Are randomised controlled trials telling us what rehabilitation interventions work?

Focus on stroke

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Neurorehabilitation: facts, fears and the future
Overview

• Stroke recovery and the aims of rehabilitation
• Current evidence for conventional and technology interventions in stroke rehabilitation
• Why do so many RCTS generate equivocal results?
• What are the alternatives?
From Timmermans et al JNE&R 2009. Illustrates stages, types of recovery and mechanisms by which they may occur. cc= cortico-cortical connections
Recovery vs. compensation?

- **Recovery**: strengthening of local spared or formation of local new connections that enable a task to be performed using the same kinematic strategies.

- **Compensation**: recovery of function through ‘normal’ learning of new strategies using undamaged cortical areas¹

- **Or substitution**: regaining the ability to perform functional tasks, but using assistive devices or unaffected limbs – e.g. performing tasks single-handed or using the hemiplegic limb purely as a support.

¹Sunderland & Tuke. NEUROPSYCHOLOGICAL REHABILITATION 2005, 15 (2), 81–96
Representation of the hand in the motor cortex of the squirrel monkey

Nudo et al., 1997
• Most stroke rehabilitation being practiced today is based on traditional concepts developed over many years
• There is little scientific evidence to support it
• New approaches informed by neuroscience and supported by technologies are emerging
• Yet evidence for effectiveness is hard to come by
• And very little has translated into clinical practice
Conventional therapy

- Shift from compensation and substitution to recovery

- No clear evidence that any particular therapy approach is superior to another\(^1\)-\(^5\)

- While conventional therapy promotes adaptation, whether it truly promotes long term recovery over spontaneous recovery is unclear

- The effect of conventional therapy on neuroplasticity following stroke is unknown

New therapies for motor recovery

- Therapy based approaches
  - Constraint-Induced Movement Training (CIMT)
  - Bimanual training
- Treadmill training with partial weight support
  - With therapy guidance
  - With robotic assistance
- Robotic training for the upper extremity
- Electrical stimulation techniques
  - FES
  - Transcranial direct current stimulation (tDCS)
  - Transcranial magnetic stimulation (TMS)
Evidence-based therapy

- Well designed, rigorously conducted randomized controlled clinical trials are a recent development in rehabilitation
- Rehabilitation does not fit into the traditional model, so useful for conducting pharmacological trials
- Why not?
Problems with RCTs in stroke rehabilitation

• We do not know which are the critical variables to control
  – Time after stroke onset
  – Type and severity of neurological deficits
• Difficulty in providing true control treatment
• Delivery of interventions
  – Therapist – patient interaction
  – Dose / delivery – clinically appropriate vs. standardized
• Is a rigidly controlled intervention protocol ever likely to be applicable to a large sample of patients?
Recent Phase 3 trials

LEAPS ($13M)

VA ROBOT

EXCITE
Phase 3 trials - definitive RCT

• VA Robot trial\(^1\) n= 127; 3-arm (dose-equivalent (time and intensity) comparison and a control group)
  - No difference between groups at 12 weeks
  - Both intensive therapy and robot therapy better than control at 36 weeks

• EXCITE Trial\(^2\) n=229 (not dose-equivalent by time or intensity)
  - Difference but control group was usual care

• LEAPS trial\(^3\) n=400, largest and most expensive ($13M) stroke rehabilitation RCT - dose-equivalent (time & intensity)
  - No between group differences

• With all studies there were large differences between responders and non-responders (small effect sizes)

• Implying a need to match therapy to the individual

\(^1\)Lo et al, Robot assisted therapy for long-term upper limb impairment after stroke. NEJM 2010; 362: 1772-83
\(^2\)http://stroke.ahajournals.org/content/41/10/2309.short
\(^3\)http://www.nejm.org/doi/full/10.1056/NEJMoa1010790
To match a therapy to a specific patient we need a longitudinal analysis of recovery:

