Functional strength training versus movement performance therapy for upper limb motor recovery early after stroke: a RCT

Valerie M Pomeroy,[1]* Susan M Hunter,[2] Heidi Johansen-Berg,[3] Nick S Ward,[4] Niamh Kennedy,[1,5] Elizabeth Chandler,[1] Christopher J Weir,[6] John Rothwell,[7] Alan Wing,[8] Michael Grey,[1] Garry Barton[9] and Nick Leavey[10]

[1]Acquired Brain Injury Rehabilitation Alliance, School of Health Sciences, University of East Anglia, Norwich, UK
[2]Institute for Applied Clinical Sciences, School of Health and Rehabilitation, Keele University, Keele, UK
[3]Oxford Centre for Functional MRI of the Brain, John Radcliffe Hospital, Oxford, UK
[4]Sobell Department of Motor Neuroscience, Institute of Neurology, University College London, London, UK
[5]School of Psychology, Ulster University, Coleraine, UK
[6]Edinburgh Clinical Trials Unit, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK
[7]Institute of Neurology, University College London, London, UK
[8]School of Psychology, University of Birmingham, Birmingham, UK
[9]Norwich Medical School, University of East Anglia, Norwich, UK
[10]Clinical Trials Unit, Norwich Medical School, University of East Anglia, Norwich, UK

*Corresponding author v.pomeroy@uea.ac.uk

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Scientific summary

Upper limb motor recovery early after stroke

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Background

The trial reported here focused on the top 10 research priorities identified by people who have had a stroke, namely upper limb recovery after stroke. This is because of the need for upper limb dexterity to perform everyday tasks, such as drinking from a cup, unscrewing the top from a bottle of water and fastening buttons/zips, for independent living. Evidenced-based physical therapy does enhance upper limb recovery, but at 6 months after stroke only 38% of people have some dexterity. Therefore, there is a need for even better methods of upper limb rehabilitation.

It is known that (1) upper limb recovery is enhanced by physical therapy based on repetitive practice of everyday tasks and (2) the 3 months immediately after stroke is when recovery is most rapid and there is most potential for brain recovery. But not everybody responds in the same way to particular forms of task-specific training. A key influence on therapy response may be the interindivdual differences in how the stroke affects the brain and, therefore, the neurobiological potential for recovery. Indeed, there is a variety of neural deficits after stroke seen in different combinations in different people. Therefore, it is important to have a greater understanding of how these neural deficits influence how people respond to specific physical therapies.

The trial reported here focused on how different neural deficits early after stroke (1) could predict how an indivdual may respond to different physical therapies (neural predictive markers) and (2) may change in response to those therapies (underlying neural mechanisms). Gaining this greater understanding will progress clinical practice in two ways. First, knowing the neural mechanisms of upper limb recovery will enable targeting of physical therapy at what needs to change. Second, knowing the neural predictors of response to specific physical therapies will enhance accuracy of evidenced-based decisions as to what is the most appropriate therapy for individuals after stroke. These decisions are currently based only on watching how people move (www.viatherapy.org; accessed 10 May 2018).

The specific forms of physical therapy employed in the trial reported here were functional strength training (FST) and movement performance therapy (MPT). FST is focused on improving ability to perform everyday functional tasks. MPT is focused on enhancing quality of movement required for everyday functional tasks. Such conceptually different physical therapies have been found to be no more or less effective than each other. However, our earlier trials found variation between people in response to MPT and FST. Therefore, a comparison of FST and MPT was the context for investigating the neural predictors of response to and mechanisms of action of specific physical therapies.

Objectives

1. To determine if upper limb motor recovery is enhanced more by FST + conventional physical therapy (CPT) than by an equal dose of MPT + CPT commenced early after stroke.
2. To identify the similarities and differences in the neural correlates of clinical (observed movement) improvement in upper limb motor function in response to (1) FST + CPT and (2) MPT + CPT.
3. To determine whether any pretreatment neural characteristics or combination of (1) anatomical location of infarction, (2) volume of the stroke lesion, (3) residual structural corticocortical connectivity, (4) residual corticospinal connectivity and (5) brain–muscle functional connectivity [derived from transcranial magnetic stimulation (TMS)] are sufficiently predictive of upper limb recovery after stroke to enable physical therapy to be targeted at those people most likely to respond.

