Long-term improvements after multimodal rehabilitation in late phase after stroke: a randomized controlled trial

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ABSTRACT

Background and Purpose: Treatments that improve function in late phase after stroke are urgently needed. We assessed whether multimodal interventions based on rhythm-and-music therapy or horse-riding therapy could lead to increased perceived recovery and functional improvement in a mixed population of individuals in late phase after stroke.

Methods: Participants were assigned to rhythm-and-music therapy, horse-riding therapy or control using concealed randomization, stratified with respect to gender and stroke laterality. Therapy was given twice a week for 12 weeks. The primary outcome was change in participants' perception of stroke recovery as assessed by the Stroke Impact Scale with an intention-to-treat analysis. Secondary objective outcome measures were changes in balance, gait, grip strength and cognition. Blinded aassessments were performed at baseline, post-intervention and at 3 and 6 months' follow-up.

Results: One hundred twenty-three participants were assigned to rhythm-and-music therapy (n = 41), horse-riding therapy (n = 41) or control (n = 41). Post intervention, the perception of stroke recovery (mean change from baseline on a scale ranging from 1 to 100) was higher among rhythm-and-music therapy (5.2 [95% CI .79 to 9.61]) and horse-riding therapy participants (9.8 [95% CI 6.00 to 13.66]), compared with controls (-.5 [-3.20 to 2.28]); p = 0.001 (one-way ANOVA). The improvements were sustained in both intervention groups 6 months later and corresponding gains were observed for the secondary outcomes.

Conclusions: Multimodal interventions can improve long-term perception of recovery, as well as balance, gait, grip strength and working memory in a mixed population of individuals in late phase after stroke.

Clinical Trial Registration: ClinicalTrials.gov, NCT01372059.

INTRODUCTION

This study addresses three important clinical questions concerning the rehabilitation of stroke survivors. Is further recovery possible once patients are returned to the community having completed an acute/subacute-stage rehabilitation program? Can interventions that address a range of functional deficits and behavioral limitations be effective and lead to improvement? Can such interventions lead to sustained recovery in late phase after stroke? Treatment strategies employing multimodal approaches and stimulating environments may hold some answers to these questions.

Multimodal interventions are designed to engage patients in concurrent physical, sensory, cognitive and social activities. They are attractive for complex conditions like stroke because they target a range of functions. There is also emerging support for the contention that a combination of different modalities, rather than the individual components, may produce additive or synergistic effects on brain plasticity underpinning stroke recovery.[1-4]

Recently, multimodal interventions such as music therapy, rhythm-and music-based therapies (R-MT), dance, and horse-riding therapy (H-RT), have demonstrated promising results when applied to people suffering from various neurological conditions.[5-13] These interventions share important core components but differ from each other with respect to their combinations of modal stimuli and can therefore lead to different outcomes. H-RT combines equestrian activities, sensorimotor stimulation--a socially supportive atmosphere--and an inherently rich multisensory environment. The 3-dimensional movements of the horse's back produce a sensorimotor experience that closely resembles normal human gait which is shown to be beneficial for stroke survivors.[12] Structured R-MT combines listening to music, while performing coordinated rhythmic and cognitively demanding hand and feet movements in

response to visual and audio cues. Individually, or in combination, these components have all shown promise for treating individuals with brain disorders including stroke,[10] and a recent meta-analyses provide evidence for positive effects of music-supported therapy and rhythmic auditory cueing in stroke rehabilitation.[7, 9, 14]

There is an urgent unmet need to evaluate multimodal interventions applied to late phase stroke survivors who often do not receive further rehabilitation after the subacute phase. We designed a 3-armed, single-blind, randomized, controlled trial to evaluate whether a heterogeneous group of late-phase stroke survivors (10 months to 5 years post stroke) benefit from 2 different multimodal group-based interventions: R-MT and H-RT. We selected outcome measures that addressed a range of physical and cognitive parameters and chose as our primary outcome 'global perception of stroke recovery' assessed using the Stroke Impact Scale (SIS),[15] which measures a participants' own global perception of degree of recovery after stroke.[16, 17] Secondary aims were to investigate whether the interventions had a positive effect on gait, balance, grip strength, and cognition. We hypothesized that R-MT and H-RT would increase global perception of stroke recovery compared with standard care when applied to a mixed population of late phase stroke survivors.

MATERIALS AND METHODS

This trial used a single-blind, three-armed, randomized, controlled design, conducted according to the CONSORT guidelines.[18] The trial was undertaken in Gothenburg, Sweden and was conducted in accordance with relevant ethical guidelines. Ethics approval was granted by the Regional Ethical Review Board in Gothenburg (Ref number: 698-09). The study protocol has been published,[19] and the trial profile is illustrated in Figure 1.

Participants

The participants were recruited from a hospital-based register covering patients treated for ischemic or hemorrhagic stroke at the Sahlgrenska University Hospital in Gothenburg, Sweden. The eligibility criteria,[19] were subsequently widened to allow recruitment of individuals who had their stroke ≥10 months and ≤5 years before enrolment (late phase; File I in the online-only Data Supplement; Panel I). This was in agreement with the CONSORT guidelines,[18] and because of difficulties enrolling participants. All participants signed a written informed consent form and were told they could withdraw from the study at any time.

Experimental design

Participants were randomly allocated to 1 of the 3 groups: R-MT, H-RT, or a control group that received R-MT 1 year after inclusion (1:1:1) (Figure 1). The randomization was stratified with respect to sex and hemispheric location of the stroke. A statistician performed computer-generated randomization using random permuted blocks for each of the 2 × 2 strata. The block size was known only by the statistician. Another independent person sequentially numbered opaque envelopes, each of which contained the name of the intervention group. The participants were consecutively recruited to the randomization list by the project leader. The envelopes were opened in sequential order. Randomization codes were not accessed until all measurements

were completed. Assessors were blinded to treatment allocation. Participants were informed of the 3 possible group allocations but were not informed about the aims of the experimental versus control conditions. Data analysts were not blinded. To keep assessors blinded, participants and intervention therapists were instructed not to reveal treatment allocation or participants' study experiences to the assessors.

