SUPPLEMENTAL MATERIAL:

Is more better? Using meta-data to explore dose-response relationships in stroke rehabilitation.

Keith R. Lohse, PhD[1,2], Catherine E. Lang, PT PhD[3], & Lara A. Boyd, PT PhD[4]

[1]School of Kinesiology, Auburn University

[2]School of Kinesiology, University of British Columbia

[3]Program in Physical Therapy, Program in Occupational Therapy, Department of Neurology, Washington University

[4]Department of Physical Therapy, University of British Columbia

Contents: 2 online supplemental tables, 3 online supplemental appendices, 1 online supplemental references.

Corresponding Author:
Keith Lohse, PhD
School of Kinesiology
University of British Columbia
210 - 6081 University Blvd.
Vancouver, B.C., V6T 1Z1
Canada
p: 1-604-822-5895
e: kelopelli@gmail.com

***Supplemental Table I**. Summary of treatment and control interventions.*

Trial [1-37]	Treatment Intervention	Control Intervention	Time Scheduled for Therapy	
			AVE Treat Time	AVE Ctrl Time
Burgar et al., 2011	Robot assisted therapy at a high dose.	Robot assisted therapy at a low dose.	15.8 hrs / 21 days	8.6 hrs / 21 days
Cooke et al., 2010	Functional strength training combined with conventional therapy.	Conventional therapy alone.	23.5 hrs / 42 days	9.2 hrs / 42 days
Dean et al., 2000	Lower-limb focused rehabilitation.	Upper-limb therapy.	12 hrs / 28 days	0 hrs** / 28 days
Di Lauro et al., 2003	Intensive rehabilitation therapy.	Conventional therapy.	28 hrs / 14 days	10.5 hrs / 14 days
Donaldson et al., 2009	Functional strength training combined with conventional therapy.	Conventional therapy alone.	17.7 hrs / 42 days	2.81 hrs / 42 days
Dromerick et al., 2000	CIMT, constraint for 6 hours per day.	Standard occupational therapy combined with a circuit training program.	62* hrs / 14 days	20 hrs / 14 days
Dromerick et al., 2009	CIMT, constraint for 90% of waking hours	ADL retraining and UE bilateral training.	80.4* hrs / 14 days	20 hrs / 14 days
Duncan et al., 2003	In-home program of thirty-six sessions.	Usual care prescribed by physician.	50.6 hrs / 84 days	29.6 hrs / 84 days
Duncan et al., 2011	Thirty-six sessions of body-weight supported treadmill therapy.	No therapy (deferred treatment).	54 hrs / 98 days	0 hrs / 98 days
Fang et al., 2003	Additional conventional therapy.	No professional rehabilitation therapy during the intervention.	15 hrs / 28 days	0** hrs / 28 days
Feys et al., 1998	Targeted UE therapy.	Sham short wave therapy on the shoulder.	15 hrs / 42 days	0** hrs / 42 days
GAPS Group, 2004	Additional conventional therapy.	Conventional therapy alone.	34 hrs / 4 weeks	21 hrs / 4 weeks
Green et al., 2002	Community physiotherapy	No intervention.	NA***	NA
Hesse et al., 2011	Intermittent high- intensity therapy.	Continuous low-intensity therapy.	120 hrs / 365 days	65 hrs / 365 days
Hunter et al., 2011	Conventional therapy plus mobilisation and tactile stimulation.	Conventional therapy alone.	8.7 hrs / 14 days	0 hrs ** / 14 days
Kuys et al., 2011	High intensity treadmill therapy in addition to conventional therapy.	Conventional therapy alone.	51.0 hrs / 42 days	42.0 hrs / 42 days
Kwakkel et al., 1999	Rehabilitation program with an emphasis on leg training.	Conventional therapy plus Immobilization with an inflatable pressure splint.	117.2 hrs / 70 days	73.5 hrs / 70 days
Langhammer et al., 2010	Conventional therapy plus treadmill training.	Conventional therapy plus outdoor walking.	49.5 hrs / 15.9 days	55.9 hrs / 16.9 days
Lin et al., 2007	Modified CIMT, constraint for 6 hours per day.	Conventional rehabilitation.	75 hrs* / 21 days	30 hrs / 21 days
Luft et al., 2008	Progressive treadmill therapy.	Comparable time in supervised stretching.	52 hrs / 168 days	0 hrs ** / 168 days
Page et al., 2004	Modified CIMT, constraint for 5 hours a day.	Control patients received no therapy during the 10-	140* hrs / 70 days	0 hrs / 70 days

