Original Contribution

Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke
A Randomized Controlled Trial

Lina Bunketorp-Käll, PhD; Åsa Lundgren-Nilsson, PhD; Hans Samuelsson, PhD;
Tulen Pekny, MD; Karin Blomvé, MD; Marcela Pekna, MD, PhD; Milos Pekny, MD, PhD;
Christian Blomstrand, MD, PhD; Michael Nilsson, MD, PhD

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 sex 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 assessments were performed at baseline, postintervention, and at 3- and 6-month 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% confidence interval, 0.79–9.61]) and horse-riding therapy participants (9.8 [95% confidence interval, 6.00–13.66]), compared with controls (−0.5 [−3.20 to 2.28]); P=0.001 (1-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—URL: http//www.ClinicalTrials.gov. Unique identifier: NCT01372059.

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This study addresses 3 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 using 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 with various neurologic 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, 3-armed, randomized controlled design, conducted according to the CONSORT guidelines[18] (Consolidated Standards of Reporting Trials). 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 (reference 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 enrollment (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 during 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, and 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 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; 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 χ^2 test was used for statistical calculations in nQuery 6.0 with an α 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 2 groups (intervention group versus 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 the last observation carried forward. Baseline and demographic characteristics were summarized using descriptive statistics. Because baseline characteristics were well balanced between the groups, 1-way ANOVA was used. To ascertain whether 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])×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 were also tested using the χ^2 test (Cochran–Mantel–Haenszel, corrected for sex 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 (ie, 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) using 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 2 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 nonparametric 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 postintervention, 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
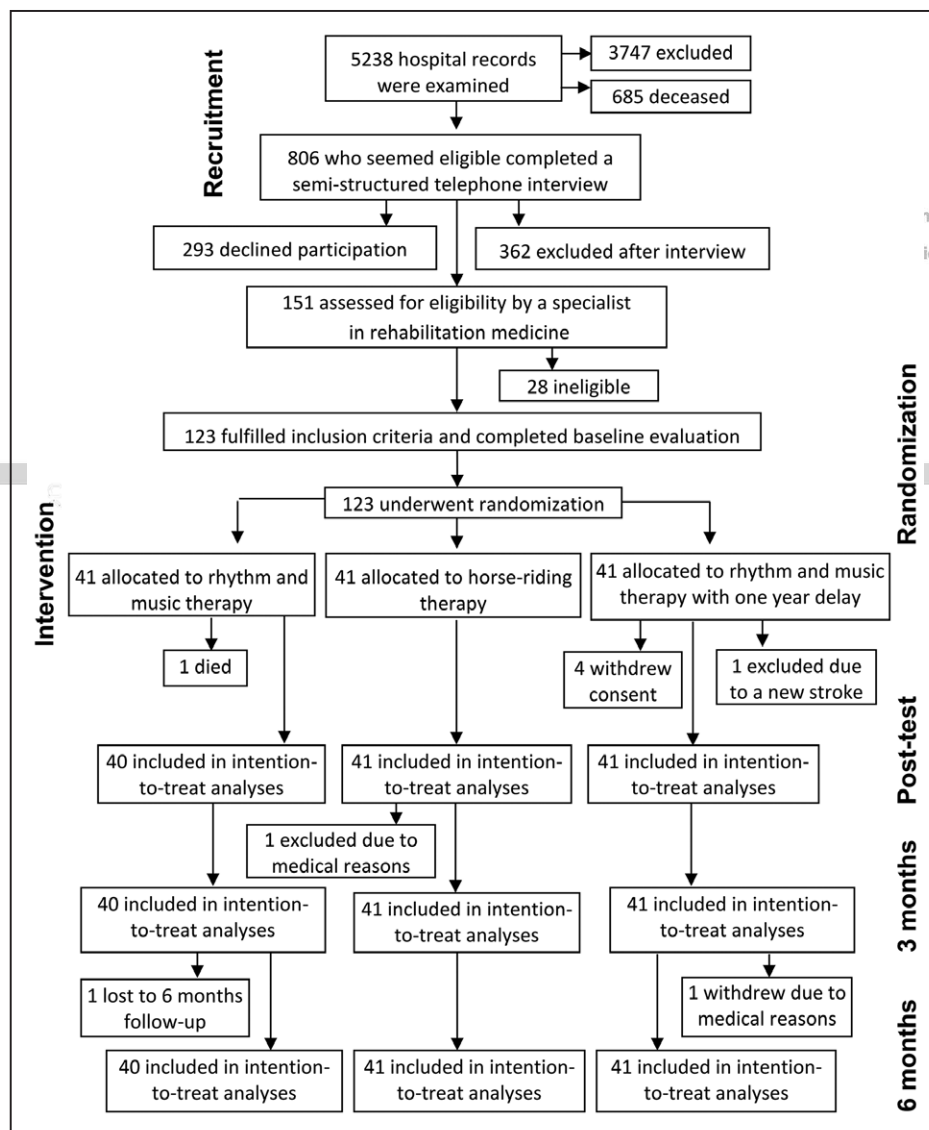

