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Advances in Sub-Acute Stroke Motor Recovery

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Advances in Sub-Acute Stroke Motor Recovery

Tuesday, 10 May 2016, 18:00-19:30 (Hall D)
Moderator: Valeria Caso, Italy

Stroke Recovery: Timing, Training, & Biological Determinants

Steven R. Zeiler

Johns Hopkins, Baltimore, USA

ABSTRACT:

Motor recovery after stroke can occur either via reductions in impairment or through compensation. 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. In contrast, compensation can occur at any time after stroke. 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. Future work will need to further characterize the interaction between types of training and post-ischemic plasticity, and find ways to augment and prolong the sensitive period using pharmacological agents or non-invasive brain stimulation.

Taking into account the enormous costs and social consequences of stroke worldwide, we should pay increased attention to four variables of major importance in stroke recovery: molecular, pharmacologic, physiologic and behavioral, said Dr. Zeiler. He went on to define the term "recovery" as improved success at task achieved either through reduction of neurological impairment or through compensation for the impaired functions. The plasticity of the central nervous system appears to be a driving force behind these two modes of recovery after stroke.

He also indicated that the topic of his lecture relates neither to recanalization (a successful intervention) nor neuroprotection (a failure in stroke trials), which are targeting different than recovery physiopathological domains of stroke. Recovery describes all the mechanisms involved in structural and functional remodeling of the brain after stroke. However, our golden standard for supporting stroke recovery – physiotherapy – is not really effective. The same is true for occupational therapy. While compensation strategies are partially effective, there is no data available showing that anything we do after stroke affects true stroke recovery (Fig. 1).

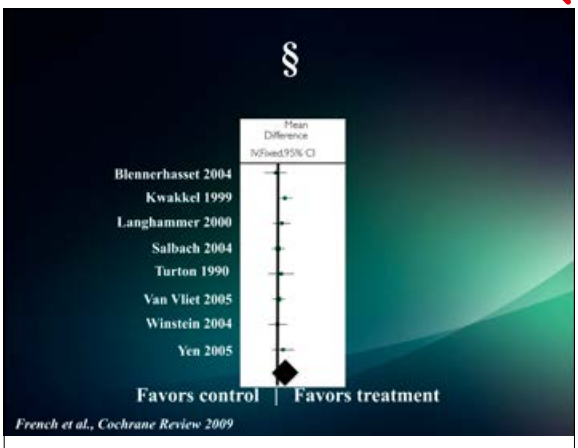


Fig. 1. Post-stroke physiotherapy does not support true functional recovery

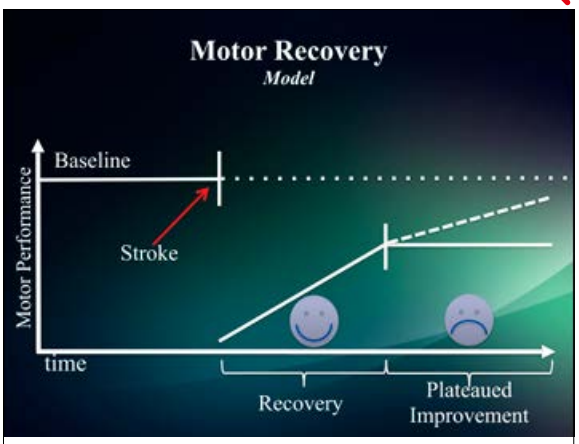


Fig. 2. The model of motor recovery post stroke

After the initial period of spontaneous recovery, the process reaches plateau and no further recovery of impaired functions is observed (Fig. 2). The active recovery period was shown to span about 3 months and the initial 4 weeks appear to represent the most dynamic hyperplasticity phase within the recovery period. Moreover, it was shown that the clinical variables at 3 days after stroke can be used with very high accuracy to predict the clinical outcome after 3 months. This means that whatever we do with patients in this period is meaningless for a patient's recovery. It seems that not the clinical input, but rather the biological input is important for the recovery. The recovery happens in spite of our clinical interventions…[1,2]

Dr. Zeiler described an animal model developed to characterize the sensitive recovery period responsible for spontaneous recovery, in which rats affected by a primary motor cortex stroke recover completely motor function of the affected arm when the training is initiated immediately (1 day) after stroke, but not after 1 week delay.[3] This window of opportunity for motor training intervention reappears after second stroke and can be successfully utilized for training-induced, complete recovery of the impaired arm function. Similar results were shown for therapeutic effects of enhanced environment on recovery (Fig. 3).

What is going on during sensitive recovery period after stroke? Several research laboratories have characterized the processes underlying spontaneous biological recovery within the sensitive recovery period. These processes overlap to significant extent, and in a timely fashion, with those induced by motor training (Fig. 4).

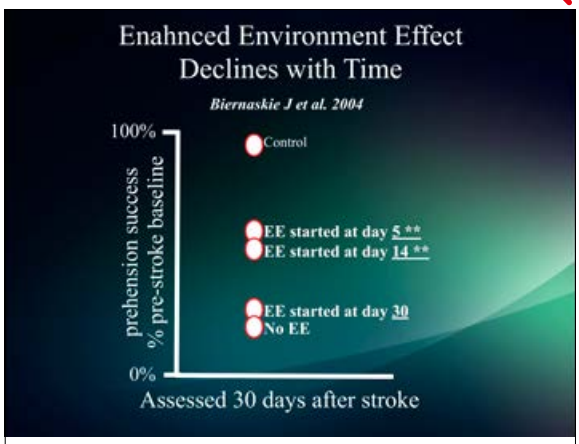


Fig. 3. The sensitive recovery period after stroke and the effect of enhanced environment on spontaneous biological recovery decline with time

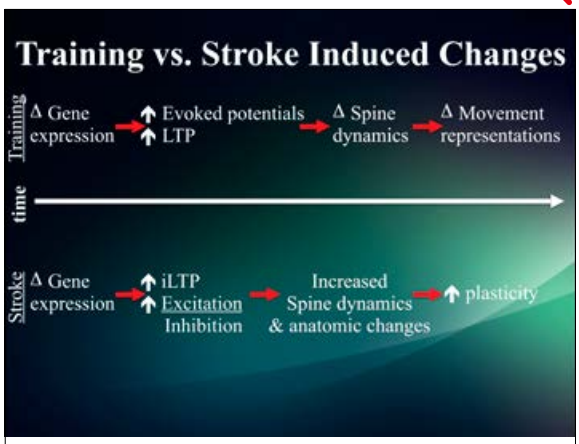


Fig. 4. Motor training and stroke induced changes in the brain are similar at molecular, physiological and structural levels

Interestingly, the plasticity processes in the normal/healthy brain do not differ significantly from plasticity processes present in the chronic post stroke brain. However, within the acute post stroke brain there is a significantly enhanced plasticity environment present indicating that this is the period particularly amenable for therapeutic intervention (Fig. 5).

The existence of sensitive recovery period early post stroke suggests that suitable therapeutic measures must be applied early post stroke and that any delay could translate into lower rate of success. However, the question of intensity of intervention remains open, especially in the case of rehabilitation procedures. These vary widely worldwide and there is no clear recom-

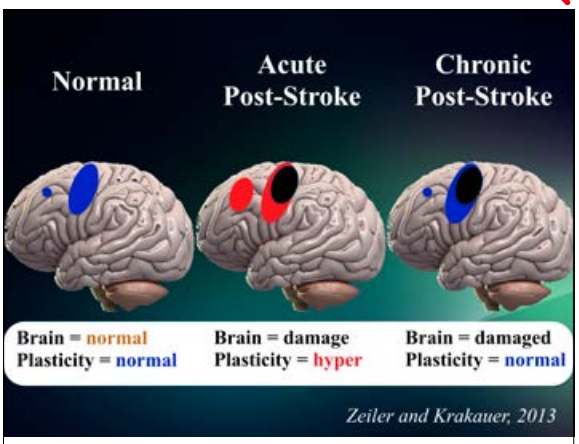


Fig. 5. The hyperplasticity environment of the acute post stroke brain characterizes sensitive recovery period – a proper target for pro-recovery therapies

mendation available regarding the dosage of rehabilitation post stroke. What we know so far is that rehabilitation should be more intensive than usually practiced and that rehabilitation should be focused on impaired functions rather than directed at compensation.