		week period.		
Page et al., 2005	Modified CIMT, constraint for 5 hours per day.	Conventional therapy for the affected arm.	140* hrs / 70 days	15 hrs / 70 days
Page et al., 2008	Modified CIMT, constraint for 5 hours per day.	Conventional therapy for the affected arm.	140* hrs / 70 days	15 hrs / 70 days
Partridge et al., 2000	Conventional therapy at a high-dose.	Conventional therapy at a low-dose.	30 hrs / 42 days	15 hrs / 42 days
Rydwik et al., 2006	Combined active and passive treatment with a Stimulo device.	No therapy (deferred treatment).	9 hrs / 42 days	0 hrs / 42 days
Smania et al., 2012	Modified CIMT, constraint for 12 hours a day.	Conventional therapy for the affected arm.	80* hrs / 14 days	20 hrs / 14 days
Sonoda et al., 2004	Combined PT/OT therapy seven days per week.	Combined PT/OT therapy five days per week.	46.7 hrs / 35 days	33.33 hrs / 35 days
Tanaka et al., 2012	Robot-assisted gait training using Gaitmaster 4.	No therapy (deferred treatment).	4 hrs / 35 days	0 hrs / 35 days
Taub et al., 2006	CIMT, constraint for 90% of waking hours.	A program of fitness training, cognitive exercises, and relaxation exercises.	116* hrs / 14 days	60 hrs / 14 days
Treger et al., 2012	Modified CIMT, constraint for 4 hours per day.	Conventional therapy.	30* hrs / 14 days	10 hrs / 14 days
Wade et al., 1992	Conventional therapy	No therapy (deferred treatment).	NA***	NA
Winstein et al., 2004	Functional task practice and strength training plus conventional therapy.	Conventional therapy alone.	40 hrs / 28 days	20 hrs / 28 days
Wolf et al., 2006	CIMT, constraint for 90% of waking hours.	No therapy (deferred treatment).	160.8 hrs* / 14 days	0 hrs / 14 days
Wu et al., 2007	CIMT, constraint for 6 hours per day.	Conventional therapy.	75* hrs / 21 days	30 hrs / 21 days
Yang et al., 2005	Conventional therapy plus additional walking training.	Conventional therapy alone.	10.5 hrs / 21 days	6.0 hrs / 21 days
Yang et al., 2007	Experimental dual-task therapy.	No therapy.	6 hrs / 28 days	0 hrs / 28 days
Yavuzer et al., 2006	Conventional therapy plus additional balance training.	Conventional therapy alone.	143.8 hrs / 56 days	140.0 hrs / 56 days

* denotes CIMT studies. In the 50% Time coding (shown) 50% of constraint time was counted as time scheduled for therapy.

** denotes studies where the control group technically received therapy but no therapy relevant for the primary outcome, thus, therapy time is coded as "0 hrs" for analysis, or the exact time for the control group was not reported, but the difference between treatment and control was explicitly stated (viz, Hunter et al., 2011).

*** denotes studies where there was no description of time scheduled for therapy. These studies were included in the overall analysis because the treatment group did receive more therapy than the control group. However, these studies were omitted from the regression analyses because no statistics on the difference in therapy time could be computed.

Supplemental Table II. *Summary statistics extracted for the meta-analysis.*

Trial[1-37]	Outcome	Time Post-Stroke (yrs)	Δ Time (hrs)	Treat.M (SD)	Treat. N	Ctrl. M (SD)	Ctrl. N
Burgar et al., 2011	FMA	0.046	7.20	14.40 (14.84)	17	6.80 (8.28)	19
Cooke et al., 2010	Gait speed	0.097	14.30	0.42 (0.39)	36	0.3 (0.35)	31
Dean et al., 2000	6MWT	1.800	12.00	42.1* (127.75)	5	7.7* (156.89)	4
Di Lauro et al., 2003	BI	0.003	17.50	1.8* (2.00)	26	1.7* (2.60)	27
Donaldson et al., 2009	ARAT	0.048	14.89	19.5* (15.05)	10	11.5* (13.51)	8
Dromerick et al., 2000	ARAT	0.016	42.00[C]	52.80 (5.90)	11	44.30 (11.10)	9
Dromerick et al., 2009	ARAT	0.026	60.40[C]	33.93 (16.64)	16	36.20 (16.69)	17
Duncan et al., 2003	FMA-LE	0.207	21.02	2.74* (3.05)	44	1.76* (3.87)	48
Duncan et al., 2011	Gait speed	.176	54.00	0.23* (0.2)	139	0.13* (0.14)	143
Fang et al., 2003	FMA	NA	15.00	9.39* (18.98)	50	5.67* (21.65)	78
Feys et al., 1998	BFMT	0.062	15.00	2.93 (0.73)[T]	50	2.77 (0.84)[T]	50
GAPS Group, 2004	MI	0.102	13.00	119 (46.00)	34	111 (45.00)	35
Green et al., 2002	Gait speed**	>1.00	NA	25.50 (12.60)	78	24.90 (13.80)	77
Hesse et al., 2011	RMI	0.299	55.00	12.20 (1.70)	25	11.30 (2.70)	25
Hunter et al., 2011	MI	0.075	8.70	17 *(22.41)[T]	19	12.4* (25.73)[T]	19
Kuys et al., 2011	6MWT	0.138	9.00	107.00* (134.58)	13	60.00* (155.21)	15
Kwakkel et al., 1999	Gait speed**	0.020	43.67	0.65 (0.46)	26	0.37 (0.41)	34
Langhammer et al., 2010	6MWT	1.052	-6.48	320.00 (153.80)	18	310.00 (164.40)	16
Lin et al., 2007	FIM	1.357	45[C]	113.06 (10.55)	17	105.67 (15.85)	15
Luft et al., 2008	Gait speed	4.461	52.00	1.11 (0.30)	37	0.88 (0.28)	34
Page et al., 2004[RM]	FMA	2.463	140[C]	18.40*[T] (7.41)	7	-2.90*[T] (7.10)	6
Page et al., 2005[RM]	FMA	0.012	125[C]	52.60 (3.04)	5	39.40 (6.99)	5
Page et al., 2008	ARAT	3.316	125[C]	40.54 (8.18)	13	29.17 (10.00)	12
Partridge et al., 2000	POR	NA	15.00	9.50 (4.80)	52	9.8 (4.60)	56
Rydwik et al.,	6MWT	4.007	9.00	46.40* (71.50)	6	21.80*	6