Procedures

The authors and therapists had extensive practical clinical experience with both R-MT and H-RT. In both intervention groups, participants attended 2 sessions a week over 12 weeks. All intervention costs were covered. Although both interventions created an enriched, multisensory environment designed to stimulate various motor and cognitive functions, they differed in dosage, execution, activities, and targeted outcomes (File II in the online-only Data Supplement; Panel II). Participants in the delayed R-MT group (controls) were instructed not to start any new therapies during the duration of the study but were allowed to continue with their regular activities and usual care. Evaluation was conducted at baseline, directly at the end of the 12-week-long intervention, as well as at 3 and 6 months post-intervention (Figure 1).

Outcomes

The primary outcome measure was the individual's global perception of stroke recovery, using item 9 (*Stroke Recovery*) of the Stroke Impact Scale (SIS, version 2.0).[15] This item was presented in the form of a visual analogue scale from zero to 100, with zero indicating "no recovery" and 100 indicating "full recovery". This scale has been shown to be well-suited for assessing stroke-specific improvements for patients undergoing rehabilitation.[15]

Observer-assessed outcome measures were reported at 0 and 6 months post intervention using validated tests. Gait and balance were measured with the Timed Up and Go test; the Berg

Balance Scale (BBS) and the Bäckstrand, Dahlberg and Liljenäs Balance Scale (BDL-BS). Hand strength was measured with Grippit, general cognitive level was measured with the Barrow Neurological Institute screen for higher cerebral functions, and working memory was measured with the letter-number sequencing test. A detailed description of all secondary outcome measures is given in File III in the online-only Data Supplement. The BDL-BS and the Grippit were added as outcome measures after the trial was initiated and therefore only 92 participants underwent these assessments. Safety and adverse events were noted throughout the trial.

Statistical analysis

A Chi-square test was used for statistical calculations in nQuery 6.0 with an alpha level of 5% and a power goal of 80%. The required sample size was determined on the basis of the SIS item *Stroke Recovery*. Based on existing literature, we considered an increase equivalent to 10% (10 points) of the total range of the scale as clinically relevant.[20] A clinically meaningful difference between the two groups (intervention group vs. control group) was defined as an absolute difference of 30%. To satisfy the power criteria of 80%, at least 41 patients were required in each of the 3 groups. A data monitoring committee oversaw the trial.

The outcome was analyzed in terms of change from baseline to each measurement point using the intention-to-treat population. Missing data were replaced using last observation carried forward. Baseline and demographic characteristics were summarized using descriptive statistics. Since baseline characteristics were well balanced between the groups, 1-way ANOVA was used. To ascertain if there were any significant between-group differences (treatment versus control), post hoc analyses with least significant difference were made. Effect size was calculated using percent improvement = [(postintervention group mean - pretest group

mean) divided by (pretest group mean)] x 100. Control participants in the delayed R-MT group were asked to complete the SIS questionnaire directly after the intervention.

Statistical differences between groups for the primary outcome variable SIS item Stroke Recovery was also tested using the chi-square test (Cochran-Mantel-Haenszel, corrected for gender and hemispheric location). On the basis of previous estimates,[20] this was done by dichotomizing data into the categories improved or unchanged/deteriorated, where improved (i.e. clinically meaningful change) was defined as any increase equivalent to 10 points of the total range of the scale. An ANCOVA for the primary outcome variable stroke recovery was performed (as a part of the analysis of change score) utilizing the baseline value as covariate. The ANCOVA and ANOVA models produced similar outcomes why conclusions are based on the outcomes of ANOVA analyses. All tests were two-sided and had $p<0.05$ as the level of significance. Analyses were done using SPSS v.22.0 (IBM Corp., Armonk, NY).

Sensitivity analyses to investigate robustness of the results were performed including a per-protocol analysis and the non-parametric Kruskal-Wallis test as a complementary sensitivity approach.[21] Any discrepancies between ANOVA and Kruskal-Wallis test in terms of significances were noted. The potential impact of outliers was assessed with respect to influence on estimates of treatment effects. Analyses of the between-group differences were performed with the outliers removed. Discrepancies between the principal results and the sensitivity analyses are presented.

RESULTS

A total of 5238 individuals with a history of stroke were screened (Figure 1). The most frequent reasons for exclusion were (in descending order): disability rated <2 on modified Rankin Scale; living >80 km from Gothenburg; disability rated >3 on modified Rankin Scale; and need for

personal assistance in activities of daily living. A total of 151 individuals were clinically tested for eligibility. Of these, 123 were eligible and agreed to participate. One participant in the R-MT group died, and of the remaining 122 subjects, 8 (7%) dropped out (5 at post-intervention, 1 at 3 months, and 2 at 6 months; Figure 1). Demographics of the study participants are presented in Table 1. All the baseline results were well-balanced with no significant between-group differences (File IV in the online-only Data Supplement). Mean attendance rates at the R-MT and H-RT were 88% and 83% respectively, equivalent to at least 21 treatment sessions (SD, 4) for the R-MT and 20 sessions (SD, 5) for the H-RT group. The interventions caused no serious adverse effects or injuries.

Findings for the primary outcome of the SIS item Stroke Recovery are summarized in Figure 2. Analyses of data dichotomized to improved or unchanged/deteriorated showed that the proportion of individuals who reported experiencing a meaningful recovery was significantly higher in the R-MT group (38%) and H-RT group (56%) compared with controls (17%), at post-intervention ($p=0.048$ and $p <0.0001$, respectively). These results were sustained at 3 ($p=0.002$ and $p=0.012$, respectively) and 6 months follow-up ($p=0.054$ and $p=0.001$, respectively) (Fig 2A). The Cochran-Mantel-Haenszel analyses revealed statistically significant outcome for group allocation at post-intervention ($p=0.002$), 3 ($p=0.008$), and 6 month ($p=0.004$), but neither sex nor hemispheric location had any statistically significant effect on the results.