- Define individual trajectories of functional recovery that may go through very different pathways

- Examples:
  - A steep trajectory might imply recovery – indicating an intervention targeting impairment
  - An early plateau might imply learnt non-use and indicate an intervention targeting reducing disability – e.g. CIMT

- The best time to introduce an intervention may be when rate of natural recovery declines – i.e. the curve begins to flatten
Predictors of recovery and response to therapy may identify good and poor responders

• Cluster analysis of a large longitudinal data set - what features / measures characterize good and poor responders and to which therapies
  – Hierarchical Cluster Analysis, Ward’s minimum variance method to measure distance between clusters
  – Principal Component Analysis to identify key variables
• Provides some idea which patients are likely to respond to what therapy and when
• But from clinical experience personalised therapy programmes are more effective than rigidly controlled protocols – one size fits very few!
• What has the research evidence shown?
Taking intensity of therapy post-stroke as a model

- Cohort studies: better outcomes related to intensity and early initiation of rehabilitation\(^1,2\)

- RCT\(^3\) (n=282) - a heterogeneous sample including low functioning patients showed no differences between usual care and intensive therapy and poor compliance (50% of patients in the intensive group did not complete the programme)

- Cluster analysis from large studies (e.g. N=114\(^4\) and N=1716\(^5\)) predicted that younger, less disabled patients had better outcomes in both RCTs\(^3\) and cohort studies

- Overall, patients in cohort studies had better outcomes than RCTs – clinical judgment, rather than random allocation?

- Cohort study (N=830)\(^6\) using Clinical Practice Improvement (CIP) approach showed that even lower functioning patients did better with intensive, early therapy when therapy time was based on clinical judgment

Evidence-based Intervention Research

- Systematic Reviews and Meta-analyses
- Randomized Controlled Double Blind Studies
- Cohort Studies
- Case Control Studies
- Case Series
- Case Reports
- Ideas, Editorials, Opinions
- Animal research
- In vitro ('test tube') research
TURN the TRIANGLE ON ITS HEAD

“New” RCT: single case or N of 1 designs

Build multiple models

Dense Longitudinal Descriptions

Mechanisms / neuroplasticity principles

RCT/Reviews/Case: what works
Pragmatic trials and N of 1 studies

- Dense longitudinal (cohort) studies provide information on what, who, how and when

- But to optimise response to an intervention (WHAT) the study sample (WHO) and delivery (HOW and WHEN) cannot be standardized

- The RCT model (as we know it) will never be an effective tool for telling us what works in neurorehabilitation

- Instead we need very loosely controlled pragmatic trials or N of 1 studies
Final comment:

• RCTs have not told us what rehabilitation interventions work.

• What evidence there is - from basic science, RCTs, systematic reviews and meta-analyses, has not translated into clinical practice.

• Other factors maybe critical:
  – Understanding mechanisms
  – Usability and acceptability of therapies
  – Changes in service provision and education
  – Knowledge of and access to technologies and new therapies
  – Generalizability of research findings
Cohort studies vs. RCTs

- Effect of therapy intensity on outcomes
  - Within the cohort studies intensity was based on clinical judgment
  - With the RCTs patients randomly assigned to high/low intensity
- Overall, cohort studies had a better outcome than RCTs
- Taking part in an RCT is not good for you!
What – Who – How - When

• We know that intensity is important, but no other interventions have shown to be of benefit in large RCTs

• An intervention may work with some people, but not all and currently selection criteria are based on scant evidence

• A rigidly controlled intervention will provide the appropriate therapy some but not all participants

• The point in recovery when an intervention will be most effective is unknown and likely to vary with recovery
Is a new approach to research needed?

• Is the RCT the best model?

• Large cohort studies with post hoc analysis?

• Incorporating studies of the neural correlates of recovery

• Are we asking the right question? Are motivation and adherence critical? If we standardize ‘dose’ we may be controlling for an important benefit of technology.
The RCT is an inadequate tool to advance stroke neurorehabilitation - Why?