2006						(107.07)	
Smania et al., 2012	WMFT	0.842	60.00 [C]	3.62 (0.78)	30	2.92 (0.86)	29
Sonoda et al., 2004	FIM	0.170	13.40	105.00 (21.70)	58	97.10 (26.20)	48
Tanaka et al., 2012	Gait speed	4.964	4.00	0.12* (0.44)	7	0.02* (0.16)	5
Taub et al., 2006	WMFT	4.450	56.00 [C]	2.30* (2.33)	21	-0.50* (3.58)	20
Treger et al., 2012	MFT	0.086	20.00 [C]	5.40* (3.40)	9	3.50 (2.20)	19
Wade et al., 1992	10MWT	4.631	NA	3.90* (27.06)	49	-6.40 (37.91)	45
Winstein et al., 2004	FMA	0.044	20.00	17.35* (17.98)	40	9.05* (22.31)	20
Wolf et al., 2006	WMFT	0.503	160.80 [C]	0.58* (1.37)	98	0.08* (1.37)	105
Wu et al., 2007	FMA	1.006	45.00 [C]	46.75 (11.58)	24	44.78 (13.08)	23
Yang et al., 2005	Gait speed	0.525	4.50	33.43 (5.20)	13	29.62 (16.35)	12
Yang et al., 2007[RM]	Gait speed	4.380	6.00	29.74* (19.01)	13	-12.84* (24.71)	12
Yavuzer et al., 2006	Gait speed	0.682	3.75	0.08 (0.20)	22	0.01 (0.20)	19

Note: ΔTime is the difference (treatment - control) in time scheduled for therapy. 6MWT = Six minute walk test; 10MWT = 10-metre walk test; ARAT = Action Research Arm Test; FIM = Function Independence Measure; FMA = Fugl-Meyer Assessment; MI = Motricity Index; POR = Profiles of Recovery Scale; RMI = Rivermead Mobility Index, WMFT = Wolf Motor Function Test, MFT = Manual Function Test.

* denotes mean differences reported as change scores in the original text (all other statistics are based on terminal post-test scores). Standard deviations refer to the inter-individual standard deviation within a group.

[T] denotes standard deviations that were estimated from inferential statistics reported in the text.

**denotes studies that did not have necessary statistics for the primary outcome (e.g., nonparametric analysis), so a secondary outcome was used.

[C] denotes the uncertain time difference for CIMT studies. In the 50% Time analysis (shown), 50% of constraint time was counted as therapy time.

[RM]denotes an outlying study that was removed from the overall analysis and from the regression models.

Supplemental Appendix I: Quality Assessment and Risk of Bias

Screening Studies and Exclusion Criteria.

An initial 832 titles were identified in the literature search. Articles were screened by title and abstract using the following exclusion criteria:

a) Lack of randomization with a control: Case-control, cohort studies, or experimental studies that did not use a control group were excluded from analysis. Review papers were excluded and tagged so that the bibliographies of relevant reviews could be searched.
b) Pediatric studies/trials were participants were <18 years old.
c) Trials were fewer than 70% of participants were post-stroke. This criterion was used to homogenize the research population (e.g., cerebral palsy, traumatic brain injury, other neurological disorders were excluded). There is, however, still heterogeneity among participants with stroke (e.g., type and location of the lesion).
d) Physical or occupational therapy in combination with a pharmaceutical treatment or electrical stimulation. This excluded trials that used pharmacological (e.g., amphetamines) or exogenous stimulation (e.g., functional electrical stimulation) as part of the study protocol.
e) Dosage matched treatment and control conditions. Because dosage matching would mean that there was no difference in time scheduled for therapy (ΔTime), these trials were excluded from the analysis.
f) Unpublished trials or trials not published/translated into English. While not an "exclusion" criterion per se, the searches were only conducted in English and therefore may miss relevant trials that were in another language and/or have not been published. Despite only searching for studies published in/translated into English, the final list of studies included papers from the UK, Belgium, Germany, Italy, Netherlands, Norway, USA, Australia, China, Taiwan, Japan, and Israel.

These criteria were first used to screen trials by title and abstract. At this stage (702 trials removed), most trials were removed for not being randomized or not having acceptable control groups. After removing review papers and removing duplicate trials, 138 articles were assessed by a full text review using the same exclusion criteria. At the full text review stage (101 trials removed), most trials were removed because treatment and control groups were dosage matched for therapy or failed to report sufficient dosage statistics. See Figure I. The remaining 37 trials were included in the assessment of study quality using the Physiotherapy Evidence Database Scale (PEDro; www.pedro.org.au).

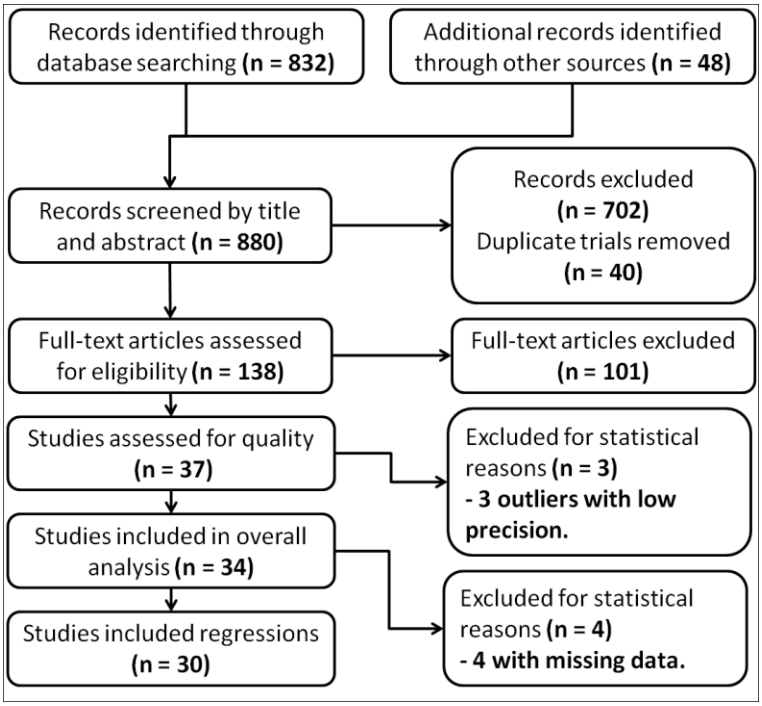

Figure I. Flow-diagram based on PRISMA guidelines showing the number of studies identified, screened, eligible, and included.