The change in the perception of stroke recovery from baseline to each evaluation point is presented as mean (95% confidence interval) in Figure 2B. Post-intervention, there was a significant difference between groups with respect to the change in the perception of stroke recovery; $p = 0.001$ (1-way ANOVA). Further analyses with least significant difference showed that the change in the perception of recovery was higher among R-MT (5.2 [95% CI = .79 to

9.61]) and H-RT participants (9.8 [95% CI = 6.00 to 13.66]), compared with controls (-.5 [95% CI = -3.20 to 2.28]) (p=0.032 and p <0.0001, respectively). The effect sizes calculated as percent improvement (95% CI) for the three study groups were R-MT: 12.4 (1.5 to 13.3); H-RT: 23.8 (12.2 to 35.4); and Control: .7 (-5.0 to 6.3). The improvements were sustained at 3 months (p=0.006 and p=0.004, respectively) and again at 6 months (p=0.001 and p=0.007, respectively). The ANCOVA models calculated at post-intervention and at the 3 and 6 month follow-up produced similar results as ANOVA. The difference between groups was still in favour of the H-RT group, and there was also a similar trend in the R-MT group (p=0.001 and p=0.066, respectively). Notably, thirty-five participants in the control group completed the SIS questionnaire after finalization of the R-MT and showed improvement on the SIS recovery scale similar to the participants in the R-MT study group (mean: 5.6; 95% CI: 2.37 to 8.86) (Fig 2b).

Changes in observer-assessed gait ability and balance for the three study groups at treatment completion and at 6 months are summarized in Table 2. At treatment completion, one-way ANOVA showed a significant difference in the mean change in gait ability, as measured with Timed Up and Go test. Further analyses with least significant difference ascertained that this difference was ascribed to the H-RT group (-3.31 [95% CI = -5.42 to -1.20]) as compared with controls (1.78 [95% CI = -1.24 to 4.77]) (p=0.001). There was also a significant difference with respect to balance, as measured with Berg Balance Scale and BDL-BS. Further group analyses revealed that the difference with respect to Berg Balance Scale was in favor of the H-RT group (1.80 [95% CI = 1.10 to 2.51]) as compared with controls (0.12 [95% CI = -0.52 to 0.76]) (p=0.001). The difference with respect to BDL BS was ascribed to both the R-MT group (2.72 [95% CI = 1.57 to 3.88]) and H-RT group (2.82 [95% CI = 1.85 to 3.78]) compared with controls (1.03 [95% CI = 0.07 to 1.99]) (p=0.011 and p=0.011, respectively). At 6 months, the difference in gait ability and balance (as measured with Timed Up and Go test and BDL-BS,

respectively) remained significant. Further analysis demonstrated that the difference in gait ability was significant in favor of the H-RT group (-2.26 [95% CI = -4.22 to -.31]) as compared with controls (1.34 [95% CI = -1.39 to 4.06]) (p=0.010). The difference in balance was significant in favor of the R-MT group (2.53 [95% CI = 1.12 to 3.28]) compared with controls (1.78 [95% CI = -0.40 to 1.23]) (p=0.014).

Changes in grip strength are summarized in Table 3. After treatment completion, 1-way ANOVA showed significant differences in the mean changes in right-sided maximum and left-sided final grip force, as measured with Grippit. A significant difference in the left-handed maximum grip force was also detected. Subsequent least significant difference analyses ascertained that the R-MT group significantly improved their right-sided maximum grip force (16.41 ([95% CI = 5.65 to 27.17]) and left-sided final grip force (17.26 [95% CI = 6.19 to 28.33]) compared with controls (-1.29 [95% CI = -7.99 to 5.41]) and (.55 [95% CI = -7.07 to 8.17]), respectively (p=0.015 and p=0.042, respectively). The left-sided improvements were sustained at the 6-month follow-up (p=0.011).

Changes in general cognition and working memory are summarized in Table 4. For working memory, measured with letter-number sequencing test, the overall group analysis exhibited a statistically significant difference at 6 months. The subsequent 2 sample comparisons demonstrated that the favorable improvement was ascribed to the R-MT group (1.15 [95% CI = 0.44 to 1.87]) as compared with controls (0.10 [95% CI = -0.57 to 0.77]) (p=0.044).

The sensitivity analyses[21] including the per-protocol analysis, showed consistency with the findings from the primary intention-to-treat analyses, and there were no discrepancies between ANOVA and the Kruskal-Wallis test in terms of significance. The potential impact of outliers

was also assessed and the exclusion of outliers did not change the reported significant results, with one exception: the overall group difference for working memory at 6 months just fell short of significance (p=.057) after this exclusion.

DISCUSSION

This randomized, controlled study showed that it is possible to enhance perceived recovery using multimodal interventions applied in late phase after stroke. Compared with standard care (controls), both H-RT and R-MT led to an increase in global perception of recovery that was sustained over 6 months. Participants in the H-RT group also had higher scores on gait and balance tests (Timed Up and Go test and Berg Balance Scale, respectively) and participants in the R-MT group had higher scores on balance (BDL-BS) and grip strength (Grippit) tests compared with controls. Most of these differences were also sustained for 6 months. A difference in working memory was also observed in the RMT group 6 months after the intervention.

The study was conducted in a mixed population of late-phase stroke survivors aged 50 to 75 years who had a range of cognitive and physical dysfunctions. This is particularly important since stroke leads to a broad range of functional deficits and behavioral limitations, and thus constitutes a major long-term challenge with respect to treatments and interventions.[22] Perceived stroke recovery -- a measure that can accommodate and reflect important aspects of this wide range and variety of deficits[15]--improved in both the H-RT and R-MT groups relative to the control group, despite the heterogeneity of the participants' functional deficits and the long time after their stroke. This is encouraging since the individuals' perception of recovery is linked to how they experience their level of handicap.[16, 17] Results from randomized control trials showing sustained improvement in the late chronic stage after stroke are still sparse. While

there is a need for larger confirmatory controlled cross-over studies, the present study provides encouraging proof of principle and supports the contention that meaningful improvements are achievable long time after the acute and sub-acute phases after stroke.

