting a region equivalent to the human primary motor cortex. When left in cage without any rehabilitation and tested a week after stroke, the animals lose ability



observed before the first stroke. Clearly, the second stroke caused more disability, but at the same time it re-opened the second sensitive plasticity period that could be used to fully recover the upper limb motor function (**Fig. 3**).

So, what is going during the sensitive recovery period after stroke, that makes it so important for the success of rehabilitation? Dr. Zeiler indicated that this can be explained by the relative activity of plasticity processes in the ischemic brain. In the normal, healthy brain the plasticity processes are maintained at certain level which is similar to that observed long time after stroke (in chronic stroke). However, immediately after stroke the plasticity is significantly increased in comparison with its level in the normal brain or in chronic stroke. In our early rehabilitation efforts we should be able to capitalize on this intrinsic capacity of the injured brain for structural and functional recovery. We can think about a few ways to take advantage of the sensitive recovery period for rehabilitation: early motor training, use of right interventions, and alteration and/or prolongation of the sensitive period. The enhanced environment early after stroke appears to have a positive effect on the functional recovery in animal models and combines both early intervention and right (various) procedures. In humans, this phenomenon has been studied by John Krakauer's group. The stroke patients in the ongoing SMARTS2 trial are randomized into two groups. The first undergoes the intense standard occupational therapy and the second uses specially designed immersive video game as a means of early rehabilitation. The idea is to bring enhanced recovery environment straight to the bed side of stroke patients, and to do it very early post-stroke.

In the last part of the lecture, Dr. Zeiler discussed the ways to alter the sensitive recovery period.

to perform the previously learned motor task. If the animals are rehabilitated after that time, they get a little bit better but never reach the previous level of functional agility. If we change the experiment and instead of letting the animal sit for a week, we actively rehabilitate it from day one after stroke, the animal quickly regains its full functional abilities. This means, that there is something very special going on just after the stroke that we can take advantage of when rehabilitating an animal. To further prove his point, Dr. Zeiler showed that when the late rehabilitated animals (with persistent motor disabilities) were given the second stroke, they could be immediately rehabilitated to the normal functional level



He mentioned two drugs studied in this context: fluoxetine and Cerebrolysin. Dr. Zeiler and coworkers showed that fluoxetine was able to enhance recovery when used during the sensitive recovery period to stimulate motor rehabilitation in their mouse stroke model. They were also able to show that this effect was linked to the brain plasticity, but not to the neuroprotective treatment effect. Cerebrolysin is known for years to enhance synaptic plasticity, and dendritic complexity as shown in various experimental models. When Dr. Zeiler used Cerebrolysin in his experimental model of stroke, the drug stimulated recovery of functions even without rehabilitation (**Fig. 4**).

This is the first time, said Dr. Zeiler, that we could see pharmacological modulation of the spontaneous endogenous repair mechanisms in the experimental model of stroke. If we train the animals early after stroke, they improve. If we don't train them after stroke and don't use any medication, or just use fluoxetine without training, the animals don't improve. However, if we use just Cerebrolysin without training, we significantly enhance the spontaneous recovery right away. This effect was independent of the changes in the stroke volume.

Summarizing his lecture, Dr. Zeiler suggested that we should rehabilitate our patients with the earliest possible exposure to the enhanced recovery environment, coupled with the medications known to safely enhance spontaneous recovery processes post-stroke, like Cerebrolysin and fluoxetine.

# Evidence based motor-rehabilitation: from established therapies to future perspectives



**Andreas Bender**

Therapiezentrum Burgau & Dept. of Neurology, University of Munich, Germany

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## ABSTRACT:

Impairment of motor function is a common clinical finding in patients with stroke or traumatic brain injury. While motor recovery seems to follow a rather typical natural course, several methods intended to increase the rate of such recovery are being applied in neurorehabilitation practice. This presentation will review the evidence for some of the most widely used motor rehabilitation therapies, based on the results of randomized clinical trials as well as on guideline recommendations. The timeline of such therapies will also be discussed in order to provide an overview of which interventions can be applied in the different phases after brain injury, i.e. acute, subacute, and chronic. Special attention will be paid to the different targets of rehabilitation interventions, i.e. a reduction of impairment, disability, or increased daily life independence or even quality of life. The presentation will provide an up-to-date summary of the evidence covering different categories of interventions, ranging from pharmacological approaches (e.g. fluoxetine, levodopa), rehabilitation robotics (e.g. electromechanical gait training), high training intensity strategies (e.g. constraint-induced movement therapy, CIMT), to mirror therapy and

mental practice. Data regarding promising future strategies, such as transcranial direct current stimulation (tDCS) will be discussed. Data regarding the effectiveness of comprehensive rehabilitation programs tailored to achieve patient-oriented goals will be examined.