Qualtiy Assessment.

One author (KRL) assessed the methodological quality and risk of bias in individual studies using the PEDro scale. The different criteria of the PEDro scale were categorized according to their risk of bias: selection bias, performance bias, detection bias, and attrition bias. Criteria that did not naturally fit into one of these categories are not discussed, but the full data for each criterion are reported in Table III. In summary, PEDro scores for the various studies were moderate, with a mean of 6.65 and SD of 1.08, but the risk of specific biases are discussed below.

Table III. Studies that meet the criteria of the PEDro scale, grouped by potential effects on bias.

			Selection Bias			Performance Bias		Detection Bias	Attrition Bias			
Author[1-37]	**Year**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**
Burgar	2011	1	1	0	1	0	0	1	1	1	1	1
Cooke	2010	1	1	1	1	0	0	0	1	1	1	1
Dean	2000	1	1	1	1	0	0	0	0	1	0	1
Di Lauro	2003	1	1	1	1	0	0	1	1	1	1	1
Donaldson	2009	1	1	1	0	0	0	1	1	1	0	1
Dromerick	2000	1	1	0	1	0	0	1	1	0	1	1
Dromerick	2009	1	1	0	1	0	0	1	1	0	1	1
Duncan	2003	1	1	1	1	0	0	1	1	1	1	1
Duncan	2011	1	1	1	1	0	0	1	1	1	1	1

Fang	2003	1	1	1	0	0	1	1	0	0	1	1
Feys	1998	1	1	0	1	0	0	1	1	0	1	1
GAPS	2004	1	1	1	1	0	0	1	1	1	1	1
Green	2002	1	1	1	1	0	0	1	1	1	1	1
Hesse	2011	0	1	1	1	0	0	1	1	1	0	1
Hunter	2011	1	1	1	1	0	1	1	1	1	1	1
Kuys	2011	1	1	1	0	0	0	1	1	1	1	1
Kwakkel	1999	1	1	1	1	0	0	1	1	1	1	1
Langhammer	2010	1	1	1	1	0	0	1	1	0	1	1
Lin	2007	1	1	1	1	0	0	1	1	0	1	1
Luft	2008	1	1	0	1	0	0	1	0	0	1	1
Page	2004	1	1	0	1	0	0	1	1	0	1	1
Page	2005	1	1	0	0	0	0	1	1	0	1	1
Page	2008	1	1	0	1	0	0	1	1	0	1	1
Partridge	2000	1	1	1	1	0	0	1	1	0	1	1
Rydwik	2006	1	1	0	1	0	0	1	1	0	1	1
Smania	2012	1	1	1	1	0	0	1	1	0	1	1
Sonoda	2004	1	1	0	1	0	0	0	0	0	1	1
Tanaka	2012	1	1	0	1	0	0	0	1	1	1	1
Taub	2006	1	0	0	1	0	0	1	1	1	1	1
Treger	2012	1	1	1	1	0	0	0	1	1	1	1
Wade	1992	1	1	0	1	0	0	1	1	0	1	1
Winstein	2004	1	1	1	1	0	0	0	1	0	1	1
Wolf	2006	1	1	0	1	0	0	1	1	1	1	1
Wu	2007	1	1	1	1	0	0	1	1	1	1	1
Yang	2005	1	1	1	1	0	0	0	1	1	1	1
Yang	2007	1	1	1	1	0	0	1	1	1	1	1
Yavuzer	2006	1	1	1	1	0	0	1	0	0	1	1

Note. A "1" indicates that a study met that particular criterion, a "0" indicates that a study did not meet that criterion or that not enough information was given to make an assessment. C1 = Eligibility criteria were specified; C2 = Participants were randomly allocated to groups; C3 = Treatment allocation was concealed; C4 = Groups were similar at baseline; C5 = Blinding of participants; C6 = Blinding of therapists administering treatment; C7 = Blinding of assessors for outcome measures; C8 = Measurement of key outcome from >85% of participants; C9 = Intention to treat analysis; C10 = Between-groups statistical comparison is reported for key outcome; C11 = Measures of central tendency and variability are provided.

Risk of selection bias (C2, C3, and C4).

Selection bias refers to initial differences between treatment and control groups at baseline, which would then obfuscate treatment effects in the data. Risk of selection bias was relatively low across the collected studies. Random allocation was specified in 97% of studies, concealment of the treatment allocation was specified in 62% of studies, and the equivalence prognostic indicators and key outcomes was specified in 89% of studies. Thus, the majority of

studies randomly allocated participants to treatment groups and this random allocation equated the groups on key outcome measures and prognostic indicators at the beginning of the trial.

Risk of performance bias (C5 and C6).

Performance bias refers to differences between groups in the type/level of care that is provided and a lack of blinding in either the participants or the therapists administering treatment. A lack of blinding increases the risk that knowledge of the intervention, beyond the intervention itself, will influence the outcome. Risk of performance bias was high in the collected studies. The blinding of participants was specified in none of the included studies and the blinding of therapists administering treatment was specified in only 5% of studies.