Although some criticism may be raised against the selection of the SIS item Stroke Recovery as the primary outcome measure, the relevance of this measure has previously been evaluated with respect to the complex, multidimensional nature of stroke sequelae.[15, 20, 23] The Stroke Recovery item is a global measure that captures all aspects of stroke that may influence health-related quality of life and the person's own perception of effect of the intervention.[15] This enabled us to evaluate a broad stroke population with a wide range and variety of deficits. The combination of this broad measure with the more specific and objective secondary outcome measures contributed to the strength of the study. However, the study was not powered to detect between-group differences for all secondary outcome measures.

In intervention studies where it is not possible to blind participants to the study design, comparison groups not obtaining the desirable treatment may suffer resentful demoralization, become discouraged and, as a result, perform worse on the outcome measures. In order to minimize the potential effects of resentful demoralization, the control group was offered R-MT 1 year after their inclusion. This was to provide an element of expectation, which in itself could contribute to perception of recovery. There was no decline in performance on the primary or secondary outcomes in the control group between baseline and follow-up, which further strengthens the validity of the study. The observed improvement of self-perceived recovery in the control group at completion of the R-MT intervention also supports the conclusion that this therapy can promote recovery in late phase after stroke.

Additional strengths of the study included: a concealed and methodologically rigorous design; randomization stratified by sex and brain laterality (factors that may affect outcomes in rehabilitation trials); an intention-to-treat analysis as well as a per-protocol analysis; adherence to the CONSORT guidelines for clinical trials;[18] and high adherence and a low drop-out rate.

Even if the outcome from this study is encouraging, it has some limitations. The participants were recruited from a comprehensive hospital-based register, including almost all stroke cases in the broader Gothenburg area. Although this is a strength, the small number of recruited subjects (123) selected from the whole primary cohort (5328), impacts on the external validity of the study. Clinical trials often use excessively strict enrolment criteria, thereby excluding many individuals who could potentially benefit from new interventions thus limiting generalizability to clinical practice.[24] Many of the excluded individuals were not randomized into the current study due to their geographical location, as that would have made it practically difficult for the individual to attend the program. In addition, an inclusion of the well-recovered participants, such as in the largest exclusion group modified Rankin Scale 0-1 would probably not have been cost-effective due to their mild deficits and individuals with severe disabilities were not considered for these therapies due to problems to participate.

Another potential limitation of this trial concerns the active intervention versus no intervention design. The design does control for the passage of time and attention from the evaluators but having a passive control group does not eliminate the attention from the study personnel carrying out the interventions.

The differences in the secondary outcome measures observed between the participants in the H-RT and R-MT groups may have several explanations including differences in dose and

intensity. The H-RT group received more total intervention time, including time for socializing, and this could be one factor underlying the slightly better overall outcome after this therapy. The results could also be explained by the nature and unique combination of modalities used in each of these interventions. H-RT involves rhythmic movement of the horse, which continually challenges the rider's posture and gives vestibular, proprioceptive and visual input that may facilitate the observed improvements in gait and balance seen in the H-RT group.[11] On the other hand, R-MT involves repeated motor skill training, postural stability and weight shifting, in combination with rhythmic, coordinated hand movements that tentatively facilitate the improvements in balance and grip strength seen in the R-MT group. The observed improvements in working memory in the R-MT group may reflect the cognitively challenging nature of R-MT. The improvements achieved by both interventions were sustained for at least 6-months post-intervention (i.e. until the final evaluation time point) showing that 12 weeks of moderately intense therapy in late phase after stroke can have long lasting effects. While earlier studies also support the potential benefits of H-RT, R-MT, and rhythmic auditory stimulation on balance, gait, mobility, language and cognition in stroke patients [5-7, 12, 13] they were based on different study designs. Whether H-RT or R-MT lead to persisting perception of recovery, changes in brain plasticity beyond 6 months or long-term life style alterations warrants further investigation.

Both R-MT and H-RT broadly create a stimulating environment in which participants, with high levels of adherence, engage concurrently in physical, mental and social activities. The combination of different modalities in multimodal interventions is expected to have additive or even synergistic effects on brain plasticity underpinning stroke recovery.[1-4] However, it is currently not known which individual component or combinations of modalities that render the best outcome in multimodal interventions. Some guidance is provided from studies where post-

stroke animals are housed in enriched environment (EE).[3] EE includes several different components such as social stimulation, sensorimotor and cognitive stimulation and exercise.[2, 4, 25] Several studies show that EE is more effective than any of the individual components in promoting recovery after brain injury.[1, 3, 4] Recent clinical studies have also shown that stroke rehabilitation in the early post-acute phase is most effective when performed in an engaging environment that provides novel and multisensory stimulation.[25, 26] This is further supported by studies showing additive effects of social activity, exercise, music and dance on cognitive improvement in healthy elderly individuals as well as in patients suffering from Parkinson's disease.[10] In the present study, we show that sustained improvement can occur in late phase after stroke as a result of multimodal intervention.

SUMMARY

This study demonstrates that multimodal rehabilitation can lead to meaningful and sustained improvement when applied to individuals with moderate levels of disability in the late post-stroke stage. It also shows the promise of using different modality combinations in order to address the individual needs of stroke survivors. These results support long-term engagement in multimodal rehabilitation programs for individuals with persistent disabilities after stroke. Future research should further assess the effectiveness of multimodal therapies post-stroke including dose and timing of the interventions. The cost-benefit aspects of these therapies should also be addressed and further investigated.

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REFERENCES

1. Pekna M, Pekny M and Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke.* 2012; 43: 2819-2828.

2. Livingston-Thomas J, Nelson P, Karthikeyan S, Antonescu S, Jeffers MS, Marzolini S, et al. Exercise and environmental enrichment as enablers of task-specific neuroplasticity and stroke recovery. *Neurotherapeutics.* 2016; 13: 395-402.

3. Corbett D, Jeffers M, Nguemeni C, Gomez-Smith M and Livingston-Thomas J. Lost in translation: rethinking approaches to stroke recovery. *Prog Brain Res.* 2015; 218: 413-434.

4. Venna V, Xu Y, Doran S, Patrizz A and McCullough L. Social interaction plays a critical role in neurogenesis and recovery after stroke. *Transl Psychiat.* 2014; 4: e351.