- There are too many (and unknown) variables to control
- If we could control them, then findings would not be generalizable
- We have such an inadequate understanding of the mechanisms of recovery that designing a RCT is based on guesswork
Objective measurement

• Lack of valid and reliable objective measurement tools is critical to:
  – Evaluating therapy
  – Understanding mechanisms of recovery
• Technology has the potential to provide this – e.g.
  – Neuroimaging and TMS
  – Wearable sensors (e.g. inertial sensors – activity)
Motor map of a rat before and after training to do a skilled task

Digit and wrist representations (green) can be seen to expand into elbow/shoulder representations (blue). (Figure adapted from Monfils et al., 2005).
EXCITE Trial

- Very selective group – excluding low functioning patients
  - 3626 potential subjects screened, 727 physically examined, 229 enrolled
- Intervention
  - Constraint 90% walking hours + 6 hours/ day training
EXCITE Outcomes measures & Results

- Treatment N=106: Control N=116
- Primary outcome measures: WMFT and MAL
- Between baseline and post-treatment assessments there was a greater improvement in the CIT group compared with controls which was statistically significant (p<0.05) in all outcome measures
- At 12 months, except for the weight and grip components of the WMFT, between group differences were maintained
VA Robot Trial\(^1\)

- 127 subjects >6 months post-stroke randomized to:
  - High intensity robot-assisted therapy (36 x 1 hour sessions)
  - Intensive conventional therapy (36 x 1 hour sessions)
  - Usual care (effectively no therapy)

- **Primary comparisons**
  - Robot vs. usual care
  - Robot vs. intensive conventional therapy

- **Outcome measures**
  - Primary: Fugl-Meyer (FM)
  - Secondary: WMFT & SIS

- **Primary endpoint** - 12 wks (immediately after therapy)
- **Secondary endpoint** – 36 wks

\(^1\)Lo et al, Robot assisted therapy for long-term upper limb impairment after stroke. NEJM 2010; 362: 1772-83
VA Robot Trial Results

• Subjects:
  – Robot-assisted therapy (RT) (n=49)
  – Intensive comparison therapy (ICT) (n=50)
  – Usual care (UC) (n=28)

• At 12 weeks there was no significant difference in motor function between any groups.

• Both intensive therapy and Robot assisted therapy were statistically significantly better than usual care (at 36 weeks) (SIS).

• There was no difference between robot and intensive therapy.
LEAPS Trial

- 400 adults with moderate or severe walking limitations identified within 30 days of stroke onset

- Randomized at two months post stroke to one of 3 treatment groups:
  - a) specialized locomotor training (LTP) – early
  - b) LTP – late
  - c) home exercise program – early

http://clinicaltrials.gov/ct2/bye/zQoPWw4lIZX-i-iSxuBcyeNsvdDxuQ7Ju6c9cXchuioyzTp9ai7HSTDxBciescgm64LD61PSQ7Hc6D65B0LVi7yg67VN6h9Ei4L3BUgWwNG0iY6vQ1gW1-He6oR9R0jcRCnWgFj.
LEAPS Results

- Patients with moderate-to-severe impairments at baseline, gained roughly 0.24 m/s in walking speed regardless of the intervention.
- 52% of patients moved to a higher functional walking level, with no between-group differences.
- The home-based physical therapy intervention was associated with fewer falls and rehospitalizations.
- The highest fall rate was in severely impaired patients in the early locomotor group.
- Fewer patients dropped out of the home therapy group (3% vs 13% for the early locomotor group).

Duncan P, et al. ASA International Stroke Conference 2011; Abstract LB 11 – now also published in the NEJM
LEAPS Trial

Locomotor training programme (LTP) partial body-weight support treadmill training

Locomotor training programme (LTP) over-ground walking

Gait focused home exercise programme