Methods

Design

A randomised, controlled, observer-blind, two-group, multicentre trial with embedded neural measures. The primary end point was at outcome, which was after the end of the 6-week intervention phase. The secondary end point was at 6 months after stroke.

Setting and participants

Participants were recruited from three stroke services (Birmingham, Staffordshire and Norfolk) and were followed up until 6 months after stroke, wherever they were residing. Study criteria (combined inclusion and exclusion) were people:

- who were between 2 and 60 days after stroke in the territory of the anterior cerebral circulation when providing informed consent
- aged ≥ 18 years
- who were able, before the index stroke, to use the paretic, contralesional, upper limb to lift and then drink from a cup
- who were defined as 'medically stable', as confirmed by the stroke service medical team
- with enough voluntary muscle contraction in the paretic upper limb to begin to move (score of at least 11 of the 33 points of the Motricity Index pinch section) but unable to complete the Nine-Hole Peg Test (9HPT) within 50 seconds
- with no obvious spatial neglect (scored 0 or 1 on the Extinction and Inattention subscale of the National Institutes of Health Stroke Scale)
- who could imitate action with the non-paretic (ipsilesional) upper limb.

Randomisation

Group allocation order was generated before the trial began and was stratified by clinical centre, time after stroke (up to 30 days and 31–60 days) and ability to use the paretic upper limb as assessed by the 9HPT (substantial = move one peg or fewer in 50 seconds and moderate = move 2–8 pegs in 50 seconds). An independent telephone randomisation service concealed treatment allocation from investigators, research therapists and blinded assessors prior to randomisation of a participant.

Interventions

All participants were provided with routine conventional physical therapy (CPT), as deemed appropriate by the clinical therapists and then either extra MPT or FST in the same dose (amount in minutes).

MPT was prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week for up to 6 weeks (CPT + MPT group). Training in delivering MPT was provided.

FST was prescribed and overseen by a research therapist, direct and non-direct contact, for up to 1.5 hours, up to 5 days a week (FST + CPT group). Training in delivering FST was provided.

Outcome measures

Clinical efficacy measures were made before randomisation (baseline), the working day (± 7 days) after the 6-week intervention ends (outcome) and 6 calendar months (± 14 days) after the index stroke. The primary outcome measure was the Action Research Arm Test (ARAT) score. Secondary outcome measures were the Wolf Motor Function Test (WMFT), and the Hand Grip Force and Pinch Grip Force tests.

Neural measures were made within 10 days after the clinical efficacy measures at baseline and at outcome. These were (1) anatomical location of infarction, (2) volume of the stroke lesion, (3) residual structural corticocortical connectivity, (4) residual corticospinal connectivity and (5) brain–muscle functional connectivity (derived from TMS).

Sample size and power

The sample size calculation considered clustered data structure (patients within therapist within treatment group) and actual ARAT score data from our earlier trial. Assuming an intraclass correlation coefficient (ICC) of 0.01 in both treatment arms and three centres with a separate therapist for each randomised arm, a sample size of 99 participants per group had 80% power to detect a clinically important mean difference of 6.2 in ARAT score change when analysing data using a two-sample *t*-test with Satterthwaite correction. This applied a 5% two-sided significance level and allowing for potentially different standard deviations (SDs) in the CPT + MPT (SD 7.9) and CPT + FST (SD 9.3) groups. To account for clustering in the design a sample size inflation factor $1 + (m - 1) \times \text{ICC}$ was applied (m = cluster size). To allow for an attrition rate of 10% (7% in our previous single-centre trial), 288 participants were recruited (144 per group).

Statistical analyses

In accordance with the intention-to-treat principle, all participants were analysed according to the group to which they were randomly allocated. The statistical analysis plan was agreed, signed and dated prior to the database lock and unblinding of the treatment allocations. There was a change to the original analysis plan from taking account of clustering by therapist to only adjusting for study site, as it was not always practical for participants to have the same therapist for all their sessions.

Clinical efficacy (objective 1)

The analysis compared the change in the efficacy parameters (baseline and outcome) between the treatment groups using analysis of covariance (ANCOVA) models adjusted for the baseline value and randomisation strata (time after stroke, ability to use paretic upper limb, clinical centre). Adjusted least squares mean difference and 95% confidence intervals are reported. When the outcome distribution deviated from a normal distribution, a log or other appropriate transformation was applied.