5. Sarkamo T, Tervaniemi M, Laitinen S, Forsblom A, Soinila S, Mikkonen M, et al. Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain.* 2008; 131: 866-876.

6. Raglio A, Oasi O, Gianotti M, Rossi A, Goulene K and Stramba-Badiale M. Improvement of spontaneous language in stroke patients with chronic aphasia treated with music therapy: a randomized controlled trial. *Int J Neurosci.* 2015: 1-8.

7. Yoo GE and Kim SJ. Rhythmic Auditory Cueing in Motor Rehabilitation for Stroke Patients: Systematic Review and Meta-Analysis. *J Music Ther.* 2016; 53: 149-177.

8. Raghavan P, Geller D, Guerrero N, Aluru V, Eimicke JP, Teresi JA, et al. Music Upper Limb Therapy—Integrated: An Enriched Collaborative Approach for Stroke Rehabilitation. *Front Hum Neurosci.* 2016; 10: 498.

9. Zhang Y, Cai J, Zhang Y, Ren T, Zhao M and Zhao Q. Improvement in Stroke-induced Motor Dysfunction by Music-supported Therapy: A Systematic Review and Meta-analysis. *Sci Rep.* 2016; 6: 38521.

10. Dhami P, Moreno S and DeSouza JF. New framework for rehabilitation–fusion of cognitive and physical rehabilitation: the hope for dancing. *Front Psychol.* 2014; 5: 1478.

11. Beinotti F, Christofoletti G, Correia N and Borges G. Effects of horseback riding therapy on quality of life in patients post stroke. *Top Stroke Rehabil.* 2013; 20: 226-232.

12. Lee CW, Kim SG and Yong MS. Effects of hippotherapy on recovery of gait and balance ability in patients with stroke. *J Phys Ther Sci.* 2014; 26: 309-311.

13. Thaut MH, Leins AK, Rice RR, Argstatter H, Kenyon GP, McIntosh GC, et al. Rhythmic auditory stimulation improves gait more than NDT/Bobath training in near-ambulatory patients early poststroke: a single-blind, randomized trial. *Neurorehabil Neural Repair.* 2007; 21: 455-459.

14. Hatem SM, Saussez G, della Faille M, Prist V, Zhang X, Dispa D, et al. Rehabilitation of motor function after stroke: a multiple systematic review focused on techniques to stimulate upper extremity recovery. *Front Hum Neurosci.* 2016; 10: 442.

15. Duncan PW, Wallace D, Lai SM, Johnson D, Embretson S and Laster LJ. The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke.* 1999; 30: 2131-2140.

16. Dennis M, Wellwood I, O'Rourke S, MacHale S and Warlow C. How reliable are simple questions in assessing outcome after stroke? *Cerebrovasc Dis.* 1997; 7: 19-21.

17. Sturm JW, Dewey HM, Donnan GA, Macdonell RA, McNeil JJ and Thrift AG. Handicap after stroke: how does it relate to disability, perception of recovery, and stroke subtype? The North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke.* 2002; 33: 762-768.

18. Altman DG, Moher D and Schulz KF. Improving the reporting of randomised trials: the CONSORT Statement and beyond. *Stat Med.* 2012; 31: 2985-2997.

19. Bunketorp Kall L, Lundgren-Nilsson A, Blomstrand C, Pekna M, Pekny M and Nilsson M. The effects of a rhythm and music-based therapy program and therapeutic riding in late recovery phase following stroke: a study protocol for a three-armed randomized controlled trial. *BMC Neurol.* 2012; 12: 141.

20. Lin KC, Fu T, Wu CY, Wang YH, Liu JS, Hsieh CJ, et al. Minimal detectable change and clinically important difference of the Stroke Impact Scale in stroke patients. *Neurorehabil Neural Repair.* 2010; 24: 486-492.

21. Thabane L, Mbuagbaw L, Zhang S, Samaan Z, Marcucci M, Ye C, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Med Res Methodol.* 2013; 13: 92.

22. Langhorne P, Bernhardt J and Kwakkel G. Stroke rehabilitation. *Lancet.* 2011; 377: 1693-1702.

23. Lin KC, Fu T, Wu CY, Hsieh YW, Chen CL and Lee PC. Psychometric comparisons of the Stroke Impact Scale 3.0 and Stroke-Specific Quality of Life Scale. *Qual Life Res.* 2010; 19: 435-443.

24. Khorsan R and Crawford C. How to Assess the External Validity and Model Validity of Therapeutic Trials: A Conceptual Approach to Systematic Review Methodology. *Evid Based Complement Alternat Med.* 2014; 2014: 94804.

25. Janssen H, Ada L, Bernhardt J, McElduff P, Pollack M, Nilsson M, et al. An enriched environment increases activity in stroke patients undergoing rehabilitation in a mixed rehabilitation unit: a pilot non-randomized controlled trial. *Disabil Rehabil.* 2014; 36: 255-262.

26. Khan F, Amatya B, Elmalik A, Lowe M, Ng L, Reid I, et al. An Enriched Environmental Programme During Inpatient Neuro-rehabilitation: A Randomized Controlled Trial. *J Rehabil Med.* 2016; 48: 417-425.

FIGURE LEGEND

Figure 1: Trial profile with the evaluation at the end of the 12-week intervention period as the primary endpoint.

Figure 2a. The proportion of participants who perceived themselves as improved at each evaluation point compared to baseline for all three study groups; **b.** The change in the perception of stroke recovery from baseline to each evaluation point is presented as mean (95% CI). The control group improved in line with the study groups after they received R-MT (cross-over).