Another important question that must be answered is how can we alter or prolong the sensitive recovery period in our stroke patients? One way to achieve this goal would be to administer specific medicines that support spontaneous biological recovery. In this context, Dr. Zeiler presented the data of clinical research with fluoxetine and Cerebrolysin. Fluoxetine was recently shown to improve motor functions in stroke patients when administered together with rehabilitation. Dr. Zeiler's lab investigated fluoxetine in the animal model of stroke and found out that fluoxetine is capable of prolonging the sensitive recovery period post stroke. This might explain why it was shown to support rehabilitation of stroke patients. Moreover, fluoxetine has no apparent neuroprotective properties. In fact, animals treated with fluoxetine displayed more widespread neuronal death than control animals. Fluoxetine is not neuroprotective, but it seems to support processes of spontaneous biological recovery.

Similar picture emerges from studies with Cerebrolysin[4], a peptide conglomerate which was extensively studied and has displayed various neurorestorative properties in the research models of neurological disorders, including stroke (Fig. 6). Cerebrolysin treatment was effective when administered early in animal models of the ischemic stroke.

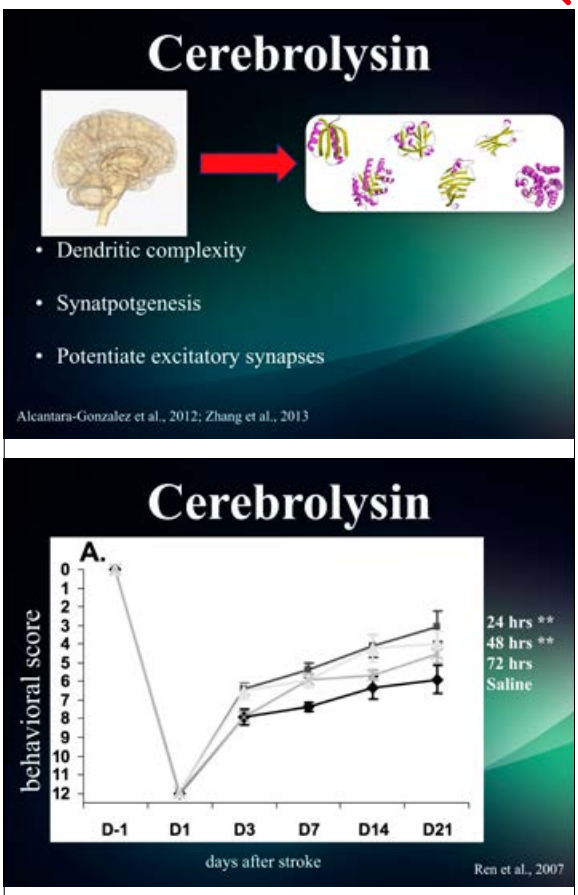


Fig. 6. Neurorestorative properties of Cerebrolysin and stimulation of spontaneous biological recovery after stroke

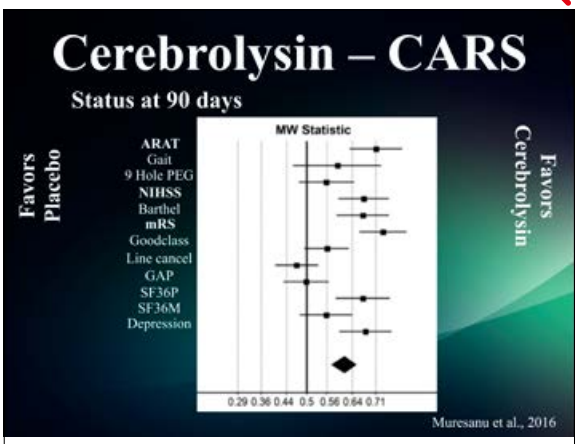


Fig. 7. Cerebrolysin supports rehabilitation of stroke patients

Additionally, the recently published rehabilitation study[5] has shown results similar to those obtained with fluoxetine, indicating that Cerebrolysin can effectively support rehabilitation of stroke patients (Fig. 7).

Dr. Zeiler offered his interpretation of the positive fluoxetine and Cerebrolysin trials indicating that both medicines appear to increase responsiveness of stroke patients to the rehabilitation therapies; especially among more severe cases which do not follow typical pattern of spontaneous recovery. The work is in progress aimed at elucidating the optimal timing of the treatment, why the proper timing of Cerebrolysin therapy is important, and what are the particular mechanisms playing the key role in this process. This work should help to further optimize Cerebrolysin treatment regimen in stroke.

Finishing his lecture, Dr. Zeiler indicated that currently stroke patients passively spend about 90% of their hospital time in a bed. If we agree with the research data defining the sensitive recovery period after stroke, we should admit that such an environment does not support natural recovery processes. We are wasting the opportunity to advance recovery of stroke patients, said Dr. Zeiler. Instead, we should create for our patients the enriched recovery environment supported by active rehabilitation combined with medicines stimulating spontaneous biological recovery after stroke (Fig. 8).

Selected literature:

1. S. Zeiler and J.W. Krakauer. The interaction between training and plasticity in postroke brain. Curr Opin Neurol 2013, 26:609-616
2. J.W. Krakauer et al., Getting neurorehabilitation right: what can be learned from animal models? Neural Repair 2012, 26(8)923-931
3. K.L. Ng et al., Fluoxetine maintains a state of heightened responsiveness to motor training early after stroke in a mouse model. Stroke. 2015;46:2951-2960
4. J. Ren et al., Cerebrolysin enhances functional recovery following focal cerebral infarction in rats. Restor Neurol Neurosci. 2007;25(1):25-31.
5. D.F. Muresanu et al., Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. Stroke. 2016 Jan;47(1):151-9

Fig. 8. Sensitive recovery period should be actively targeted by enriched environment, and early and intensive rehabilitation supported by medicines stimulating spontaneous biological recovery after stroke

Significance

The success of the motor rehabilitation appears to depend on sensitive recovery period lasting for about 3 months after stroke. The sensitive recovery period is characterized by hyperplasticity processes that can be targeted and stimulated with enriched environment for the optimal neurorehabilitation. The enriched environment consists of several key elements, including intensive motor and cognitive impairment rehabilitation, as well as medicines that amplify the mechanisms underlying spontaneous biological recovery post stroke. Attention should be paid to apply these measures as soon as possible in order to take advantage of short-living enhanced plasticity environment present early after stroke.

Motor Recovery after Stroke – Challenges & Opportunities

Andreas Winkler

Neurological Rehabilitation Clinic Bad Pirawarth, Bad Pirawarth, Austria

ABSTRACT:

Advances in our understanding of neural plasticity that occurs after stroke have contributed to the generation of new theories and concepts of post stroke motor recovery. Modern theories of post stroke motor-recovery arise from several neurophysiological and neuroimaging investigations performed with brain injured adult humans and animals. They have contributed 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. Additionally, current research aims to determine, whether using combinations of different strategies can synergistically improve motor recovery. 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 CARS-Study, where the neurotrophic drug Cerebrolysin was given within the first 3 days after stroke onset for 3 weeks showed to improve upper limb function to a clinically significant extent. The implications of these findings in regard to contemporary motor rehabilitation strategies will be discussed and a pragmatically based perspective provided.

The everyday practice of rehabilitation in an Austrian rehabilitation center has been discussed by Dr. Winkler. One important aspect is an access of a stroke patient to a rehabilitation center. In Austria, the access to rehabilitation is integreated within the stroke management system and follows the acute management phase. Several important elements constitute a complex environment of stroke therapy, like: the fact that stroke is fundamentally a chronic disease; necessity of lifestyle modification; controlling for cardio-vascular risk factors/primary and secondary prevention; improving access to stroke unit (SU) – i.v Thrombolysis/Thrombectomy; and rehabilitation and motor recovery. When we talk about motor rehabilitation, there are a few fundamental factors determining its success or failure: timing, intensity, the therapy itself (how we treat a patient and what kind of medicines are we employing to support the process of recovery) and finally, what is the target of rehabilitation? (Fig. 1).