Figure 1. Trial profile with the evaluation at the end of the 12-week intervention period as the primary end point.

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 postintervention ($P=0.048$ 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; Figure 2A). The Cochran–Mantel–Haenszel analyses revealed statistically significant outcome for group allocation at post-intervention ($P=0.002$), 3 months ($P=0.008$), and 6 months ($P=0.004$), 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 [CI]) 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, 0.79–9.61]) and H-RT participants (9.8 [95% CI, 6.00–13.66]), compared with controls (−0.5 [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 3 study groups were R-MT, 12.4 (1.5–13.3); H-RT, 23.8 (12.2–35.4); and control, 0.7 (−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 postintervention and at the 3- and 6-month follow-up produced similar results as ANOVA. The difference between groups was in favor 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, 35 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, 2.37–8.86; Figure 2B).

Changes in observer-assessed gait ability and balance for the 3 study groups at treatment completion and at 6 months are summarized in Table 2. At treatment completion, 1-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 the 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, 1.10–2.51]), 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, 1.57–3.88]) and H-RT group (2.82 [95% CI, 1.85–3.78]) compared with controls (1.03 [95% CI, 0.07–1.99]; $P=0.011$ 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 −0.31]), 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, 1.12–3.28]) 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

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, y	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, d	969.8 (422.9)	1101.9 (576.1)	1096.3 (439)
Site of the stroke lesion			
Right/left, %	20 (48.8)/21 (51.2)	20 (48.8)/21 (51.2)	18 (43.9)/23 (56.1)
Stroke type			
Hemorrhage/infarct, %	9 (22)/32 (78)	14 (34.1)/27 (65.9)	13 (31.7)/28 (68.3)
Modified Rankin Scale			
Grade 2/grade 3, %	24 (58.5)/17 (41.5)	23 (56.1)/18 (43.9)	25 (61)/16 (39)
NIHSS score	3 (2.9)	2.7 (3.1)	2.8 (3.6)