TABLES

Table 1: Demographic characteristics of study participants.			
	R-MT **(n=41)**	H-RT **(n=41)**	Control **(n=41)**
Variable			
Sex: Women/Men (%)	18 (43.9)/ 23 (56.1)	17 (41.5)/ 24 (58.5)	19 (46.3)/ 22 (53.7)
Age in years	62.7 (6.7)	62.6 (6.5)	63.7 (6.7)
Years of schooling	14.2 (4.1)	12.5 (4.2)	13.5 (4.3)
Time since stroke onset in days	969.8 (422.9)	1101.9 (576.1)	1096.3 (439.0)
Site of the stroke lesion			
Right (%)/Left (%)	20 (48.8)/ 21 (51.2)	20 (48.8)/ 21 (51.2)	18 (43.9)/ 22 (53.7)
Stroke type			
Haemorrhage (%)/Infarct (%)	9 (22.0)/ 32 (78.0)	14 (34.1)/ 27 (65.9)	13 (31.7)/ 28 (68.3)
Modified Rankin Scale			
Grade 2 (%)/Grade 3 (%)	24 (58.5)/ 17 (51.5)	23 (56.1)/ 18 (43.9)	25 (61.0)/ 16 (39.0)
NIHSS	3.0 (2.9)	2.7 (3.1)	2.8 (3.6)
Data are number (%) or mean (SD). H-RT = Horse-riding therapy; R-MT = Rhythm-and-music therapy; NIHSS = The National Institutes Health Stroke Scales.			

Table 2: Changes in gait and balance for the three study groups post intervention and at the 6-month follow-up according to ITT.

	Within-group changes from baseline to follow-up			Between-group differences	
				F-ratio	ANOVA
	R-MT (n=40)	**H-RT** (n=41)	**Control** (n=41)	P	P
	Change from baseline to post-intervention				
TUG (sec)	-0.54 (-1.10 to 0.02)	-3.31 (-5.42 to -1.20)§	1.78 (-1.24 to 4.77)	5.75	0.004
BBS	0.98 (0.11 to 1.84)	1.80 (1.10 to 2.51)§	0.12 (-0.52 to 0.76)	5.35	0.006
BDL-BS	2.72 (1.57 to 3.88)‡ *	2.82 (1.85 to 3.78)‡ †	1.03 (0.07 to 1.99)†	4.50	0.013
	Change from baseline to 6-month follow-up				
TUG (sec)	-1.08 (-1.77 to -0.39)	-2.26 (-4.22 to -.31)‡	1.34 (-1.39 to 4.06)	3.51	0.033
BBS	1.21 (-0.04 to 2.44)	1.12 (-0.03 to 2.21)	0.20 (-0.44 to 0.84)	1.23	0.294
BDL-BS	2.53 (1.12 to 3.28)§	1.02 (-0.12 to 2.17)†	1.78 (-0.40 to 1.23)†	3.20	0.044

Data are mean (95% CI). Data available for: * 36; † 38; participants.

Single group difference vs. controls: ‡ = P <.05; § = P <.01.

BBS = Berg balance scale; BDL-BS = Bäckstrand, Dahlberg, and Liljenäs balance scale; H-RT = Horse-riding therapy; R-MT = Rhythm-and-music therapy; TUG = Timed up and go.

Table 3: Changes in hand strength for the three study groups at post-intervention and at the 6-months follow-up according to ITT.

				F-ratio	ANOVA
	R-MT (n=29)	**H-RT** (n=31)	**Control** (n=32)		P
Change from baseline to post-intervention					
Right hand					
GRIPPIT max (N)	16.41 (5.65 to 27.17)*	6.49 (-5.69 to 18.68)	-1.29 (-7.99 to 5.41)	3.09	0.050
GRIPPIT mean (N)	12.24 (2.69 to 21.79)	7.86 (-1.83 to 17.55)	2.89 (-3.56 to 9.34)	1.15	0.320
GRIPPIT final (N)	9.79 (-3.28 to 22.87)	8.86 (-1.47 to 19.19)	5.13 (-1.99 to 12.24)	0.23	0.798
Left hand					
GRIPPIT max (N)	17.01 (4.43 to 29.59)	6.33 (-5.56 to 18.22)	.46 (-5.23 to 6.15)	2.54	0.085
GRIPPIT mean (N)	13.90 (3.58 to 24.21)	7.04 (-3.59 to 17.67)	.58 (-4.80 to 5.97)	2.13	0.125
GRIPPIT final (N)	17.26 (6.19 to 28.33)*	2.88 (-8.52 to 14.27)	.55 (-7.07 to 8.17)	3.09	0.050
Change from baseline to 6-month follow-up					
Right hand					
GRIPPIT max (N)	12.18 (-2.36 to 26.72)	1.02 (-9.98 to 12.02)	-2.64 (-12.18 to 6.91)	1.74	0.181
GRIPPIT mean (N)	13.48 (2.70 to 24.26)	3.72 (-7.39 to 14.83)	1.15 (-6.36 to 8.66)	1.72	0.184
GRIPPIT final (N)	10.80 (-1.76 to 23.37)	8.88 (-2.23 to 19.99)	-1.33 (-10.10 to 7.43)	1.53	0.223
Left hand					
GRIPPIT max (N)	16.49 (4.41 to 28.57)*	3.23 (-7.36 to 13.82)	-2.96 (-12.19 to 6.27)	2.50	0.034
GRIPPIT mean (N)	12.14 (2.53 to 21.76)	5.29 (-4.56 to 15.15)	0.08 (-8.31 to 8.47)	1.69	0.190
GRIPPIT final (N)	15.06 (4.95 to 25.17) †	5.68 (-5.26 to 16.61)	-7.22 (-16.26 to 1.82)	5.07	0.008

Data are mean (95% CI). Single group difference vs. Controls: * = P <.05; † = P <.01.

H-RT = Horse-riding therapy; R-MT = Rhythm-and-music therapy; GRIPPIT final = The sustainability of grip force measured during the last 0.5 second.