A critical discussion of how this evidence is reflected in common day rehabilitation practice (with a focus on the German health care system) will try to provide some perspective on where we currently stand regarding the implementation of current guideline recommendations.

Dr. Bender opened his lecture by indicating that it will contradict to some extent Steven Zeiler's lecture; with the caveat that rather than talking about pure motor recovery, he will focus on activities of daily living. There is still a lot of controversy about the dose, time and kind of intervention that should be given to stroke patients. However, the reassuring fact is that it seems to be working, said Dr. Bender. Especially



when comparing the structured rehabilitation to doing nothing. The most prominent effects are decreased risk of dependency and death, as well as increased functional recovery and activities of daily living (ADL) scores (**Fig. 1**).

Regarding the pharmacological interventions, fluoxetine (as assessed in the FLAME study) appeared to enhance the motor recovery when used in patients within 5-10 days post-stroke. The enrolled patients suffered from severe hemiparesis/hemiplegia, with Fugl-Meyer Motor Scale (FMMS) at inclusion of less or equal 55. Fluoxetine belongs to the selective serotonin uptake inhibitors (SSRI) and is routinely used as antidepressant. Therefore, the important exclusion factor of the study was the lack of depression, as well as NIHSS>20, severe aphasia, previous residual motor deficit and use of psychopharmacological agents. At day 90 endpoint the group of patients treated with fluoxetine had significantly improved motor functions as assessed with FMMS. This was a clinically meaningful 10 points difference. The upper extremity improved more than the lower extremity and the clinical depression had no influence on the scores, while its incidence was significantly lower in the treatment group. The treatment was safe. Regarding the overall clinical

outcomes, the treated patients were more independent at day 90 endpoint than the placebo group, as measured with modified Rankin Scale (mRS) score (**Fig. 2**).

The FLAME findings were later confirmed by the Cochrane meta-analysis which included results from studies investigating clinical disability outcomes in 1300 patients treated with various SSRIs. The latest results came from the Chinese study with the longer observation time of 180 days and the outcome measured by NIHSS and Barthel Index (BI). The results showed that the significant improvement was maintained also after six months. All these results prompted a new development aimed at designing a new large



scale, multinational and multicenter approach. The resulting FOCUS, AFFINITY and EFFECTS trials have comparable protocols and assess the therapeutic effect of fluoxetine in recent stroke patients. Among them, the FOCUS trial already enrolled 100% of patients (3100), whereas the other two trials are still in the recruitment process. Together, they will include 6000 patients (**Fig. 3**).



There is a long history of L-dopa use in stroke patients, too. The recent DARS study enrolled 570 patients, administered 6-weeks-long treatment with a daily dose of 2000 mg, used 12 months observation point and ability to walk independently after 8 weeks as a primary end-point. The study showed no benefit of L-dopa treatment. This result was somewhat surprising to Dr. Bender who used L-dopa in the treatment of stroke patients and was convinced that some patients benefited from this therapy.

In the second part of his lecture Dr. Bender focused on non-pharmacological interventions. He began with presenting the results of Cochrane review of interventions for improving the upper limb function after stroke. This analysis revealed that while bilateral arm training is not effective, such interventions as non-invasive brain stimulation (rTMS, tDCS), constraint induced movement therapy (CIMT), mental practice, mirror therapy, repetitive task training, robotics, sensory interventions and virtual reality tools are beneficial. Interestingly, it was shown that while these rehabilitation measures improve outcomes in short term, their benefits disappear in long term observations.

Finally, Dr. Bender introduced the audience to future therapies and new developments in stroke rehabilitation. The use of stem cells therapy was recently investigated in a small group of stroke patients. This pilot trial enrolled the chronic stroke patients with stable baseline clinical parameters and no rehabilitation has been applied post-transplantation. The cells were injected to the areas adjacent to the infarct zone and observation was carried on for 12 months. There was a significant improvement in the motor functions as measured with FMMS during the observation period with plateau reached already 2 months



after the transplantation. Dr. Bender's group performed a trial investigating the rehabilitation of a mixed group of patients, suffering from both stroke and acquired chronic brain injuries, which happened on average 4 years earlier. This was an outpatient structured rehabilitation program lasting for 4 weeks, with a daily dose of 4 hours of therapy. The therapy was a goal-oriented approach in which a patient was able to choose a therapeutic goal. The goal attainment was significantly higher (78%) in the treatment group in comparison with the control group (42%). Also, the Functional Independence Measure (FIM) scores showed significant improvement in the active rehabilitation group (**Fig. 4**).