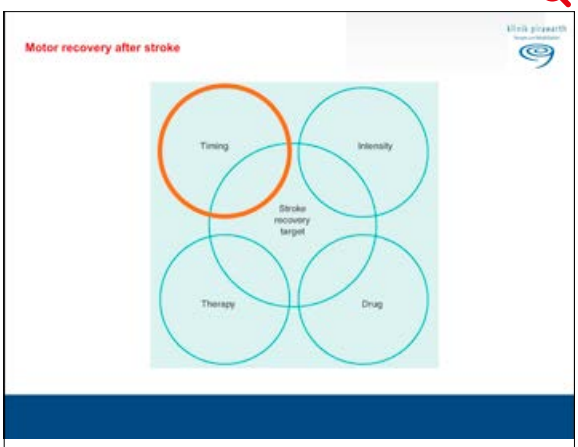


Fig. 1. Essential factors influencing motor rehabilitation after stroke

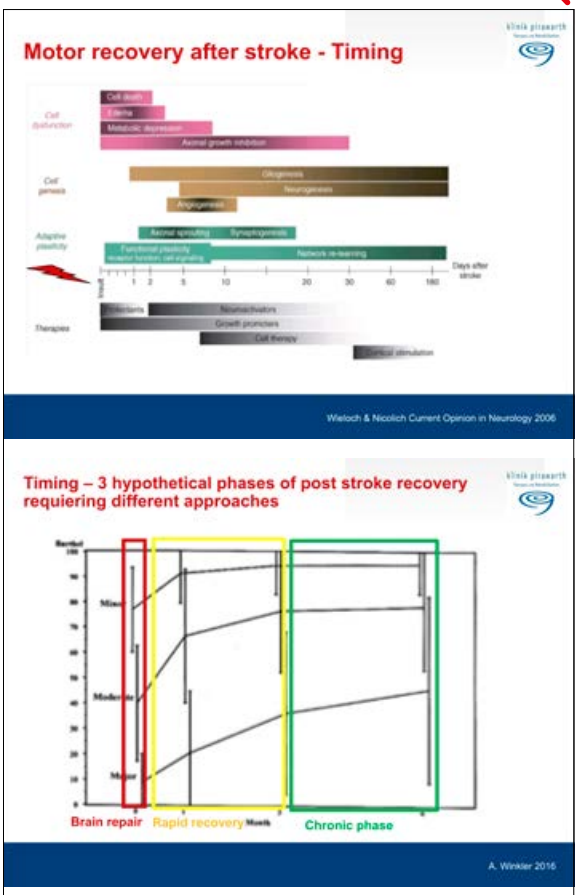


Fig. 2. Pathological and biological processes influencing different phases of recovery after stroke

The timing of rehabilitation is determined by pathological and biological processes occurring after stroke, as well as their duration (Fig. 2). The very early stage might be amenable for using neuroprotectants while the later stages – for the therapies stimulating biological recovery processes.[1]

When assessing the potential usefulness of the motor rehabilitation it is important to analyze the integrity of corticospinal tract (CST) first. Early predicting the outcome of motor rehabilitation can be done with finger extension and shoulder abduction within 72 hours post stroke. The PREP (Predicting REcovery Potential for the hand and arm) algorithm has been further developed to accurately analyze potential of motor arm recovery after stroke (Fig. 3).[2]

Transcranial magnetic stimulation (TMS) is used in Dr. Winkler's clinic as part of a comprehensive approach to advance rehabilitation of motor functions. Combination of different rehabilitation methods is increasingly practiced including also Brain-Computer-Interface/Motor Imagery therapy.

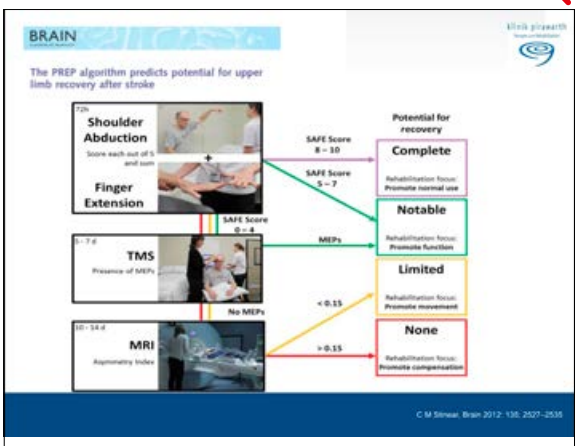


Fig. 3. Predicting motor recovery after stroke using PREP algorithm

The standardization of different rehabilitation methods and technologies is progressing and American Heart Association (AHA) guidelines constitute a good benchmark for the current practice and the future development in this field (Fig. 4).[3]

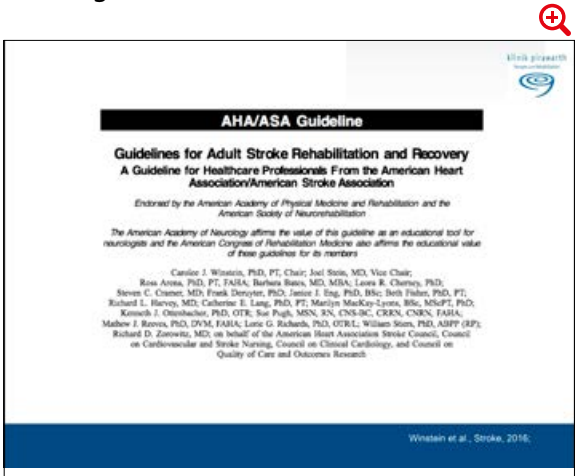


Fig. 4. The guidelines of American Heart Association for rehabilitation after stroke

Dr. Winkler dedicated the last part of the lecture to pharmacological support of motor rehabilitation. There is a long history of using medicines to advance rehabilitation, however with very limited success (Fig. 5). Only recently, the FLAME trial employing selective serotonin re-uptake inhibitor (SSRI) fluoxetine showed a promise of effective support of motor rehabilitation.[4] The large scale trial including 6000 patients is under way and should further elucidate the role of SSRI is treatment of stroke. Similarly, the recent results of rehabilitation trials

with Cerebrolysin, a neuropeptide drug, suggest that pharmacological support of rehabilitation can soon become a working therapeutic concept in stroke rehabilitation. In this case we have learned how to better use an agent which was already in clinical practice for a long time.

Significance

In the rehabilitation of motor impairments after stroke, a combination of different therapeutic approaches is increasingly being viewed as a preferred standard. Especially, non-invasive techniques of rehabilitation are being enriched by novel approaches to pharmacological stimulation of natural recovery processes. Fluoxetine and Cerebrolysin are agents that are known for long time already, but their positive role in comprehensive approach to motor rehabilitation after stroke is just beginning to be elucidated.

Selected literature:

1. T. Wieloch & K. Nicolich. Mechanisms of neural plasticity following brain injury. Curr Opin Neurobiol. 2006 Jun;16(3):258-64
2. C.M. Stinear et al., The PREP algorithm predicts potential for upper limb recovery after stroke. Brain 2012: 135; 2527–2535
3. C.J. Winstein et al., Guidelines for Adult Stroke Rehabilitation and Recovery A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association Stroke. 2016;47:e98-e169
4. N.S. Ward & L.G. Cohen. Mechanisms underlying recovery of motor function after stroke. Arch Neurol. 2004 Dec;61(12):1844-8