The extent of this risk depends on how "blinding" is considered. We used a strict definition of blinding, meaning that participants or therapists were not aware of the condition to which they were assigned. For most physical and occupational therapy protocols, blinding at this level is not feasible. For instance, in bodyweight-supported treadmill walking or in constraint induced movement therapy both the participant and the therapist administering treatment will be aware of what treatment the participant has been allocated to. Although it is not specifically reported, it might be better to ask if participants were naive to the hypotheses of the trial rather than being truly blind to their condition. Therefore, the high risk of performance bias across studies is a concern, but it is a general concern for physical and occupational therapy protocols in which the treatment being received is clear to the participant and the therapist administering the treatment. Thus, although the risk of performance bias is high in the collected studies, we do not think it is higher than the risk of performance bias in physical and occupational therapy studies in general.

Risk of detection bias (C7).

Detection bias refers to potential differences in how outcomes were measured for each group. Blinding of the outcome assessor helps reduce the risk that knowledge of the treatment allocation is affecting the outcome measurement. Successful blinding of assessors was reported in 81% of studies. While this means that assessors were successfully blinded in all but a minority of studies, it is not clear to what extent a lack of blinding could influence the results of several of the outcomes. Some outcome measures are more objective (e. g., the 6-metre walk test, gait speed on a treadmill) and probably less susceptible to bias, but other measures (e. g., the Action Research Arm Test or Fugl-Meyer Assessment) maybe more susceptible to assessor bias. This suggests the risk of detection bias was low to moderate across studies.

Risk of attrition bias (C8 and C9).

Attrition bias refers to differences in the withdrawal rates between each group that might affect the outcome of the study. Protocols were completed by >85% of the randomized participants in 86% of studies and an intention to treat analysis was specified in 54% of studies. The intention to treat criterion was granted if the study specified that all subjects received treatment according to their initial allocation even if "intention to treat" was not specifically stated in the analyses (as per PEDro guidelines). It should also be noted that none of the included studies specifically reported violating an intention to treat analysis. Thus, for studies

that failed to meet this criterion, it is not clear if this is due to non-adherence or to a lack of reporting. Given the high completion rates for participants in these studies and the ambiguity regarding intention to treat analysis, we think that the risk of attrition bias was generally low across studies.

Supplemental Appendix II: Supplemental Analyses

Removal of Outlying Studies

Prior to statistical analysis, we constructed a funnel plot of all of the 37 studies that were assessed for quality[1-37]. Three of these studies (Page et al., 2004[21]; Page et al., 2005[22]; and Yang et al., 2007[36]) had extremely positive effect sizes but low levels of precision (Figure II). A statistical test of asymmetry in the funnel plot was significant, $t(35) = 2.49$, $p = 0.02$, (using the regtest() function in R). Thus, these three studies were removed from subsequent analyses. Removal of these studies makes the estimated overall effect more conservative (because extreme positive values have been removed) and improves the quality of the data (because extreme values with low precision have been removed).

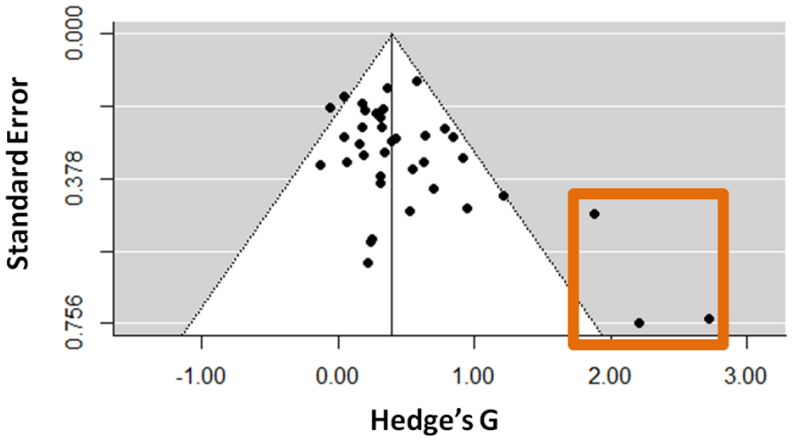

Figure II. A funnel plot showing the effect size and standard error for all 37 studies that were included in the quality assessment. The three outlying studies (highlighted by the box) were removed from all subsequent analyses.

Max-Time and Min-Time Calculations

As mentioned in the methods, including data from constraint induced-movement therapy studies presents a unique problem for calculating the time scheduled for therapy because it is not clear how constraint time should be counted. In the main text, we presented the results of our "50% Time" calculation. We think that this calculation is the most reasonable because it counts 50% of constraint time as therapy time and thus assumes that at least some time under constraint is spent in active movement practice. We also conducted a "Max Time" calculation, in which all of constraint time is counted as time scheduled for therapy, and a "Min Time" calculation, in which none of constraint time is counted as time scheduled for therapy. The assumptions of neither of these models are truly feasible, but they provide a useful reference point for understanding the relationship between time scheduled for therapy and magnitude of recovery. Furthermore, time scheduled for therapy is a significant predictor of recovery under two of the three calculations, suggesting that time scheduled for therapy is a relatively robust predictor of recovery.

The different values of the Min Time, 50% Time and Max Time calculations are shown in Table IV. These calculations change the difference in time scheduled for therapy (ΔTime) for constraint studies by changing the time scheduled for therapy for the treatment groups; time

scheduled for therapy for the control groups is the same in all three calculations. As such, only the linear (e.g., $\Delta Time_{MAX}$) and quadratic (e.g., $\Delta Time^2_{MAX}$) predictors of time scheduled for the therapy are affected in the meta-regressions.