At the end of his lecture, Dr. Bender remarked that we have accumulated a lot of evidence for various therapeutic approaches and we need to translate it now properly into the rehabilitations programs. Simply, reality of stroke disabilities is much more complex than research reality suggested by the clinical trials designs. The practicability of many seemingly effective therapeutic approaches must be tested in real life, when they are just a part of the complex rehabilitation program. However, this aim is difficult to accomplish in the daily rehabilitation routine. Therefore, the rehabilitation programs must not present a simple collection of the effective rehabilitation approaches. Rather, they must be tailored to individual needs of a particular stroke patient.

# Challenges & Opportunities in Motor Recovery



**Dafin Muresanu**

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## ABSTRACT:

Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes.

Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization- related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care.

It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke.

The study showed a statistically significant group difference in the upper- limb motor function (ARAT) at day 90 – primary end point. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better quality of life.

In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach. Furthermore, CARS 1 and CAR 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.

The lecture of Dr. Muresanu continued the topic of motor rehabilitation from the perspective of new opportunities and challenges ahead. He set the tone for the lecture by stating that both the limitations of the individual's disability and this individual's biological reserve, or recovery potential, must be taken into account when making therapeutic decisions about rehabilitation after stroke. Among many different neurological conditions treatable by rehabilitation, stroke appears as probably the most amenable for multimodal interventions. Dr. Muresanu echoed Dr. Binder's view on the discrepancy between the medical model of intervention, represented by the evidence based medicine driven clinical investigations, and the real life rehabilitation approaches which often lack the rigor of the medical model and exist in much more complex therapeutic environment. In effect, one of the major challenges in neurology is to merge both models and to bring the evidence based medicine closer to the real life experience.

Dr. Muresanu went on to discuss the importance of the multidisciplinary approach in stroke services. He underlined that in both the acute and post-acute/rehabilitation treatment a structured and dedicated approach (stroke unit, rehabilitation and comprehensive stroke unit etc) is needed. This also concerns the acute rehabilitation concept. Here, the careful evaluation of a patient before initiating rehabilitation is very important. Then, the initiation of rehabilitation as soon as possible is recommended for eligible patients. In this context, the timing and intensity of acute rehabilitation remain controversial. Early mobiliza-

tion is recommended in many clinical guidelines worldwide. However, the results of the AVERT trial showed to us that too early and too intense early mobilization can be also harmful to many stroke patients. The decision about early mobilization must be taken on the case by case base taking into account vital clinical parameters of an individual patient.

Regarding the pharmacological support in neuroprotection and neurorecovery, which are important undercurrents of the rehabilitation, Dr. Muresanu divided available options into three categories: 1. Monomodal neuroprotective suppressive agents with singular or pleiotropic mechanism of action (e.g. calcium channel blockers); 2. Monomodal pleiotropic agents which stimulate neuroplasticity (e.g. SSRIs); and 3. Multimodal, modulating agents with pharmacological properties contributing to both neuroprotection and long term recovery processes (e.g. Cerebrolysin). Unfortunately, majority of clinical trials in rehabilitation are initiated long after the incidence of stroke, while our rehabilitation efforts are being often undertaken much earlier in the clinical practice. This discrepancy adds to our relatively poor understanding of the therapeutic potential of the pharmacological support of rehabilitation. One notable exception to this situation are efforts undertaken in studying the therapeutic potential of fluoxetine/SSRIs as support for motor rehabilitation, as mentioned already by previous speakers.



Another progressing area of research relates to multimodal drugs. Dr. Muresanu presented a short history of the development of the multimodal treatment concept for stroke patients. Cerebrolysin emerged as the example of a multimodal agent with high therapeutic potential **(Fig. 1)**.

The neurotrophic mode of action of Cerebrolysin allows it to act simultaneously as a neuroprotectant and a stimulator of the natural recovery processes. To date, a compelling evidence has been collected for Cerebrolysin treatment in stroke, which is based on about 5000 patients.