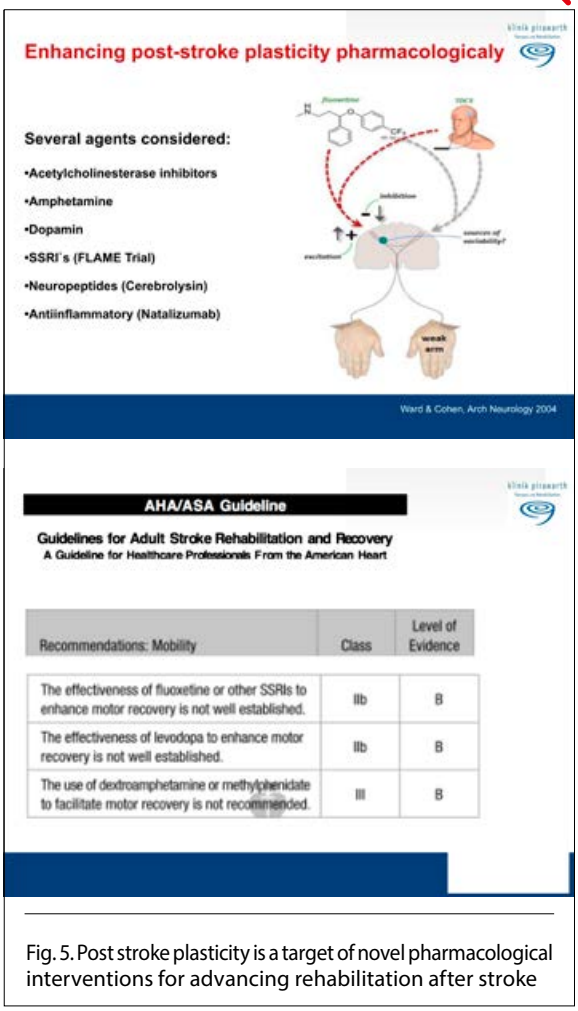


Fig. 5. Post stroke plasticity is a target of novel pharmacological interventions for advancing rehabilitation after stroke

Modulation of Neural Plasticity after Stroke: A Strategy for Noninvasive Brain Stimulation in Neurorehabilitation

Yun-Hee Kim

Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Republic of Korea

ABSTRACT:

Neuroplasticity plays an important role in coordinating neural interactions on different levels from cellular changes to wide-range cortical remapping for recovery from ischemic brain injury such as stroke. An experience-dependent synaptic and circuit plasticity remodels synaptic buttons and connections by repeated sensory experience. Modulation of neuroplasticity may enhance the rehabilitative outcome and functional restoration after stroke; therefore, it is a crucial topic of neurorehabilitation. Noninvasive brain stimulation (NBS) is one of recently developed techniques to modulate neural plasticity in a noninvasive manner. The cortical modulating effect of NBS was proved to expand to the interconnected subcortical network areas beyond the site of stimulation. The most popular noninvasive methods of neuromodulation include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). By TMS, rapidly changing magnetic field induces electric current on the cortical surface that activates neuronal element of the cortex. In the other hand, tDCS induces excitability changes of human cerebral cortex by weak DC stimulation through glutamatergic and membrane mechanisms. One of the considerations for using NBS in clinical setting is individual variation of its responsiveness. Diverse factors such as individual skull and cortical morphology, lesion location, BDNF genotype are considered as the intrinsic factors of this response variability. Methods for proper electrode location, focal stimulation, multichannel stimulation, and real-time monitoring of stimulation effect were topics of future investigation to reduce the inter-individual variability of NBS effect. A novel neurorehabilitation strategy of using customized brain stimulation methods in combination with various rehabilitation techniques and newly developed neurotrophic medications such as Cerebrolysin can provide enhancement of functional recovery after stroke.

In the comprehensive lecture about the new strategies for supporting recovery from brain injuries, Dr. Kim focused on non-invasive methods of stimulation of the natural plasticity processes. The lecture has been divided into following sections: neuroplasticity after stroke; noninvasive brain stimulation; pharmacologic enhancement of neural plasticity; and future perspectives.

Dr. Kim began by analyzing phases of ischemic stroke as representing discrete windows of opportunity for rehabilitation. The initial 3-months-long period has been confirmed to represent a greatest chance for advancing recovery of stroke patients. Within this period, a restoration of cortical functions as well as reorganization of motor cortexes has been described (Fig. 1).

The multifunctional neuroimaging methodology (Fig. 2) is increasingly being used for monitoring functional and structural reorganization of the relevant brain regions post-injury. These tools are also valuable in noninvasive monitoring and fine tuning the rehabilitation and its effects on plasticity processes during the sensitive recovery period.[1,2]

Among many currently used or still experimental interventions aimed at supporting natural recovery from stroke are environmental modifications, neuroprotective and neurorestorative agents,

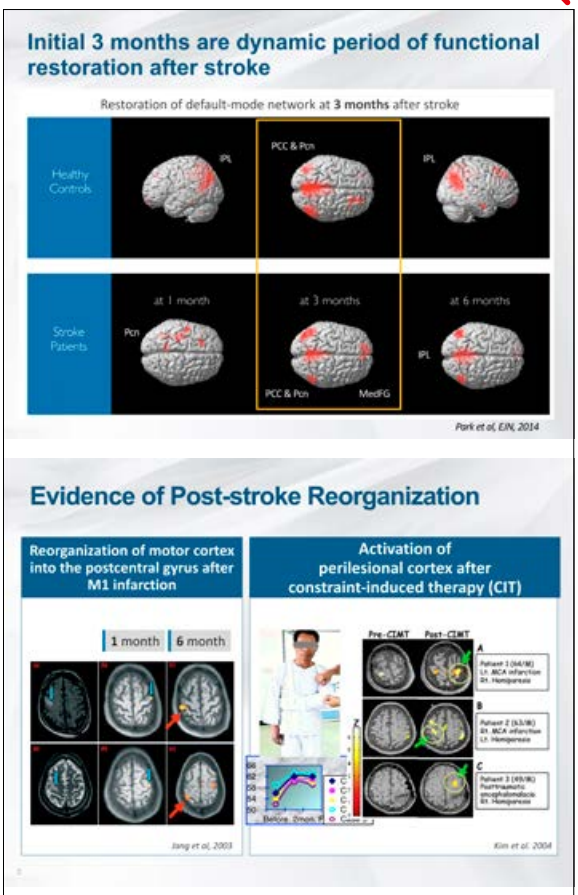


Fig. 1. The sensitive recovery period after stroke is characterized by spontaneous reorganization and functional restoration of the affected cortical functions

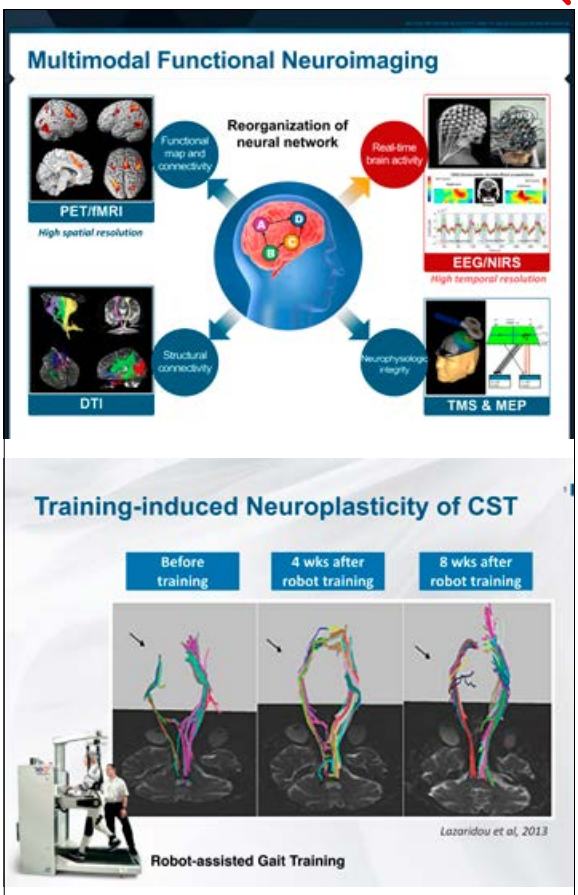


Fig. 2. Multimodal functional and structural neuroimaging techniques can be used to inform optimal rehabilitation strategies

stem cell transplantation, and the brain stimulation techniques which can be invasive and non-invasive (Fig. 3).

