The enigma of "proportional recovery" What does it mean for future neurorehabilitation?

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Within the last 10 years the number of survivors after stroke and traumatic brain injury (TBI) has dramatically increased due to advances in acute medical care.

In parallel the need for intensive neurorehabilitation to combat resulting impairment and handicap has increased. Fortunately also over the last 20 years neurologic rehabilitation has more and more been conceived as applied neuroscience:

Dramatic progress has been made in the application of evidence based medical principles and the number of well designed randomized controlled trials in the field is increasing. Nevertheless there is a remaining epistemological problem in how far the rationales of EBM originally designed for pharmaceutical studies are really suited to serve as a source of best evidence :Due to heterogeneity of populations ,usually comparably small sample sizes and resulting difficulties to interpretation of metaanalyses the EBM rationale my sometimes be misleading.

Nevertheless a reasonable approach to design reasonable treatment strategies is to follow elementary rules derived from behavioural and neurosciences concerning neuroplasticity and learning mechanisms. This has resulted in the invention of better scientifically founded procedures for neurological treatment of motor ,cognitive and language problems. A good example is the very successful application of the principle of forced use and avoidance of learned non use in constrained in used movement therapy. This concept now also spreads to non motor fields as language , cognitive and perceptual rehabilitation.

The classical physiotherapy schools such as the Bobath , the Vojta or the Kabat concepts and many more have been challenged very much recently Also their claim to be based on "neurophysiological bases" has been critisized . Metaanalyses of the Bobath concept for instance stated that "the Bobath Concept ist not superior to other approaches. Based on best evidence synthesis, no evidence is available for the

superiority of any approach .Evidence-based guidelines rather than therapist preference should serve as a framework from which therapists should derive the most effective treatment.."

Most of these classical concepts failed to include knowledge about brain plasticity and learning processes.

Especially the application of elementary rules of motor learning (see table below) has brought forward strategies for motor improvements (for a review see Hömberg 2013).

Table

Rules for learning-oriented motor therapy

- Repetition
- Task orientation
- Active behavior
- Ecological validity
- Shaping
- Knowledge of results
- Motivation

Furthermore the use of intelligent mechanical training devices (often loosely called "robots") has opened new therapeutic windows especially in the early stage of treatment in severely impaired patients.

Over the last two decades there has been a remarkable change in our thinking in the invention, design and efficacy evaluation of motor therapies in neuro-rehabilitation which can be described by three paradigmatic changes

Paradigmatic changes

First there is a change from confession to profession i.e. more and more evidence based approaches rather than intuitively driven procedures have come into use.

This was accompanied by a change from "hands on" treating to "hands off" coaching approaches, which now dominate most of the evidence based procedures. This change in treatment philosophy has had a marked impact also on the self-understanding of the therapists in their relation to the patient mutating from treaters to teachers.

Thirdly these developments were accompanied by a transition from intuitevely marshaled individual one to one treatments to quality proven group treatments.

Especially the distinction between treatment strategies targetted to restore function and thereby decrese impairments is contrasted to approaches to compensate function in order to improve activities is becoming more and more important.

Are we really able to influence impairment i.e. can we reduce the amount of paresis e.g. after stroke. "The enigma of proportional recovery "

First published in 2008 (Prabhakaran et al 2008) an interesting phenomenon was described: The spontaneous impairment recovery after stroke at day 90 after the ictus (with or without treatment) for upper extremity was usually 70% oft he maximum possible difference between initial score and the maximum possible. There were outliers from this rule attributable to severe pathology in the primary descending motor tracts especially the corticospinal tract. In the meantime this "proportional recovery rule was also demonstratesd to apply for impairments in non-motor domains as neglect and language abilities (Lazar et al 2010, Marchi et al 2017). Also in animals similar proportional recovery has been observed (Strider Jeffers et al 2018). If this 70% proportional spontaneous recovery is a universal rule and cannot be influenced, this of course would mean that impairment oriented rehab is not possible. The challenge is to change the slope (i.e.from 70% to 80% or more) or to make outliers inliers.