Table IV. Time-scheduled for therapy in the min time, 50% time, and max time calculations for studies included in meta-regression.

Trial	Ctrl. Time	$\Delta Time_{MIN}$	$\Delta Time_{50\%}$	$\Delta Time_{MAX}$	Change
[1]Burgar et al., 2011	8.6	7.2	7.2	7.2	
[2]Cooke et al., 2010	9.2	14.3	14.3	14.3	
[3]Dean et al., 2000	0	12	12	12	
[4]Di Lauro et al., 2003	10.5	17.5	17.5	17.5	
[5]Donaldson et al., 2009	2.81	14.89	14.89	14.89	
[6]Dromerick et al., 2000	20	0	42	84	***
[7]Dromerick et al., 2009	20	10	60.40	110.8	***
[8]Duncan et al., 2003	29.64	21.02	21.02	21.02	
[9]Duncan et al., 2011	0	54	54	54	
[11]Feys et al., 1998	0	15	15	15	
[12]GAPS Group, 2004	21	13	13	13	
[14]Hesse et al., 2011	65	55	55	55	
[15]Hunter et al., 2011	0	8.7	8.7	8.7	
[16]Kuys et al., 2011	42	15	15	15	
[17]Kwakkel et al., 1999	73.5	43.67	43.67	43.67	
[18]Langhammer et al., 2010	55.95	-6.48	-6.48	-6.48	
[19]Lin et al., 2007	30	0	45	90	***
[20]Luft et al., 2008	0	54	48	54	
[23]Page et al., 2008	15	0	125	250	
[25]Rydwik et al., 2006	0	9	9	9	
[26]Smania et al., 2012	20	0	60	120	***
[27]Sonoda et al., 2004	33.33	13.40	13.40	13.40	
[28]Tanaka et al., 2012	0	4	4	4	
[29]Taub et al., 2006	60	0	56	112	***
[30]Treger et al., 2012	10	0	20	40	***
[32]Winstein et al., 2004	20	20	20	20	
[33]Wolf et al., 2006	0	60	160.80	261.60	***
[34]Wu et al., 2007	30	0	45	90	***
[35]Yang et al., 2005	6	4.5	4.5	4.5	
[37]Yavuzer et al., 2006	140	3.75	3.75	3.75	

Note. *** denotes CIMT studies in which the time scheduled for therapy changes from the min time, to the 50% time, to the max time calculation.

Meta-Regression Using the Min-Time Calculation

We constructed meta-regression models to predict a standardized measure of effect-size (g; see Figure 1 in the main text) using linear and quadratic effects of time post-stroke (see Supplemental Table II for time post-stroke in years) and linear and quadratic effects of time scheduled for therapy ($\Delta Time_{MIN}$, shown in Table AII, and $\Delta Time^2_{MIN}$). Model 1 tested the simple effect of $\Delta Time_{MIN}$ (in 10 hr units) and was not significant, Q(1) = 0.09 , p = 0.76, and the parameter estimate of $\Delta Time_{MIN}$ was not significant, b = 0.008, 95% CI = [-0.04, 0.06] , p = 0.77). Model 2 controlled for the linear and quadratic effects of Yrs.PS. Overall, Model 2 was not significant, Q(2) = 1.44, p = 0.48, and the parameter estimates of Yrs.PS (b = 0.100, 95% CI = [-0.34, 0.54] , p = 0.65) and $Yrs.PS^2$ (b = -0.010, 95% CI = [-0.11, 0.08] , p = 0.85), were not significant individually.

Model 3 added the linear effect of $\Delta Time_{MIN}$ controlling for time post-stroke. Overall, the test of moderators was not significant, $Q(3) = 1.93$, $p = 0.58$, and the test of residual heterogeneity was not significant, $Q(26) = 20.02$, $p = 0.79$. Details of Model 3 are shown in Table V. This model showed that, when controlling for other variables, there was a no effect of time post-stroke ($p = 0.60$), $Yrs.PS^2$ (p =0.78), or $\Delta Time_{MIN}$ ($p = 0.54$).

Table V. Details of regression Model 3: Using the min time calculation.

	Parameter Estimate	**95% Confidence Interval**	**Z-value**	**P-value**
Intercept	0.3200	[0.09, 0.55]	2.73	.006
Yrs.PS (yrs)	0.1238	[-0.34, 0.58]	0.53	.597
$Yrs.PS^2$	-0.0143	[-0.12, 0.09]	-0.27	.784
$\Delta Time_{MIN}$ (10 hrs)	0.0173	[-0.04, 0.07]	0.62	.538

Note. The parameter estimates for Yrs.PS are in years and the estimates for $\Delta Time_{MIN}$ are in 10 hour units. An additional model included the interaction of $\Delta Time_{MIN}$ x Yrs.PS, but this interaction was not significant ($p = 0.95$).

Model 4 further added the quadratic effect of $\Delta Time^2_{MIN}$. Overall, the test of moderators was not significant, $Q(4) = 3.81$, $p = 0.43$, and the test of residual heterogeneity was not significant, $Q(25) = 19.82$, $p = 0.76$. Details of Model 4 are shown in Table VI. This model showed that, when controlling for other variables, there was no significant effect of time post-stroke ($p = 0.93$), no effect of $Yrs.PS^2$ ($p = 0.95$), no effect of $\Delta Time_{MIN}$ ($p = 0.56$), and no effect of $\Delta Time^2_{MIN}$ ($p = 0.47$). Adding the interaction term did not change the significance of any of the predictors and did not substantially alter the magnitude of the slopes. Therefore, the main-effects model is presented in Table VI.