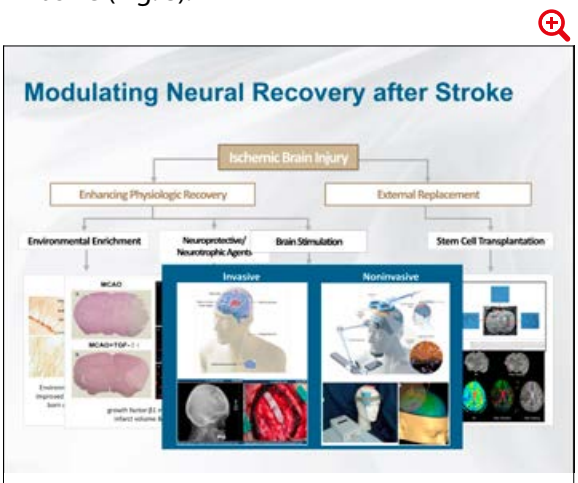


Fig. 3. Various approaches utilized for enhancing recovery after the ischemic stroke

The invasive techniques are not considered satisfactory at this point, as there is still lacking the conclusive clinical data. In comparison, non-invasive brain stimulation (NBS) has been shown to effectively modulate neuronal network with resulting enhanced recovery (Fig. 4).

Especially, the repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are currently used to modulate cortical excitability with resulting activation of neuronal network and enhancement of recovery after stroke.[3] The suppression of hyperexcitability of the contralateral hemisphere appears as the most prominent and effective way to recover interhemispheric balance after stroke, which is conductive of enhanced reorganization and plasticity in the region of an injury. The evidence based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) give it the level B recommendations. Among major limitations of the NBS are: effect size is

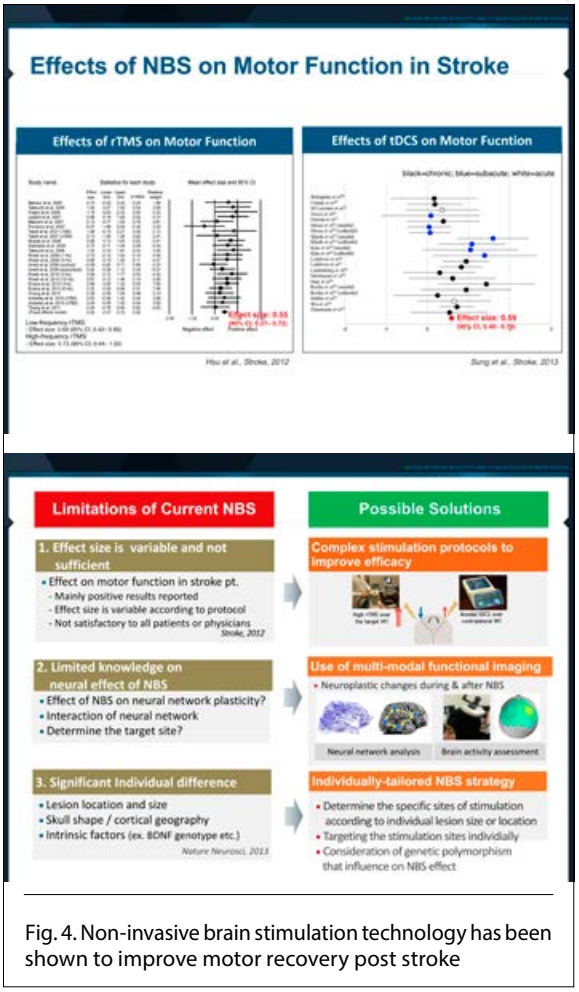


Fig. 4. Non-invasive brain stimulation technology has been shown to improve motor recovery post stroke

variable and still not sufficient; there is a limited knowledge on neural effects of NBS; and there is significant individual difference between treated patients that must be better controlled in the future. The complex stimulation protocols, a wider use of multimodal functional imaging for better monitoring and targeting the plasticity changes in the affected area, and individually tailored NBS strategy utilizing array of suitable biomarkers are possible solutions for the observed limitations. Brain derived neurotrophic factor (BDNF) is one of such biomarkers and its genetic polymorphism appears to affect both neural plasticity and the outcomes of rTMS.

Dr. Kim went on to discuss her experience with a neurotrophic agent, Cerebrolysin, as an example of the approach to modulating natural recovery post stroke. Cerebrolysin appears to mimic the activity of endogenous neurotropic factors, like BDNF, and its use in supporting recovery post stroke is well justified by available research data (Fig. 5).[4]

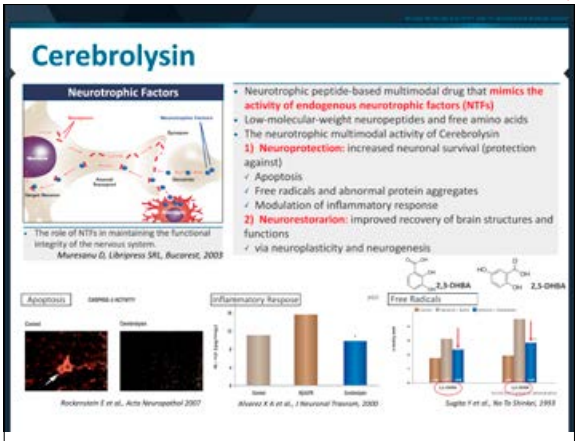
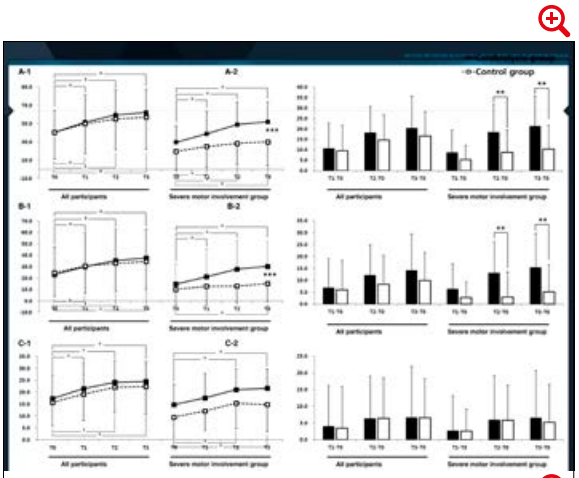
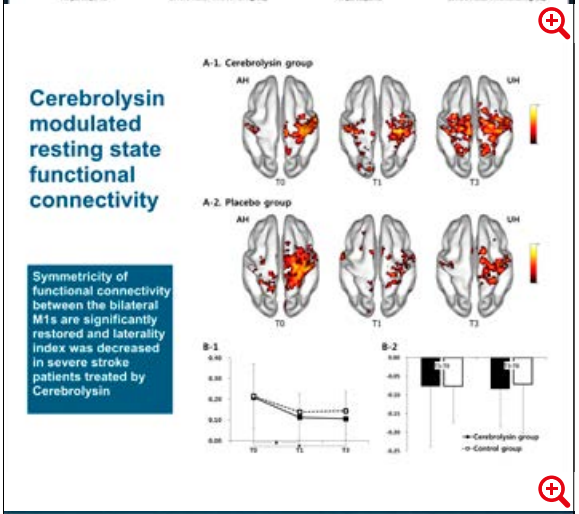


Fig. 5. Cerebrolysin is a neurotrophic agent supporting natural recovery after stroke

Dr. Kim described a protocol of the recently accomplished clinical study investigating, for the first time, the effect of Cerebrolysin on rehabilitation of motor functions in the sub-acute ischemic stroke patients (E-COMPASS).[5] The purpose of this study was to investigate whether a 3 weeks of Cerebrolysin treatment in the subacute phase of stroke on top of a standardized rehabilitation therapy provides additional benefit on motor recovery in patients with moderate to severe motor impairment. Cerebrolysin was administered at day 8 post-stroke. The primary efficacy criterion was Fugl-Meyer Assessment scale (FMA). The secondary efficacy criteria were diverse functional outcome scales and also the neuroplasticity assessment using multimodal imaging technology: resting-state functional MRI (rfMRI) and diffusion tensor imaging (DTI). The major results of the study were outlined and discussed (Fig. 6).