Data are number (%) or mean (SD). H-RT indicates horse-riding therapy; NIHSS, National Institutes of Health Stroke Scale; and R-MT, rhythm-and-music therapy.
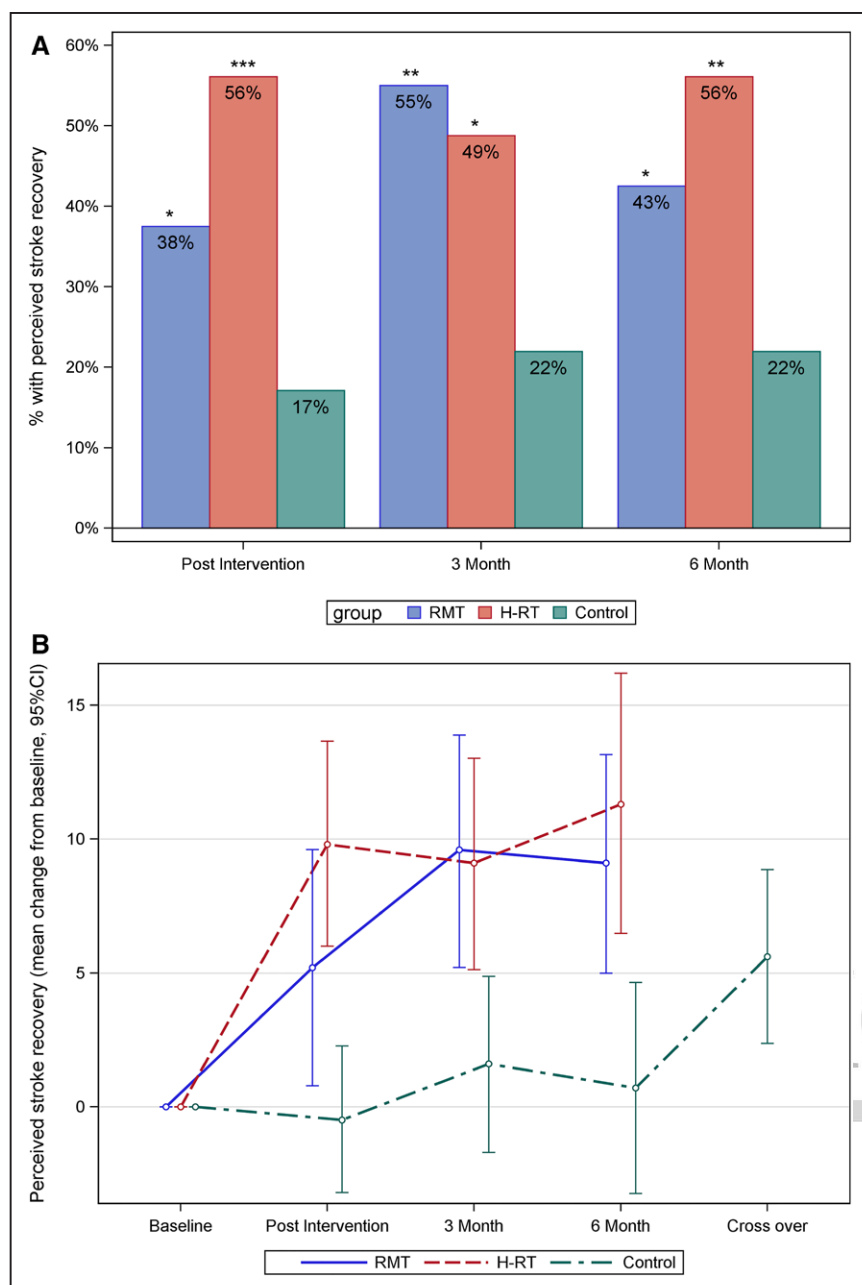
Figure 2. A, The proportion of participants who perceived themselves as improved at each evaluation point compared with baseline for all 3 study groups, *P<0.05; **P<0.01; ***P<0.001; **B,** The change in the perception of stroke recovery from baseline to each evaluation point is presented as mean (95% confidence interval). The control group improved in line with the study groups after they received rhythm-and-music therapy (crossover). CI indicates confidence interval; H-RT, horse-riding therapy; and R-MT, rhythm-and-music therapy.

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, 5.65–27.17]) and left-sided final grip force (17.26 [95% CI, 6.19–28.33]) compared with controls (−1.29 [95% CI, −7.99 to 5.41]) (0.55 [95% CI, −7.07 to 8.17]; $P=0.015$ 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, 0.44–1.87]), 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 1 exception: the overall group difference for working memory at 6 months just fell short of significance ($P=0.057$) 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

Table 2.   Changes in Gait and Balance for the 3 Study Groups Post-Intervention and at the 6-Month Follow-Up According to Intention-to-Treat Analysis

				Between-Group Differences	
	Within-Group Changes From Baseline to Follow-Up			F Ratio	ANOVA
	R-MT (n=40)	H-RT (n=41)	Control (n=41)	P Value	P Value
	Change from baseline to postintervention				
TUG, s	−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 (0.11–1.84)	1.80 (1.10–2.51)*	0.12 (−0.52 to 0.76)	5.35	0.006
BDL-BS	2.72 (1.57–3.88)†‡	2.82 (1.85–3.78)†§	1.03 (0.07–1.99)§	4.50	0.013
	Change from baseline to 6-mo follow-up				
TUG, sec	−1.08 (−1.77 to −0.39)	−2.26 (−4.22 to −0.31)†	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 (1.12–3.28)*	1.02 (−0.12 to 2.17)§	1.78 (−0.40 to 1.23)§	3.20	0.044

Data are mean (95% CI). BBS indicates Berg Balance Scale; BDL-BS, Bäckstrand, Dahlberg, and Liljenäs Balance Scale; CI, confidence interval; H-RT, horse-riding therapy; R-MT, rhythm-and-music therapy; and TUG, Timed Up and Go test.

Single group difference vs controls: *$P<0.01$, †$P<0.05$.

‡Data available for 36 participants.

§Data available for 38 participants.

(controls), both H-RT and R-MT led to an increase in global perception of recovery that was sustained during 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 R-MT group 6 months after the intervention.