In animal experimentation so called "enriched environments" have been proven to facilitate brain repair. There has however been no translation from this experimental animal world to the clinical bedside

So far only three major strategies have been shown to help decrease impairment in the subacute stage e.g. after stroke: The forced use or constraint induced movement therapy approach has been proven to be effective in the multicenter prospective EXCITE trial (Wolf et al 2008)). Also the use of fluoxetine an antidepressant agents was shown to be effective in the FLAME trial (Chollet et al 2011). This could however not be corroborated in larger trials (FOCUS trial)

Recently in the the CARS trial we (Muresanu et al 2016) documented for the first time after decades of frustrane attempts to achieve some sort of neuroprotective and/or neurorestorative effects that cerebrolysin, a mutimodal drug ,can improve impairment after stroke. This was further corroborated in a consecutive trial (Guekt et al 2017)

Possible additional candidates for a true "impairment" oriented treatment approach are neuromodulatory techniques such as peripheral neuromuscular and/ or sensory stimulation (eg. whole hand subliminal "mesh-glove" stimulation)and more and more also non invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation and transcranial DC stimulation. Also the use of non fatiguable robotic devices to enable a high intensity massed movement treatment appear promising. As treatment intensity is likely to be the key element for impairment reduction we certainly have to find clever and affordable ways: to increase the daily treatment time of our patients. To day even during inpatient rehabilitation treatment times hardly exceed three hours a day i.e. that we use only a small percentage of waking hours leaving long "idling" time not field by any treatment. In this sense we have to "reinvent" neurorehabilitation within this sensitive post injury period to combat impairment with high frequency treatments combined with neuromodulatory techniques (robot use, peripheral and central stimulation , pharmaceuticals).

Probably the most important impact in facilitating impairment reduction will however have clever ,economically feasible, approches to increase the net number of therapy or activity hours per day by creating true " enriched environment" for severely impaired patients . They should enable 6-8 hours of daytime treatment to avoid leaving our patients "inactive and alone" in future.

Neurorehabilitation after the "Proportional Recovery Rule"?

To address also the worst possible scenario: If the proportional recovery rule cannot be influenced ,there is still ample space if not even more need for neurorehabilitation exploiting our knowledge about compensatory interventions including motor learning. This means optimizing residual motor function at a given a (and unchangeable) impairment level.

References:

Wolf SL, Winstein CJ, Miller JP, Thompson PA, Taub E, Uswatte G, Morris D, Blanton S, Nichols-Larsen D, Clark PC

Retention of upper limb function in stroke survivors who have received constraintinduced movement therapy: the EXCITE randomised trial.

Lancet Neurol. 2008 Jan;7(1):33-4

Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, Bejot Y, Deltour S, Jaillard A, Niclot P, Guillon B, Moulin T, Marque P, Pariente J, Arnaud C, Loubinoux I.

<u>Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised</u> placebo-controlled trial.

Lancet Neurol. 2011 Feb;10(2):123-30. doi: 10.1016/S1474-4422(10)70314-8. Epub 2011 Jan 7. Muresanu DF, Heiss WD, Hoemberg V, Bajenaru O, Popescu CD, Vester JC, Rahlfs VW, Doppler E,Meier D, Moessler H, Guekht A

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

Stroke.2016 Jan;47(1):151-9. doi: 10.1161/STROKEAHA.115.009416. Epub 2015 Nov 12

Guekht,,A. Johannes Vester,Wolf-Dieter Heiss,Eugene Gusev,Volker Hoemberg,Volker W. Rahlfs,Ovidiu Bajenaru,Bogdan O. Popescu,Edith Doppler,Stefan Winter,Herbert Moessler,Dafin Muresanu

Safety and efficacy of Cerebrolysin in motor function recovery after stroke: a meta-analysis of the CARS trials

Neurol Sci 2017 DOI 10.1007

Matthew Strider Jeffers, Sudhir Karthikeyan, Dale Corbett,

Does stroke rehabilitation really matter? Part A: Proportional stroke recovery in the Rat

NNR(Jan 2018)

Bernhardt J. Dewey H, Thrift A, Donnan G.

Inactive and alone: physical activity within the first 14 days of acute stroke unit care.

Stroke. 2004 Apr;35(4):1005-9.

Lazar RM, Minzer B, Antoniello D, et al.

Improvement in aphasia scores after stroke is well predicted by initial severity.

Stroke 2010;41:1485–1488.

Marchi NA¹, Ptak R¹, Di Pietro M¹, Schnider A¹, Guggisberg AG

Principles of proportional recovery after stroke generalize to neglect and aphasia.

<u>Eur J Neurol.</u> 2017 Aug;24(8):1084-1087. doi: 10.1111/ene.13296. Epub 2017 Jun 6.

Prabhakaran S, Zarahn E, Riley C, et al. Inter-individual variability in the capacity for motor recovery after ischemic stroke. **Neurorehabil Neural Repair 2008;22:64–71.**

Hömberg, V. Neurorehabilitation approaches to facilitate motor recovery. Handbook Clin Neurol. Vol 110:161-73. Elsevier 2013

The Focus trial collaboration Effects of fluoxetine on functional outcoemes after acute stroke Lancet 393 :1-102 (Jan 2019)