Table VI. Details of regression Model 4: Using the min time calculation.

	Parameter Estimate	95% Confidence Interval	Z-value	P-value
Intercept	0.4264	[-0.00, 0.85]	1.95	.051
Yrs.PS (yrs)	0.0281	[-0.59, 0.65]	0.09	.929
$Yrs.PS^2$	0.0040	[-13, 0.14]	0.06	.952
$\Delta Time_{MIN}$ (10 hrs)	-0.1034	[-0.46, -0.25]	-0.58	.565
$\Delta Time^2_{MIN}$ (10 hrs)	0.0209	[-0.04, 0.08]	0.72	.472

Note. The parameter estimates for Yrs.PS are in years and the estimates for $\Delta Time_{MIN}$ are in 10 hour units. An additional model included the interaction of $\Delta Time^2_{MIN}$ x $Yrs.PS^2$, but this interaction was not significant (p = 0.67).

Meta-Regression Using the Max-Time Calculation

Based on the data above we constructed meta-regression models to predict a standardized measure of effect-size (g; see Figure 1 in the main text) using linear and quadratic effects of time post-stroke (see Supplemental Table II for time post-stroke in years) and linear and quadratic effects of time scheduled for therapy ($\Delta Time_{MAX}$, shown above, and $\Delta Time^2_{MAX}$). Model 1 tested the simple effect of $\Delta Time_{MAX}$ and the model was significant, Q(1) = 5.17, p = 0.02, and the parameter estimate of $\Delta Time_{MAX}$ was, b = 0.021, 95% CI = [0.00, 0.04] , p = 0.023). Model 2 controlled for the linear and quadratic effects of Yrs.PS. Overall, Model 2 was not significant, Q(2) = 1.44, p = 0.48, and the parameter estimates of Yrs.PS (b = 0.100, 95% CI = [-0.34, 0.54] , p = 0.66) and $Yrs.PS^2$ (b = -0.010, 95% CI = [-0.11, 0.09] , p = 0.85), were not significant individually.

Model 3 added the linear effect of $\Delta Time_{MAX}$ controlling for time post-stroke. Overall, the test of moderators approached significance, $Q(3) = 6.29$, $p = .09$, and the test of residual heterogeneity was not significant, $Q(26) = 20.82$, $p = 0.75$. Details of Model 3 are shown in Table VII. This model showed that, when controlling for other variables, there was no effect of years post-stroke ($p = 0.92$) and no quadratic effect of years post-stroke ($p = 0.78$). There was, however, a positive effect of $\Delta Time_{MAX}$ ($p = 0.05$).

Table VII. Details of regression Model 3: Using the max time calculation.

	Parameter Estimate	95% Confidence Interval	Z-value	P-value
Intercept	0.3007	[0.12, 0.48]	3.36	<.001
Yrs.PS (yrs)	-0.0257	[-0.51, 0.45]	-0.11	.916
$Yrs.PS^2$	0.0150	[-0.09, 0.12]	0.28	.779
$\Delta Time_{MAX}$ (10 hrs)	0.0201	[-0.00, 0.04]	1.95	.051

Note. The parameter estimates for Yrs.PS are in years and the estimates for $\Delta Time_{MAX}$ are in 10 hour units. An additional model included the interaction of $\Delta Time_{MAX}$ x Yrs.PS, but this interaction was not significant (p = .07), so the main-effects model was chosen instead.

Model 4 further added the quadratic effect of $\Delta Time^2_{MAX}$. Overall, the test of moderators was not significant, $Q(4) = 7.017$, $p = .13$, and the test of residual heterogeneity was not significant, $Q(25) = 17.09$, $p = 0.88$. Details of Model 4 are shown in Table VIII. This model showed that, when controlling for other variables, there was not a significant effect of time post-stroke ($p = 0.96$), $Yrs.PS^2$ ($p = 0.82$), $\Delta Time_{MAX}$ (p = 0.14), nor an effect of $\Delta Time^2_{MAX}$ (p = 0.36).

Table VIII. Details of regression Model 4: Using the max time calculation.

	Parameter Estimate	**95% Confidence Interval**	**Z-value**	**P-value**
Intercept	0.2484	[0.04, 0.45]	2.35	.018
Yrs.PS (yrs)	-0.0132	[-0.49, -0.46]	-0.05	.957
$Yrs.PS^2$	0.0122	[-0.09, 0.12]	0.23	.819
$\Delta Time_{MAX}$ (10 hrs)	0.0435	[-0.01, 0.10]	1.47	.141
$\Delta Time^2_{MAX}$ (10 hrs)	-0.0010	[-0.00, 0.00]	-0.92	.357

Note. The parameter estimates for Yrs.PS are in years and the estimates for $\Delta Time_{MAX}$ are in 10 hour units. An additional model included the interaction of $\Delta Time^2_{MAX}$ x $Yrs.PS^2$. This interaction was marginally significant ($p = .06$), but did not substantially alter the magnitude or direction of the other effects, so the main effects model is presented instead.

Summarizing the Different Meta-Regression Models

With three different calculations and several models for each calculation it can be difficult to see how the models tell a cohesive story. However, in looking at the various parameters across the different models and calculations, there is a generally positive effect of time scheduled for therapy. These data are summarized in Table IX, showing the effects for Model 3 and Model 4 under the three different calculations (min time, 50% time, and max time).

Table IX. Summary of parameter estimates across the different models.