Table 3.   Changes in Hand Strength for the 3 Study Groups at Post-Intervention and at the 6-Month Follow-Up According to Intention-to-Treat Analysis

	R-MT (n=29)	H-RT (n=31)	Control (n=32)	F Ratio	ANOVA P Value
	Change from baseline to postintervention				
Right hand					
Grippit max	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	12.24 (2.69–21.79)	7.86 (−1.83 to 17.55)	2.89 (−3.56 to 9.34)	1.15	0.320
Grippit final	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	17.01 (4.43–29.59)	6.33 (−5.56 to 18.22)	0.46 (−5.23 to 6.15)	2.54	0.085
Grippit mean	13.90 (3.58–24.21)	7.04 (−3.59 to 17.67)	0.58 (−4.80 to 5.97)	2.13	0.125
Grippit final	17.26 (6.19–28.33)*	2.88 (−8.52 to 14.27)	0.55 (−7.07 to 8.17)	3.09	0.050
	Change from baseline to 6-mo follow-up				
Right hand					
Grippit max	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	13.48 (2.70–24.26)	3.72 (−7.39 to 14.83)	1.15 (−6.36 to 8.66)	1.72	0.184
Grippit final	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	16.49 (4.41–28.57)*	3.23 (−7.36 to 13.82)	−2.96 (−12.19 to 6.27)	2.50	0.034
Grippit mean	12.14 (2.53–21.76)	5.29 (−4.56 to 15.15)	0.08 (−8.31 to 8.47)	1.69	0.190
Grippit final	15.06 (4.95–25.17)†	5.68 (−5.26 to 16.61)	−7.22 (−16.26 to 1.82)	5.07	0.008

Data are mean (95% CI). CI indicates confidence interval; Grippit final, the sustainability of grip force measured during the last 0.5 s; H-RT, horse-riding therapy; and R-MT, rhythm-and-music therapy.

Single group difference vs controls: *$P<0.05$, †$P<0.01$.

Table 4. Changes in General Cognitive Level and Working Memory for the 3 Study Groups at Post-Intervention and at the 6-Month Follow-Up According to Intention-to-Treat Analysis

	R-MT (n=40)	H-RT (n=41)	Control (n=41)	F Ratio	ANOVA P Value
	Change from baseline to postintervention				
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 (0.16–1.69)	0.45 (−0.35 to 1.25)	0.18 (−0.51 to 0.87)	1.02	0.37
	Change from baseline to 6-mo follow-up				
BNIS	1.29 (0.25–2.33)	1.33 (0.36–2.3)	1.7 (0.74–2.65)	0.21	0.81
LNS*	1.15 (0.44–1.87)†	0 (−0.77 to 0.77)	0.10 (−0.57 to 0.77)	3.2	0.04

Data are mean (95% CI). BNIS indicates Barrow Neurological Institute screen for higher cerebral functions; CI, confidence interval; H-RT, horse-riding therapy; LNS, letter–number sequencing; and R-MT, rhythm-and-music therapy.

*Participants not able to do LNS because of severe aphasia: R-MT=1; H-RT=1; Control=2.

†Single group difference vs controls: $P<0.05$.

The study was conducted in a mixed population of late-phase stroke survivors 50 to 75 years of age who had a range of cognitive and physical dysfunctions. This is particularly important because 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 because 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. Although there is a need for larger confirmatory controlled crossover studies, the present study provides encouraging proof of principle and supports the contention that meaningful improvements are achievable long time after the acute and subacute 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 experience resentful demoralization, become discouraged, and as a result, perform worse on the outcome measures. 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 and 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 because of their geographic location, because 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 to 1, would probably not have been cost-effective because of their mild deficits, and individuals with severe disabilities were not considered for these therapies because of 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 contrary, 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 postintervention (ie, until the final evaluation time point) showing that 12 weeks of moderately intense therapy in late phase after stroke can have long-lasting effects. Although 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 lifestyle 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 poststroke animals are housed in enriched environment.[3] Enriched environment includes several different components, such as social stimulation, sensorimotor and cognitive stimulation, and exercise.[2,4,25] Several studies show that enriched environment 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 postacute 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 and in patients with Parkinson 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 poststroke stage. It also shows the promise of using different modality combinations 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 poststroke, including dose and timing of the interventions. The cost–benefit aspects of these therapies should also be addressed and further investigated.

Disclosures

None.