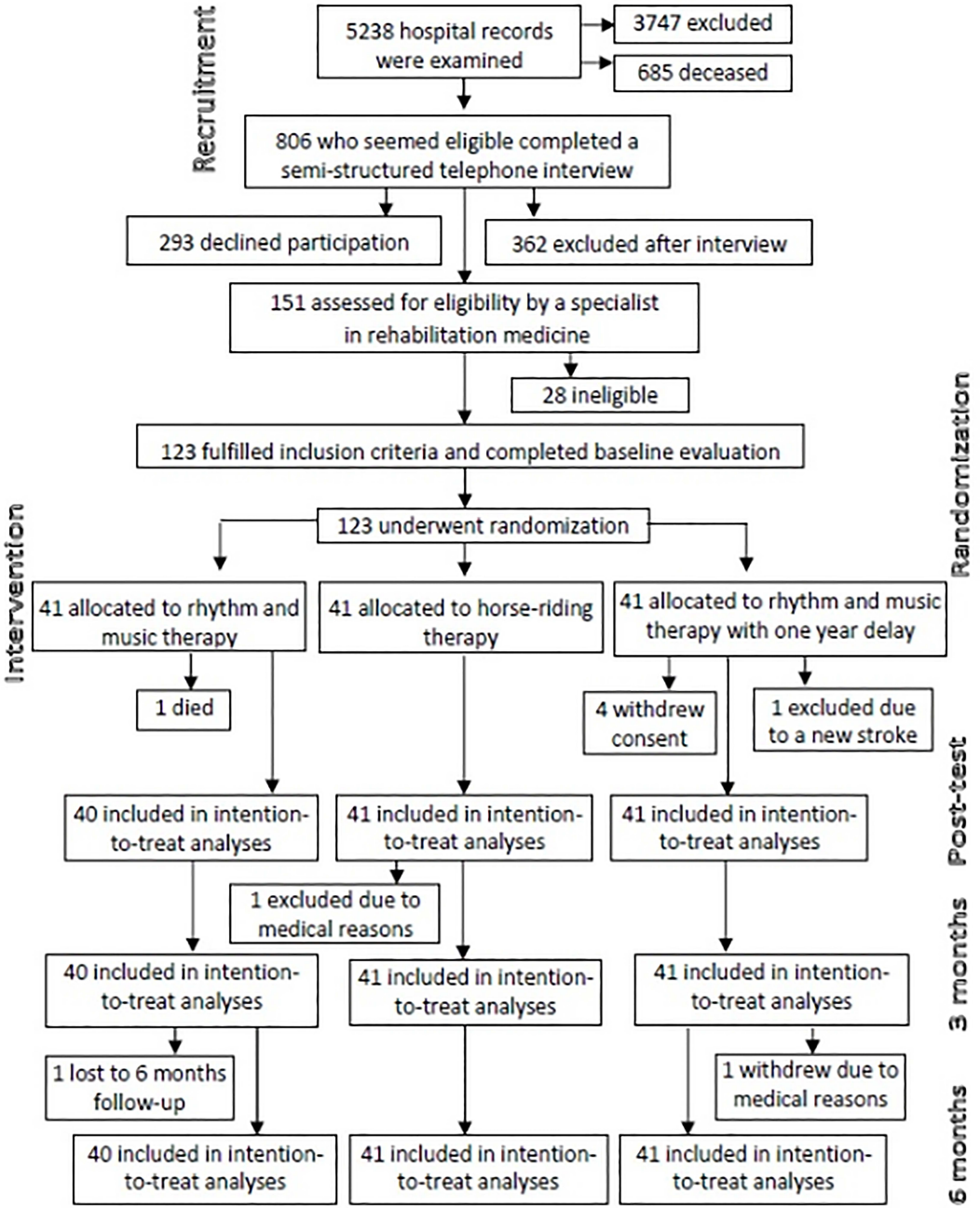
Table 4: Changes in general cognitive level and working memory for the three study groups at post-intervention and at the 6-month follow-up according to ITT.

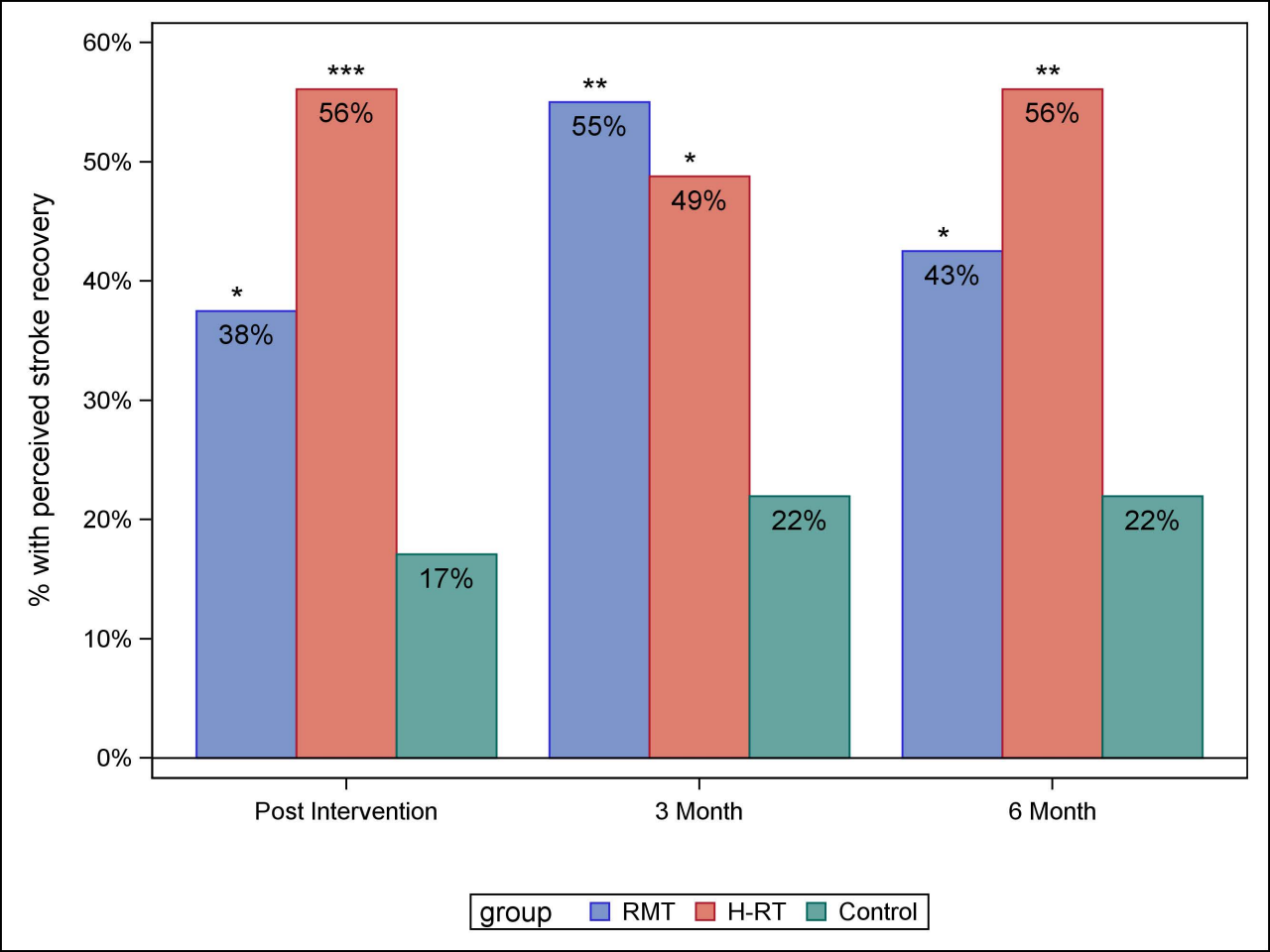
				F-ratio	ANOVA
	R-MT (n=40)	**H-RT** (n=41)	**Control** (n=41)		P
	Change from baseline to post-intervention				
BNIS	0.66 (-0.23 to 1.56)	1.06 (-0.01 to 2.13)	0.56 (-0.23 to 1.35)	0.34	0.72
LNS†	0.92 (0.16 to 1.69)	0.45 (-0.35 to 1.25)	0.18 (-0.51 to 0.87)	1.02	0.37
	Change from baseline to 6-month follow-up				
BNIS	1.29 (0.25 to 2.33)	1.33 (0.36 to 2.3)	1.7 (0.74 to 2.65)	0.21	0.81
LNS†	1.15 (0.44 to 1.87) *	0 (-0.77 to 0.77)	0.10 (-0.57 to 0.77)	3.2	0.04