Neural correlates of clinical improvement (objective 2)

Associations between the changes in neural variables were compared with the changes in clinical efficacy measures (baseline to outcome). Correlation coefficients were calculated for the two treatment groups separately and for the groups combined.

Predictive neural markers of clinical improvement (objective 3)

For each baseline covariate being investigated as a potential predictive marker of clinical improvement, the treatment effect (change in ARAT score) was calculated within each level of the subgroup (adjusted as for the first objective) and an interaction term between randomised treatment and baseline covariate was included in the model.

Adverse events

All adverse events (AEs) were recorded from date of randomisation to end of trial. To report serious adverse events (SAEs) the trial team used the Norwich University Hospital NHS Trust and University of East Anglia joint standard operating procedure (SOP). The latest version can be found at www.nnuh.nhs.uk/publication/sop-205-adverse-events/ (accessed 11 May 2018). All SAEs were followed up until a documented end date and resolution could be provided, or the participant ended the trial.

Results

A total of 5064 stroke survivors were screened for eligibility. Of these stroke survivors, 2929 were excluded as they did not meet the initial study inclusion criteria. Of the remaining potential participants, 536 declined participation and, consequently, 481 provided informed consent. Of these, 138 did not meet the eligibility criteria and a further 55 withdrew informed consent. Therefore, 288 participants were randomised. Informed consent was provided within 30 days of stroke by 59% of participants and at ≥ 31 days by 41%. Baseline characteristics were balanced across groups.

Clinical efficacy (objective 1)

The mean age of participants was 72.2 (SD 12.5) years ($n = 288$) and the mean ARAT score was 25.5 (SD 18.2) ($n = 283$).

For the 240 participants with a total ARAT score at baseline and outcome, the mean change scores were 9.70 (SD 11.72) for FST + CPT and 7.90 (SD 9.18) for MPT + CPT. The group difference did not reach statistical significance ($p = 0.298$).

For the 204 participants with a total ARAT score at baseline and follow-up, the mean change scores were FST + CPT = 11.10 (SD 14.68) and MPT + CPT = 10.30 (SD 10.74). The group difference did not reach statistical significance ($p = 0.743$).

For secondary outcomes, WMFT and Hand Grip Force and Pinch Grip Force tests, there were small differences between the groups in change from baseline at outcome and follow-up. But these differences did not reach statistical significance.

Neural correlates of clinical improvement (objective 2)

Analysis was undertaken per neural variable for those people with that variable and a total ARAT score at both baseline and outcome. Consequently, the number of participants varied across aspects of the analysis. Correlations between change in total ARAT change scores and baseline neural values ranged from –0.147 ($p = 0.385$) for whole-sample corticospinal connectivity ($n = 37$) to 0.199 ($p = 0.320$) for MPT + CPT resting motor threshold paretic biceps brachii ($n = 27$).

Predictive neural markers of clinical improvement (objective 3)

Analysis was undertaken per neural variable for those people with that variable at baseline and a total ARAT score at both baseline and outcome.

No statistically significant interaction effects were found between baseline neural variables and change in ARAT score.

Adverse events

There were no differences between groups in the number of AEs.

Conclusions

Clinical efficacy (objective 1)

The trial found small differences in the clinical efficacy of upper limb recovery between FST + CPT and MPT + CPT, but these did not reach statistical significance. Both groups showed increase in ARAT score (primary outcome measure) above the clinically important change, but variation around the mean change from baseline scores was substantial in both groups.

Neural correlates of clinical improvement (objective 2)

The neural correlates of change were similar for the two forms of physical therapy.

Objective 3

The trial reported here found that none of the pretreatment neural characteristics of interest predicted response to either FST + CPT or MPT + CPT.

Implications for health care

The findings of the trial reported here confirm clinical impressions and emerging research evidence of variation in response to specific therapies among people early after stroke.

Research recommendations

There is still an urgent need for evidence to guide decisions about (1) appropriate prescription of physical therapy for individuals and (2) the recovery mechanisms at which physical therapy should be targeted.

Trial registration

This trial is registered as ISRCTN 19090862 and National Research Ethics Service reference number 11/EE/0524.

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