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Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke: A Randomized Controlled Trial

Lina Bunketorp-Käll, Åsa Lundgren-Nilsson, Hans Samuelsson, Tulen Pekny, Karin Blomvé, Marcela Pekna, Milos Pekny, Christian Blomstrand and Michael Nilsson

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SUPPLEMENTARY FILE I; PANEL I

Panel 1. Eligibility criteria

- Aged 50 – 75 years
- Disability grade 2 or 3 on mRS*
- Chronic impairment after stroke (minimum 10 months to maximum 5 years)
- An ischaemic or haemorrhagic stroke or subarachnoid haemorrhage with initial presence of hemispheric impact/symptoms
- Ability to understand written and oral information and instructions in Swedish
- Live in their own home
- Able to travel to the place of intervention and evaluation
- No need for personal assistance in the following activities of daily living while participating in the treatment (going to the toilet, transport/transportation services for disabled, walking)
- No pronounced fear of horses or allergy constituting a risk for the patients to participate in the therapeutic riding
- No heart conditions constituting a risk for the individual to participate in the interventions
- No history of non-controlled epileptic seizures constituting a risk for the patients to participate in the interventions
- No lack of cognitive and/or verbal ability or visual impairment that would make it difficult for the individual to understand instructions and/or evaluation
- No total arm paralysis
- No injury, disease or addiction that would render the individual unsuitable for the trial
- Bodyweight ≤97 kg (to optimise safe horseback riding)
- No more than half-time employment
- No participation in RMT or HRT <10 months prior to inclusion
- No additional stroke within the past year (TIA is however accepted)
- Accepting allocation to either of the three groups which might mean accepting staying without any of the treatment procedures for one year

* Modified Rankin Scale: An ordinal disability rating scale ranging from zero to 6 (0 = no symptoms). mRS grade 1: No significant disability despite symptoms; able to carry out all usual duties and activities; mRS grade 2 = *Slight disability*: unable to carry out all previous activities but able to look after own affairs without assistance; mRS grade 3 = *Moderate disability*: requiring some help, but able to walk without assistance; mRS grade 4: *Moderately severe disability*: unable to walk without assistance and unable to attend to own bodily needs without assistance; mRS grade 5: *Severe disability*: bedridden, incontinent and requiring constant nursing care and attention; mRS grade 6: Dead.

Panel 2. Comparison of rhythm-and-music-based therapy and horse-riding therapy

Rhythm-and-music-based therapy (RMT)*

Location. RMT was performed at a community centre for the disabled and others in need of rehabilitation outside the hospital environment.

Staff. The sessions were led by a RMT-certified therapist.

Outline. 2 x 90-minute sessions each week for 12 weeks. Each session consisted of the RMT itself, a coffee break, and a summary at the end.

Session content.

While listening to music, participants carried out rhythmic- and cognitively-demanding hand and feet movements, by clapping their hands, tapping their hands on their knees or stamping their feet on the floor in time to the beat, in various sequences and combinations and sometimes simultaneously. These movements were originally derived from drumming, which requires simultaneous use of both arms and legs. There can be up to 18 specific movements (we used 9 in our protocol), each with an associated symbol, representing hand or foot, as well as an associated sound code (derived from a drum sound). Symbols were colour-coded, to distinguish between right-sided movements (blue) and left-sided movements (red). The therapist's clothing was color-coded to help participants remember which colour represented each side of the body. The shirt had a black, neutral front and the left arm, collar and left side of the back was red. The right arm, collar and right side of the back is blue. Body symbols in red and blue were combined with the audio codes and movements into note systems. The sequences and combinations were continuously changed in order to cognitively challenge the participants. During the session the symbols were projected onto a screen, accompanied by their associated sound codes. Participants needed to remember which particular movement each symbol represented as well as its associated sound code. Depending on the individual capability, the therapy was provided to the participants while they were standing or sitting on a chair. The level of difficulty was adjusted to the level of mobility and capabilities of the participants. As a result, participants could, at their own pace, perform increasingly complex sequences of movements. If a participant could not

Horse-riding therapy (HRT)

Location. HRT was performed at a riding centre purpose-built for the disabled where trained therapy horses were used. The sessions were held outside in the paddock or, in bad weather, inside in the ring.

Staff. The sessions were led by a physiotherapist and an occupational therapist specialised in HRT as well as in stroke rehabilitation. Depending on the level of mobility and capabilities of the participants, there were 2-4 supporting staff who assisted the participants with mounting (on a ramp) and dismounting (on the ground), and also walked beside or led the horses while participants were riding.