It encompasses two periods in research: one, related to the traditional acute treatment studies design and second, represented by modern approach of supporting the early rehabilitation post-stroke. In the former approach, the short term acute treatment resulted in temporary clinical benefits that could not be maintained until day 90 endpoints of these trials.

In the novel approach, represented by the CARS trial, the longer treatment period was applied (21 days instead of 10 days) as well as association of pharmacotherapy with the structured motor rehabilitation **(Fig. 2)**.

The idea of pharmacological stimulation of the biological capacity of a patient for recovery was proven right. The Cerebrolysin therapy started within 24-72 hours post-stroke. The standardized rehabilitation program (2h per day) began within 48-72 hours post-stroke and both types of intervention continued for 21 days. The primary outcome measure was change from baseline in ARAT (Action Research Arm Test) score at day 90. The secondary outcome measures were a battery of 12 various tests including NIHSS, mRS, BI, gait velocity and other (**Fig. 3**).

The primary endpoint analysis showed significantly improved ARAT scores in the treatment/combination group in comparison with the patients undergoing rehabilitation without the pharmacological support. Moreover, the clinically meaningful effect was observed early on, already after the second week of treatment (**Fig. 4**). This is highly relevant for reduction of complications as well as for cognitive development of a patient, underlined Dr. Muresanu.





The distribution of the mRS scores was also significantly in favor of the Cerebrolysin treated group (42% vs 14% of patients with no disability symptoms). The forest plot analysis of all 12 outcome measure tests showed the overall significant positive effect of the treatment with the combination Cerebrolysin: motor rehabilitation. The safety profile was confirmed as excellent, in line with the previously obtained clinical data for acute treatment with Cerebrolysin (**Fig. 5**).

Closing his lecture, Dr. Muresanu underlined the importance of early multimodal intervention and of achieving early clinical outcome changes. These should be in the focus of our stroke recovery efforts. The concept of early/acute multimodal intervention as well as of individualization of stroke therapy is valid and should be further explored in the near future.

# Emerging concepts in multi-modal motor rehabilitation after stroke



**Andreas Winkler**

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## ABSTRACT:

The neurophysiological principles of motor recovery after stroke are still not fully understood and subject to ongoing investigations. After stroke basic processes of motor recovery involve developing new neural connections, acquiring new functions, and compensating for impairments. These processes are related to neural plasticity. Advances in our understanding of neural plasticity that occurs after stroke have led to the formulation of at least two complementary theories of motor-recovery after hemiparetic stroke: the “reactivation” and “rebalancing” theory. Both strategies seem to provide promising grounds for new rehabilitation strategies, especially those implementing upper limb immobilization for patients with sustaining low-functioning upper limb paresis. An increasing number of studies have reported various motor learning-based stroke rehabilitation strategies (CIMT, mental practice, virtual reality, mirror therapy etc.). Additionally, current research aims to determine, whether using combinations of different strategies can synergistically improve motor recovery. NIBS (tDCS, rTMS) and neuromuscular electrical stimulation can “boost” motor recovery by ameliorating use-dependent plasticity impairment after stroke. Additionally it has been shown, that the effects of motor rehabilitation training

can be further promoted, when combined with systemically administered drugs: Antidepressants affect the reuptake and metabolism of central neurotransmitters and meta-analysis of the effect of SSRI's on post stroke disability have shown relevant improvements on the functional outcome on recovery. The neurotrophic drug Cerebrolysin®, when given early after stroke, improved upper limb function to a clinically significant extent. The implications of these findings have strongly influenced contemporary concepts in motor rehabilitation strategies.

Searching for clear answers in the field of rehabilitation after stroke is difficult, but we have to get them in order to help our patients. With this in mind, Dr. Winkler presented his view on the development of multimodal therapies for motor rehabilitation of stroke patients. More than 80% of them suffer from some kind of motor deficits, one-third is unable to walk, one-third remain severely disabled, and one-third suffer from





aphasia. Notably, arms rehabilitation is much less successful than legs rehabilitation (2/5 vs 4/5 regaining functional use respectively), about 75% of patients continue to experience upper limb symptoms, 60% of patients with non-functional arms one week post-stroke remain disabled, and 4 years after stroke only 50% of patients have fair to good recovery of arm function. Therefore, we have to ask ourselves some important questions: 1. Can we improve accuracy of prognosis? 2. Can we be more effective in motor rehabilitation? 3. Can we enhance the brain plasticity? and 4. Can we transfer our concepts into a real-world setting of rehabilitation?