The subgroup of patients with moderate to severe motor impairment (FMA < 50 at admission) showed additional significant benefits from combination Cerebrolysin plus structured rehabilitation. In this patients group, Cerebrolysin modulated resting state functional connectivity. Symmetry of functional connectivity between bilateral motor cortices was significantly restored; lateralization index (LI) was decreased in patients treated with Cerebrolysin. At the white matter level, the effect of Cerebrolysin was investigated using template CST and DTI-derived metrics; with Cerebrolysin apparently improving white matter integrity of the treated patients. Following these positive fundings, the group of Dr. Kim has designed a new confirmatory study (E-COMPASS II) focusing on severe motor impairment patients.





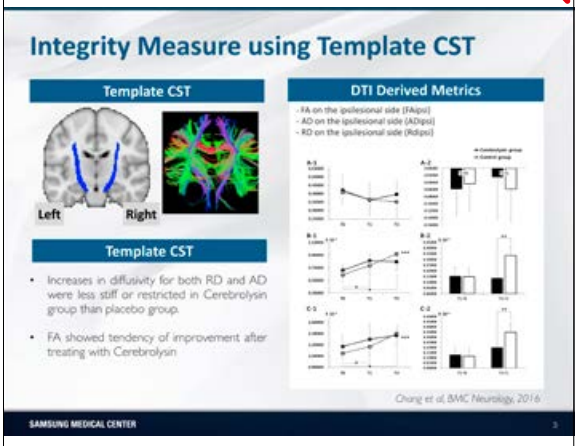
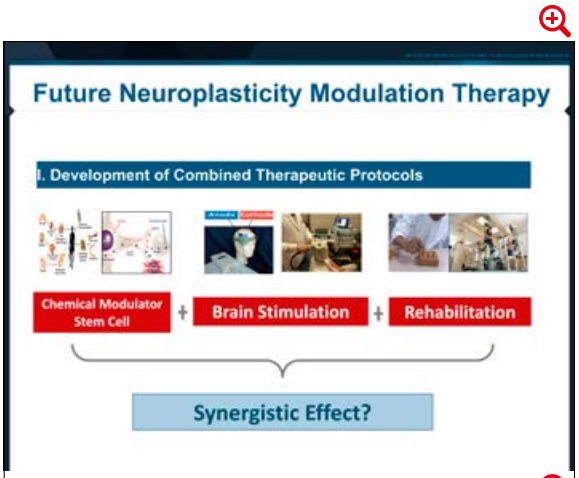
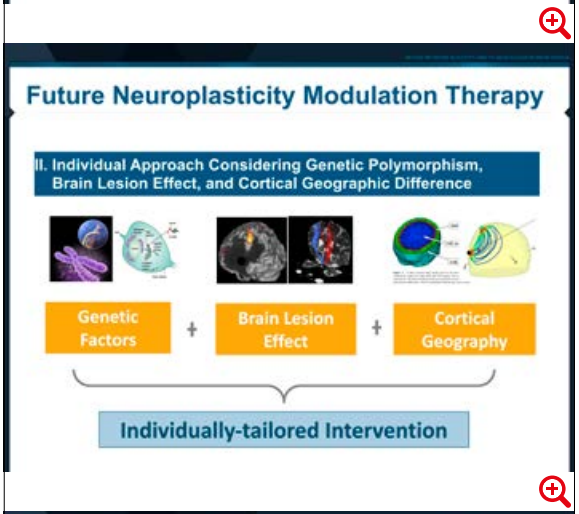


Fig. 6. The results of E-COMPASS study showed improved motor functions of upper extremities as well as stimulation of plasticity within corticospinal tract (CST) by Cerebrolysin





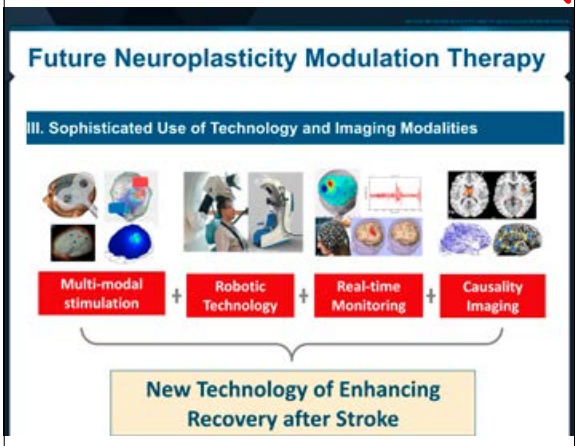


Fig. 7. Perspectives of neuroplasticity modulation in patients recovering from brain injuries

Dr. Kim finished her lecture by outlining the perspectives for further development in rehabilitation therapies after stroke (Fig. 7). By combining different therapeutic protocols we should be able to capitalize on synergies between them and natural recovery processes after stroke. The efficacy of the multimodal clinical protocol would depend on the careful assessment of patient-specific clinical parameters, allowing for individually-tailored interventions. Finally, sophisticated imaging and rehabilitation technology would allow for increasingly precise targeting and execution of the therapeutic protocols.

Significance

The non-invasive brain stimulation plays increasingly important role in the organized stroke care and in the rehabilitation of impaired motor functions in particular. Accumulating evidence suggests that a multimodal approach to rehabilitation creates better chances of recovery for stroke patients. This approach includes pharmacological stimulation of endogenous recovery processes. Cerebrolysin appears to act in synergy with motor rehabilitation when administered in early phases of the ischemic stroke.

Selected literature:

1. J.Y. Park et al., Significance of longitudinal changes in the default-mode network for cognitive recovery after stroke. Eur J Neurosci. 2014 Aug;40(4):2715-22
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Pharmacological and Early Rehabilitation Treatment – The CARS – Trial Results

Dafin F. Muresanu

University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania

ABSTRACT:

BACKGROUND AND PURPOSE: The aim of this early neurorehabilitation trial was to investigate whether patients randomized to Cerebrolysin showed improved motor function of the upper extremities over 90 days in comparison with patients randomized to placebo. METHODS: This study was designed as a prospective, randomized, double-blind, placebo-controlled, multicenter and parallel-group study. Patients were treated with Cerebrolysin (30ml/day) or placebo (saline) once daily over 21 days starting the treatment 24-72 hours after stroke onset. In addition, patients participated in a standardized rehabilitation program over 21 days starting within 72 hours after stroke onset. Primary endpoint was the action research arm test (ARAT) score on day 90. Safety assessment was based on adverse events, vital signs and laboratory parameters. RESULTS:The nonparametric effect size on the ARAT score on Day 90 indicated a large superiority of Cerebrolysin as compared to placebo (MW=0.71, 95%CI 0.63-0.79). The multivariate effect size on the global status, as assessed by twelve different outcome scales, showed a small superiority (MW 0.60, P <0.0001). The rate of premature discontinuations was below 5% (3.8%). Cerebrolysin was safe and well tolerated. CONCLUSIONS: Cerebrolysin had a beneficial effect on function and global outcome in early rehabilitation patients after stroke. The safety aspects of Cerebrolysin were comparable to placebo, thus suggesting a favorable benefit-risk ratio. Due to the size of the study the results should be confirmed by a high precision, large-scale randomized clinical trial.

Dr. Muresanu stated from the beginning that his lecture is not merely about positive results of CARS trial, but rather about the evolving new therapeutic concept in which multimodal drugs with neurotrophic properties can play increasingly important role. For years, we have been using inadequate pharmacological approach to brain protection and recovery due to the lack of knowledge about biological processes underlying recovery after stroke.[1-3] These suppressing or stimulating strategies employed monomodal acting molecules targeting pathophysiological mechanisms considered in isolation from the complex biological reality. Numerous inconsistencies in clinical trials design contributed to the picture. This resulted in a virtual failure of all so called neuroprotective trials. However, we are now ready for a paradigm shift in stroke therapy, said Dr. Muresanu. At the core of the new approach lays the knowledge about endogenous modulation of the central nervous system. There are three major modulation levels observed: cellular, circuitries, and dynamic network level. The ischemic stroke and its pathophysiological consequences must be analyzed taking into account the fact that pathophysiological processes are affecting and are being affected by these neuromodulatory mechanisms. Moreover, pathophysiological processes must be regarded as imbalances of the normal processes and therefore should be treated accordingly, with neuromodulatory approaches.[1] This is also the reason why multimodal

pharmacological agents, like those based on neurotrophic factors activity, make biological and therapeutic sense (Fig. 1).