Outline. 2 x 240-minute sessions each week for 12 weeks. Each session consisted of riding and time for interaction with the horse either before or after the riding. Lunch or refreshments were served after conclusion of each session and were shared with the therapists and assisting personnel.

Session content. The therapy program, selection of horses and choice of equipment were defined and selected in order to facilitate the goals of the therapy. The HRT included preparation of the horse (grooming and equipping the horse with a shabrack, voltage girth and a bridle before the start of the riding session and/or removing it after the session). Groups of 2-6 participants rode in pairs for 30 minutes, while the others were watching awaiting their turn. For comfort, riders sat on a shabrack (thick soft cover), while for safety, one assistant walked alongside the horse and another one led the horse. Throughout the lesson, riders engaged in specific exercises individually tailored to their physical needs and horse-riding ability; all exercises were, if possible, performed while the horse was moving. (Our participants mostly rode at a walking pace, although some trotted for a few laps.) The lesson begun and ended with riders doing relaxation and body awareness exercises, while being instructed to sense the horse's movements through their own body. Whenever the horse moved or there was a change in pace or direction, the rider had to adjust his or her posture. The main part of the lesson included the following exercises:

1. *Balance exercises*: maintaining balance while: holding one or both arms sideways; putting the hand/s on the head; riding in diagonals, circles, over low poles and weaving through cones.

perform a certain movement, they were guided to initiate/imagine the movement. Each session included breaks when the participants relaxed with their eyes shut, while listening to music.

Targeted outcomes. The RMT offers a multisensory environment encompassing rhythm, music, colour, voice, text, shapes and movement. Together, these elements are intended to stimulate and improve motor functions on the right- and left-hand sides of the body (balance, gait, coordination, muscular control, body awareness), cognitive functions of the left- and right-brain hemispheres (sense of rhythm) mental endurance, cognition (attention, concentration and memory), reading, speech, body image and consciousness. The RMT is considered engaging, motivating, and enjoyable and gives participants an opportunity to engage socially.

* The principles of the RMT method were originally conceptualised and developed by the professional jazz drummer Ronnie Gardiner. The 'Ronnie Gardiner Therapy' is designed to help people with injuries and diseases of the central nervous system, and has been practiced in health care and rehabilitation in Sweden since 1993. From 1999, the method has been further refined and developed to what currently is branded RGRM^{TM}.

2. *Trunk rotation exercises*: activities such as touching different parts of the horse e.g. the mane, neck, flank and back which involved crossing the midline of the horse while maintaining balance and posture. Participants were also holding a stick with both hands with their elbows at the waist and then rotating the trunk to the sides.

3. *Exercises to train participants' affected body parts*: simulating bicycling with the legs; reaching for the horse's ears; lying prone with the arms around the horse's neck and then rising again; grasping a tennis ball from the instructor in different directions; controlling the horse by holding the reins.

4. *Cognitive component*: taking part in planning the individual riding route and exercises after thorough oral instructions; paying attention to the other horses/riders in the paddock while riding; following repetitive oral instructions.

Targeted outcomes. HRT offered a multisensory environment designed to stimulate and improve motor functions (posture, balance, gait, coordination, muscular and trunk control, body awareness), muscular strength, mental and physical endurance, cognitive functions, attention and concentration, body image and self-esteem. It also offered enjoyment, social interaction and potentially also induced a sense of mastery, and the human–animal interaction may also have had a stress-reducing and calming effect.

Supplementary file III

Secondary outcome measures

Mobility and walking capacity

Lower extremity function and mobility were measured using the Timed Up and Go (TUG), a well-documented balance test with high validity and reliability.[1] Subjects are instructed to sit straight on a chair with armrests, with their hands on their thighs and their backs touching the back of the chair. When they are given the 'go' signal by the evaluator, they rise from the chair, walk 3m at their normal speed, turn around after passing the tape at the end of the pathway, return to the chair, and sit down. The time taken to complete the TUG is measured in seconds with a stopwatch.

Gross motor skills

Balance ability was evaluated with the Berg balance scale (BBS), a psychometrically sound measure of balance impairment for use in post-stroke assessment.[2] The test contains 14 elements, which assess the ability to maintain a position with or without volitional movement, and the ability to change position. Each element is scored using a five-point scale (0-4), adding up to a total score (maximum 56). People who score below 45 may be at increased risk of falling and may therefore need assistance.