The preservation of the corticospinal tract (CST) must be considered as very important prognostic factor, because the existence of the residual structural and functional architecture is a prerequisite for effective recovery. Further on, the predicting recovery potential (PREP) algorithm appears to be a good and practical diagnostic tool (**Fig. 1**).

Regarding the effectivity of motor rehabilitation, the known rule applies which says that mild to moderately affected patients (70% of stroke population) recover in a linear fashion, while the severely affected group does not behave in similar way.

Theoretically, all stroke patients should benefit from improved effectivity of rehabilitation. Increasing the dose and frequency of rehabilitation is one way toward achieving this goal. While in the animal models the positive changes in the primary motor cortex appear after about 400 repeats of the movement, in our rehabilitation practice the patients rarely receive more than 30 moves per daily cycle. It is often too difficult to reach a threshold of the effective dose of motor rehabilitation in the real-world rehabilitation setting.



earlier, suggested Dr. Winkler. The non-invasive brain stimulation technology (like tDCS and rTMS) appear to be effective when used together with the physical rehabilitation (even in chronic stroke patients) of upper extremities. The potential of pharmacological interventions was discussed in the previous lectures. One additional piece of data recently announced concerns a TALOS trial (Citalopram in Patients with Acute Ischemic Stroke) which enrolled 642 stroke patients and investigated the efficacy of SSRI administered in standard dose. There was no benefit of the treatment as assessed with mRS. The concept of boosting neuroprotection and neurorecovery post-stroke with Cerebrolysin is investigated and discussed already for some time. Dr. Winkler mentioned the available clinical data for Cerebrolysin treatment of stroke and suggested that they show biological signals of improvement in recovery processes. These data indicate that Cerebrolysin induces a favorable milieu for enhanced plasticity and motor recovery, said Dr. Winkler. However, we need to apply this knowledge into our clinical practice of rehabilitation. For example, the recently published resting state functional MRI (rsfMRI) data showed that Cerebrolysin enhances symmetrical functional connectivity between brain hemispheres, which correlated with the improved recovery of motor cortical function (**Fig. 2**). The increased use and availability of modern imaging modalities helps to explain why certain pharmacotherapies support rehabilitation at the structural level. This should encourage a more widespread use of the treatments like Cerebrolysin.

Nevertheless, CIMT and neuromuscular stimulation are examples of therapies where very high frequencies/dose of training were achieved.

It was recently shown that significant increase of upper limb training intensity can be achieved with help of robotics (up to 300 h) which in fact resulted in 15% improvement of functions. The timing of rehabilitation is also an important success factor. The experience of AVERT trial indicates that shorter but more frequent sessions of early mobilization appear to be most effective in the first weeks after stroke.

It is also very important to think about the ways to enhance brain plasticity in order to break through the 70% rule of recovery mentioned



Finally, Dr. Winkler suggested that we should try to transfer our research concepts into a real-world rehabilitation settings. The promising future of rehabilitation would most probably rely on the multimodal approach which combines various concepts into a tailored, individualized rehabilitation programs (**Fig. 3**).

Dr. Winkler illustrated this approach with a clinical case: a chronic stroke patient with left side hemiparesis who underwent the second stroke. About 3 months post-stroke, the patient was given a two-weeks course of multimodal therapy consisting of intensive occupational therapy (>1h/day), Cerebrolysin (30ml/day for 14 days), and tDCS (2x20 min/day, 5 days/week ). This multimodal approach improved significantly the patient's ARAT score. Such a case suggests that multimodal approach is feasible in real-world rehabilitation setting and has potential for making a difference for our stroke patients.

Concluding his lecture, Dr. Winkler indicated that we witnessed in recent years profound changes in our understanding of the recovery processes. We know that one of the most important prognostic factors in the motor rehabilitation is the integrity of CST. Moreover, we have the tools suitable for early and accurate prognosis. The manipulation of plasticity potential of the injured brain is possible, but we still don't know what is the right dose, frequency, and timing of the interventions. We also understand that using multimodal approach in rehabilitation makes a lot of sense, but needs further clinical evaluation. Finally, the combination of various rehabilitation approaches should be considered for any individual clinical picture. This should produce tailored rehabilitation programs as required on case by case basis.



ABBREVIATED PRESCRIBING INFORMATION: Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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