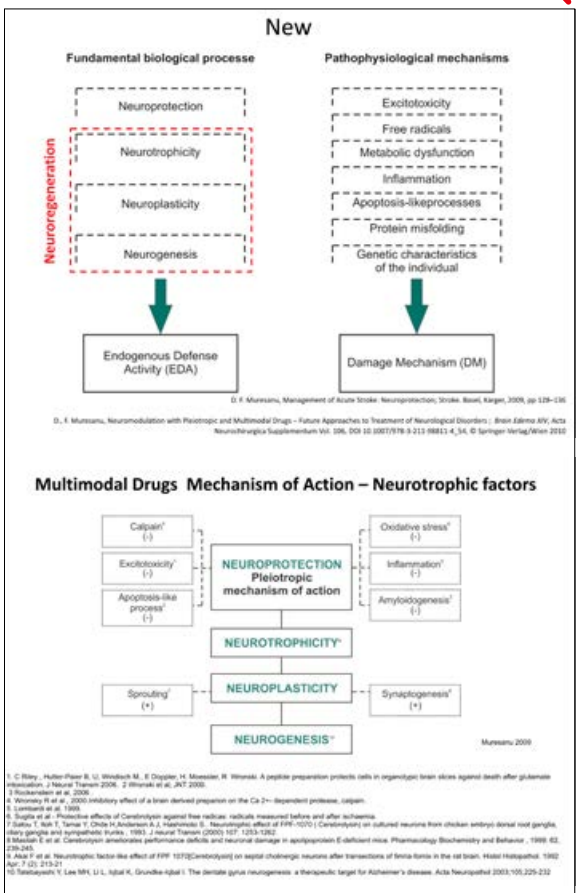


Fig. 1. Interdependence of damage and repair processes after stroke and the rationale for utilizing multimodal therapies for stroke patients

In real life clinical situation we need to consider proper and optimal matching between many elements and phases of rehabilitation and pharmacological multimodal intervention. For example, the timing of motor rehabilitation is an important topic that must be revisited carefully. The analysis of already published trials[4] indicates that in a vast majority of cases rehabilitation was initiated late post stroke (Fig. 2). Consequently, majority of these trials missed important therapeutic window in which endogenous processes of neurorecovery are most active.

Among these trials, only 12 included pharmacological support of rehabilitation. Dr. Muresanu mentioned the results of the most prominent combination trials with fluoxetine, amphetamine, levodopa, methylphenidate and piracetam as add on to

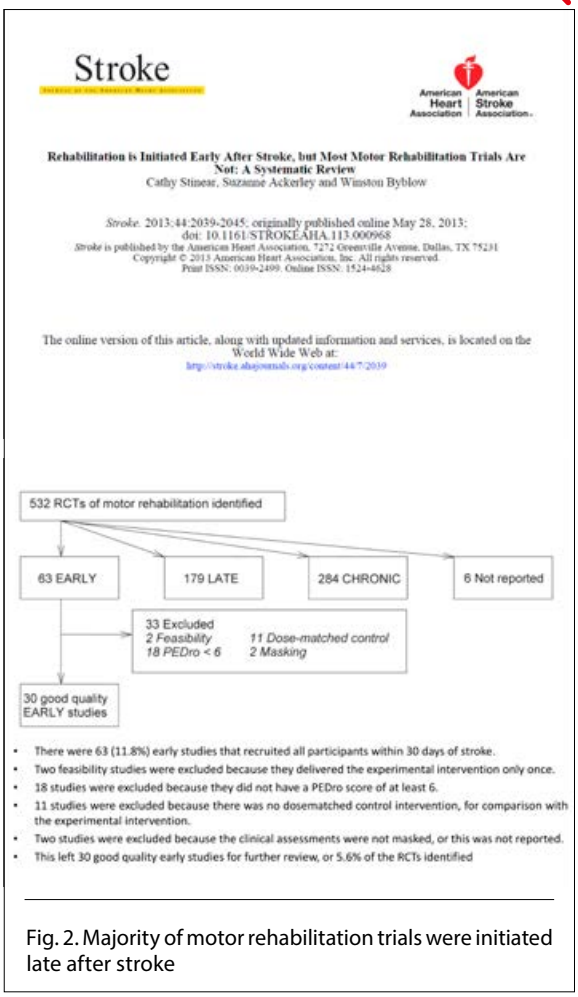
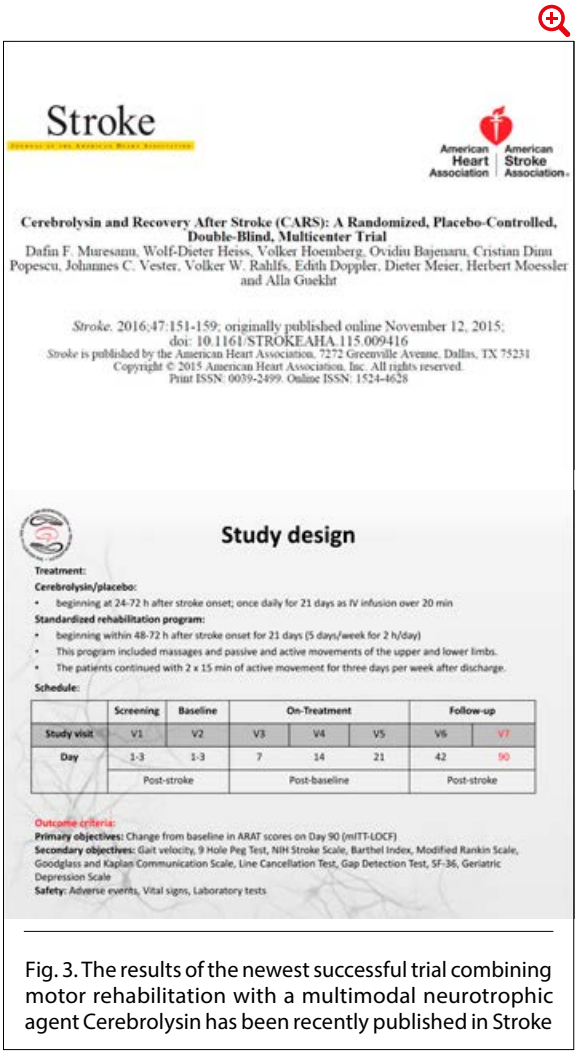


Fig. 2. Majority of motor rehabilitation trials were initiated late after stroke

motor rehabilitation. Among them, the fluoxetine showed some interesting results which are being now assessed in an ongoing, large scale rehabilitation trial.

In the last part of his lecture, Dr. Muresanu discussed recently published results of the CARS trial in which he was the principal investigator (Fig. 3). This trial focused on early rehabilitation of impairment of upper extremities as a particularly challenging (and more difficult than rehabilitation of lower extremities) and, at the same time, desirable therapeutic goal.[5]

The primary endpoint of this study was an outcome in motor function of an affected arm measured with ARAT (The Action Research Arm Test) score at day 90. The ARAT is a complex and reliable measure of arm function rehabilitation. After discussing the methodological prerequisites and the key elements of the study design, Dr. Muresanu outlined major results of the study. In the primary endpoint, there was a statistically



Stroke

American Heart Association | American Stroke Association

Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

Dafin F. Muresanu, Wolf-Dieter Heiss, Volker Hoemberg, Ovidiu Bajenaru, Cristian Dinu Popescu, Johannes C. Vester, Volker W. Rahlfs, Edith Doppler, Dieter Meier, Herbert Moessler and Alla Guekht

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Study design

Treatment:

Cerebrolysin/placebo:

- beginning at 24-72 h after stroke onset; once daily for 21 days as IV infusion over 20 min

Standardized rehabilitation program:

- beginning within 48-72 h after stroke onset for 21 days (5 days/week for 2 h/day)
- This program included massages and passive and active movements of the upper and lower limbs.
- The patients continued with 2 x 15 min of active movement for three days per week after discharge.