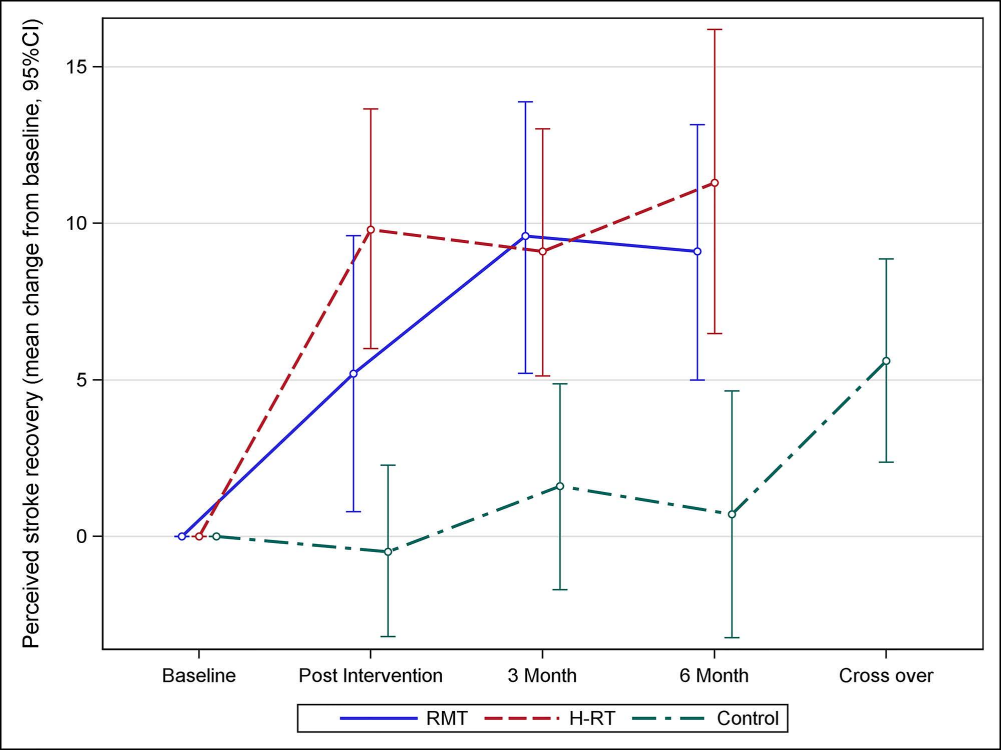
Data are mean (95% CI). Single group difference vs. controls: * = P <.05.

†Not able to do LNS due to severe aphasia: R-MT=1; H-RT=1; Control=2; participants.

BNIS = Barrow Neurological Institute Screen for Higher Cerebral Functions; LNS = Letter-Number Sequencing.


Recruitment
5238 hospital records were examined
3747 excluded
685 deceased
806 who seemed eligible completed a semi-structured telephone interview
293 declined participation
362 excluded after interview
151 assessed for eligibility by a specialist in rehabilitation medicine
28 ineligible
123 fulfilled inclusion criteria and completed baseline evaluation
123 underwent randomization
Randomization
Intervention
41 allocated to rhythm and music therapy
41 allocated to horse-riding therapy
41 allocated to rhythm and music therapy with one year delay
1 died
4 withdrew consent
1 excluded due to a new stroke
Post-test
40 included in intention-to-treat analyses
41 included in intention-to-treat analyses
41 included in intention-to-treat analyses
1 excluded due to medical reasons
3 months
40 included in intention-to-treat analyses
41 included in intention-to-treat analyses
41 included in intention-to-treat analyses
1 lost to 6 months follow-up
1 withdrew due to medical reasons
6 months
40 included in intention-to-treat analyses
41 included in intention-to-treat analyses
41 included in intention-to-treat analyses


60%
50%
40%
30%
20%
10%
0%
% with perceived stroke recovery
*
38%
***
56%
17%
**
55%
*
49%
22%
*
43%
**
56%
22%
Post Intervention
3 Month
6 Month
group
RMT
H-RT
Control


Perceived stroke recovery (mean change from baseline, 95%CI)
15
10
5
0
Baseline
Post Intervention
3 Month
6 Month
Cross over
RMT
H-RT
Control