After the first intervention group had been enrolled and randomised, it was decided to add another balance test to the outcome measures: the Bäckstrand, Dahlberg and Liljenäs balance scale (BDL-BS). It has been suggested to use the BBS in conjunction with other balance measures because of the floor and ceiling effects.[2] The BDL-BS has excellent to good intra-rater reliability and fairly good test-retest reliability and can distinguish between people with mild to moderate balance problems and healthy people of the same age.[3] The BDL-BS provokes balance ability to a larger extent than the BBS and is designed for people with neurological impairment who have mildly to moderately disturbed balance.[3] The scale consists of 11 items that require the patient to maintain positions and perform activities of varying difficulty. Each item is scored along a five-point ordinal scale from 0 - 4 (0 = minimum score and 4 = maximum score) giving a total maximum score of 44. Scores are based on how long the position is maintained or how well the task is performed.

Grip strength

Grip force was assessed using the Grippit[4], a reliable electronic dynamometer that registers grip strength in Newton during a 10 second period of time and the instrument generates three measures: 1. Maximum grip force 2. The mean value for the 10 seconds or sustained maximal voluntary contraction, and 3. The sustainability of grip force measured during the last 0.5 second. The sustainability value is refered to as Grippit final. The Grippit is placed on a table in front of the subject who is seated on an adjustable chair.

General cognitive level and working memory

The Barrow Neurological Institute Screen for Higher Cerebral Functions (BNIS) was used for screening general cognitive level. It consists of 30 different items covering seven cognitive domains. The scores range from 0 to 50, with higher scores indicating superior functioning. BNIS has demonstrated high reliability and adequate validity.[5] The subtest of Letter-Number Sequencing (LNS) from Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)[6] was used to assess working memory. LNS is a typical working memory task that involves the maintenance and manipulation of given information. Series of numbers and letters are presented orally in random order for participants, who have to rearrange them in their minds and repeat the numbers in ascending order, and the letters in alphabetical order. Participants unable to answer verbally are permitted to answer by pointing at letters and numbers on a sheet or on a keyboard.

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Supplementary file IV

Mean scores of the primary and secondary outcome measures at baseline			
	R-MT **(n=41)**	H-RT **(n=41)**	Control **(n=41)**
Variable			
SIS Stroke Recovery	58.9 (22.9)	55.9 (19.2)	63.1 (17.0)
Median (IQR)	65 (38)	60 (30)	60 (30)
Gait and balance			
TUG	11.5 (5.1)	17.2 (17.0)	17.4 (19.3)
BBS	52.0 (5.8)	49.9 (8.4)	51.1 (7.2)
BDL-BS*	20.8 (12.6)	17.1 (14.0)	20.1 (14.2)
Hand strength‡			
Right hand			
GRIPPIT max (N)	228.0 (104.3)	271.5 (128.3)	219.3 (111.2)
GRIPPIT mean (N)	188.3 (87.9)	222.7 (111.1)	181.4 (97.8)
GRIPPIT final (N)	173.8 (89.1)	201.5 (102.9)	166.2 (94.3)
Left hand			
GRIPPIT max (N)	197.6 (88.9)	212.4 (115.3)	218.1 (101.3)
GRIPPIT mean (N)	161.8 (84.3)	175.6 (98.6)	181.1 (93.8)
GRIPPIT final (N)	144.4 (77.4)	160.1 (93.3)	168.7 (92.5)
General cognitive level			
BNIS - total score	39.4 (7.0)	37.7 (7.8)	37.8 (8.1)
Working memory			
LNS - total score†	6.4 (2.4)	5.8 (2.6)	5.9 (2.5)

Data are number (%) or mean (SD) unless otherwise indicated. 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. * Included for the following number of participants: R-MT=36; H-RT=38; Control=38. † Not able to do LNS due to severe aphasia: R-MT=1; H-RT=1; Control=2. ‡ Included for the following number of participants: R-MT=31; H-RT=31; Control=32. BBS = Berg balance scale; BDL-BS = Bäckstrand, Dahlberg, and Liljenäs balance scale; BNIS = Barrow Neurological Institute Screen for Higher Cerebral Functions; IQR = Interquartile Range; LNS = Letter-Number Sequencing; SIS = Stroke Impact Scale; TUG = Timed up and go.