Schedule:

	Screening	Baseline	On-Treatment			Follow-up	
Study visit	V1	V2	V3	V4	V5	V6	V7
Day	1-3	1-3	7	14	21	42	90
	Post-stroke		Post-baseline			Post-stroke	

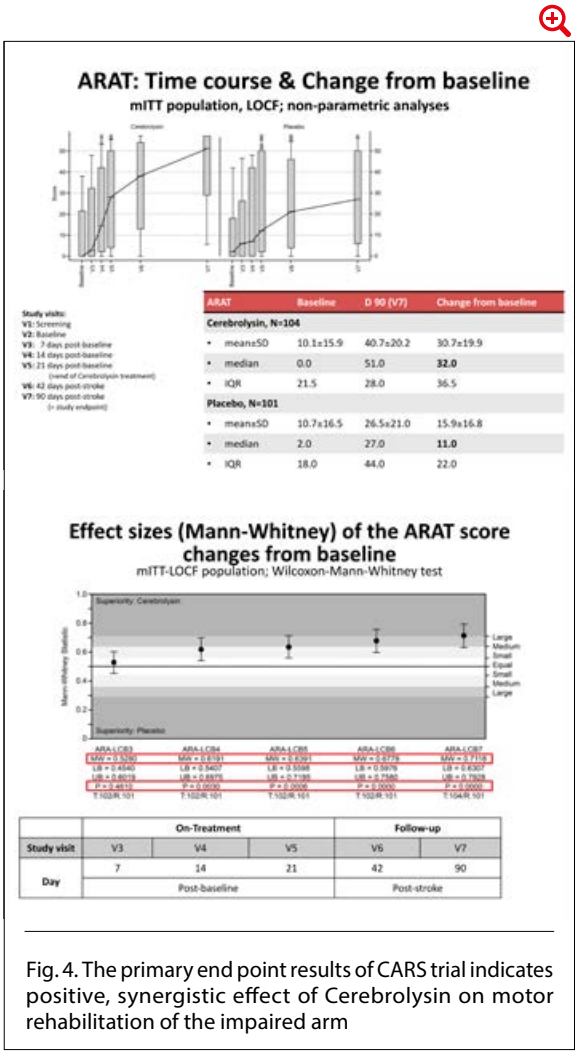
Outcome criteria:

Primary objectives: Change from baseline in ARAT scores on Day 90 (mITT-LOCF)

Secondary objectives: Gait velocity, 9 Hole Peg Test, NIH Stroke Scale, Barthel Index, Modified Rankin Scale, Goodglass and Kaplan Communication Scale, Line Cancellation Test, Gap Detection Test, SF-36, Geriatric Depression Scale

Safety: Adverse events, Vital signs, Laboratory tests

Fig. 3. The results of the newest successful trial combining motor rehabilitation with a multimodal neurotrophic agent Cerebrolysin has been recently published in Stroke



ARAT: Time course & Change from baseline

mITT population, LOCF; non-parametric analyses

ARAT	Baseline	D 90 (V7)	Change from baseline
Cerebrolysin, N=104			
• mean±SD	10.1±15.9	40.7±20.2	30.7±19.9
• median	0.0	51.0	**32.0**
• IQR	21.5	28.0	36.5
Placebo, N=101			
• mean±SD	10.7±16.5	26.5±21.0	15.9±16.8
• median	2.0	27.0	**11.0**
• IQR	18.0	44.0	22.0

Effect sizes (Mann-Whitney) of the ARAT score changes from baseline

mITT-LOCF population; Wilcoxon-Mann-Whitney test

	On-Treatment			Follow-up	
Study visit	V3	V4	V5	V6	V7
Day	7	14	21	42	90
	Post-baseline			Post-stroke	

Fig. 4. The primary end point results of CARS trial indicates positive, synergistic effect of Cerebrolysin on motor rehabilitation of the impaired arm

significant improvement of arm motor function in the Cerebrolysin group in comparison with placebo (Fig. 4).

Importantly, the significant improvement has been observed already after 14 days of treatment. This early response can positively impact many aspects of recovery and rehabilitation downstream, including improved cognitive performance, said Dr. Muresanu. Also the distribution of the modified Rankin Scale scores indicated highly positive treatment effects of combination rehabilitation therapy with Cerebrolysin. Together with other various secondary endpoints, with 6 out of 12 showing statistically significant improvement in the Cerebrolysin group, the CARS trial results confirm earlier clinical findings with Cerebrolysin and reinforce the rationale for employing multimodal therapeutic agents in the early support of stroke rehabilitation (Fig. 5).

Summarizing the results, Dr. Muresanu indicated that Cerebrolysin had a positive influence on the patient's condition during stroke recovery in terms of the motor function of the paretic side, related neurological deficits, activities of daily living, the quality of life, and depression. Treatment with Cerebrolysin has shown a fast initial improvement in the ARAT; the time course revealed a constant growth of the effect size, which reached a maximum on day 90. The beneficial effects of Cerebrolysin were stable over a long period: the distribution of mRS scores were in favor of Cerebrolysin at day 90, and the results of sensitivity analyses (observed cases; stratifications for age, gender, baseline ARAT score and site; ARAT values >0 at baseline) were consistent with the results of the primary analysis. The safety of the treatment was also confirmed and did not differ from other trials with Cerebrolysin.

Dr. Muresanu finished his lecture by suggesting that the new concept of pharmacological support of neurorehabilitation with multimodal agents makes therapeutic sense and that the results of the new rehabilitation trials, including CARS, open the doors for future successful development in the organized stroke care.

Significance

A new paradigm in the stroke therapy is defined by clinical approaches that take into consideration the biological complexity of the brain structure and function. The stroke-related imbalances of normal molecular and cellular processes must replace classically defined pathological events as targets for therapeutic intervention. The combination of intensive rehabilitation with the neurotrophic, multimodal treatments, which target regulatory imbalances in the ischemic brain, showed already positive results in the recent clinical trials. Further development in this field will also depend on focusing our efforts on early versus late therapeutic interventions.

Selected literature:

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4. C. Stinear et al., Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. Stroke. 2013 Jul;44(7):2039-45.
5. D.F. Muresanu et al., Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial. Stroke. 2016 Jan;47(1):151-9

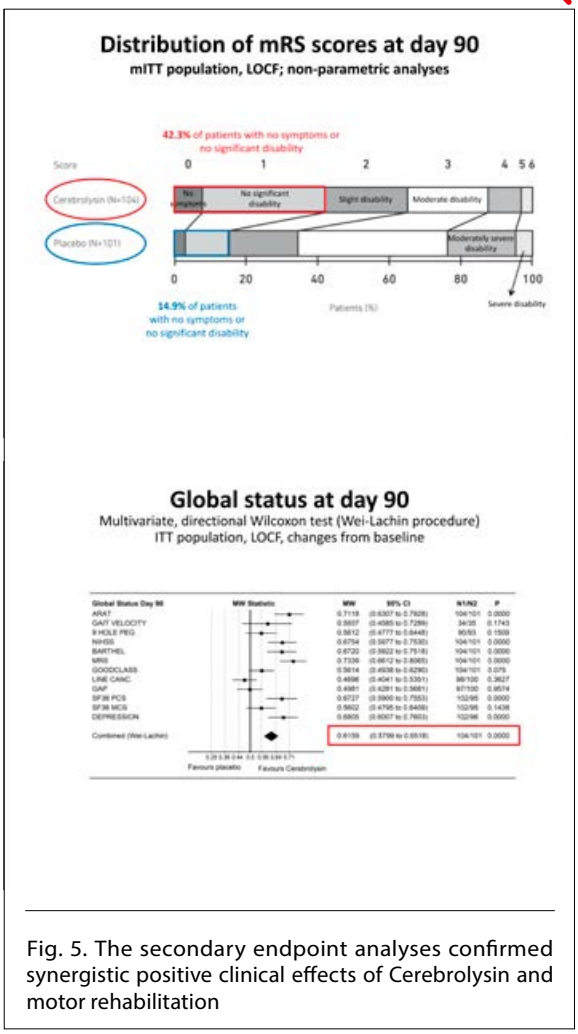

Fig. 5. The secondary endpoint analyses confirmed synergistic positive clinical effects of Cerebrolysin and motor rehabilitation

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EVER PHARMA

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. 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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Oberburgau 3
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