	Min Time		**50% Time**		**Max Time**	
Parameter	**Model 3**	**Model 4**	**Model 3**	**Model 4**	**Model 3**	**Model 4**
Yrs.PS	0.1238	0.0281	0.0110	0.0338	-0.0257	-0.0132
$Yrs.PS^2$	-0.0143	0.0040	0.0078	0.0022	0.0150	0.0122
$\Delta Time$	0.0173	-0.1034	0.0344*	0.0983*	0.0201*	0.0435
$\Delta Time^2$	*NA*	0.0209	*NA*	-0.0047†	*NA*	-0.0010

Note. Yrs.PS and $Yrs.PS^2$ are in units of years. $\Delta Time$ and $\Delta Time^2$ are in units of 10 hours. NA = not applicable because Model 3 did not contain $\Delta Time^2$. † denotes $p \leq 0.10$. * denotes $p \leq 0.05$.

Additionally, when looking at the linear effect of time scheduled for therapy without controlling for other factors, the effect of time scheduled for therapy was positive in all three analyses (Table X). Across these models, the effect of ΔTime ranged from 0.0079 to 0.0365. Only in the minimum time calculation was the effect of ΔTime not significant but even in that case the parameter estimate was positive (but not significantly different from zero).

Table X. The simple effect of ΔTime for all time calculations.

	Intercept		**Slope of ΔTime**	
Calculation	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Min Time	0.4132	[0.24, 0.58]***	0.0079	[-0.04, 0.06]
50% Time	0.3041	[0.13, 0.48]***	0.0365	[0.01, 0.07]*
Max Time	0.3210	[0.16, 0.48]***	0.0208	[0.00, 0.04]*

Note. The slope estimate for ΔTime is in units of 10 hours. * denotes $p < 0.05$. *** denotes $p < 0.001$.

Supplemental Appendix III: Analysis Scripts for R, using the 'Metafor' Package

```
##Script for analyzing the effects of INTENSITY in the therapy dosage project##
library(metafor)
library(lattice)

#################################################
#Overall model of all studies (including outliers)
#################################################

##INTENSITYmetadata has not excluded any studies and includes the full database
FULL<-read.table("INTENSITYmetadataFULL.txt", header = TRUE, sep="\t")
fulldata<-rma(g,v,data=FULL)
fulldata
confint(fulldata)

#Creating a forest plot to show the RE model of all of the data
forest(fulldata, slab=paste(FULL$author, FULL$year, sep=", "), cex=1.5)

#Creating a funnel plot to show potential bias in the full dataset
funnel(fulldata)

#Statistical test of symmetry
regtest(fulldata, model = "lm")


#############################################################################
##Overall model removing the three outliers: Page et al., 2004; 2005; Yang et al, 2007##
#############################################################################

##INTENSITYmetadata2 has low precision large effect studies, Yang 2007 and Page 2004,
removed.
OUTLIERS<-read.table("INTENSITYmetadata2.txt", header = TRUE, sep="\t")
head(OUTLIERS)

nooutliers<-rma(g,v,data=OUTLIERS, method = "ML")
nooutliers
confint(nooutliers)

FEnooutliers<-rma(g,v,data=OUTLIERS, method="FE")
FEnooutliers
confint(nooutliers)

#Visualizing the data#
#Generating a forest plot with the 3 outlying studies removed:
```

```
forest(nooutliers, slab=paste(OUTLIERS$author, OUTLIERS$year, sep=", "), cex=1.5)

#Generating a funnel plot with the outlying studies removed:
funnel(nooutliers)

#Statistical test of symmetry with the outliers removed
regtest(nooutliers, model = "lm")

##########################################
##Meta-Analytic Regressions: NAs are removed##
##########################################

#Calculating a random effects model for the overall effect of therapy (i.e., intercept only)
MASTER<-read.table("INTENSITYmetadata.txt", header = TRUE, sep="\t")
head(MASTER)
overall<-rma(g,v,data=MASTER)
overall
confint(overall)

#The meta-regression data removes the three outliers and any studies with missing data
forest(overall, slab=paste(MASTER$author,MASTER$year, sep=", "), cex=1.5)
funnel(overall)
radial(overall, main = "Random-Effects Model")

#Statistical test of symmetry
regtest(overall, model = "lm")

#Plotting the data using the 50% time calculation
plot(g~tenh.50, data = MASTER, cex.lab=1.2)
plot(g~yrs.ps, data = MASTER, cex.lab=1.2)
plot(g~exp.dur, data = MASTER, cex.lab=1.2)
cor.test(MASTER$g,MASTER$exp.dur)

plot(tenh.50~yrs.ps, data = MASTER, cex.lab=1.2)
plot(tenh.50~exp.dur, data = MASTER, cex.lab=1.2)
cor.test(MASTER$tenh.50,MASTER$exp.dur)

plot(yrs.ps~exp.dur, data = MASTER, cex.lab=1.2)

#Calculating descriptive statistics for the 50% time calculation
head(MASTER)
mean(MASTER$exp.50) #Mean time scheduled for therapy using the 50% time calculation in
the treatment group
sd(MASTER$exp.50)
```

```
range(MASTER$exp.50)
sum(MASTER$exp.n)

mean(MASTER$ctrl.time) #Mean time scheduled for therapy for the control group
#Note: the time scheduled for the control group does not change in the min, 50%, or max time calculation
#Time scheduled for therapy in the control group is the same in all three calculations
sd(MASTER$ctrl.time)
range(MASTER$ctrl.time)
sum(MASTER$ctrl.n)

#Descriptives of the MIN TIME calculation
mean(MASTER$exp.MIN)
sd(MASTER$exp.MIN)
range(MASTER$exp.MIN)

#Descriptives of the MAX TIME calculation
mean(MASTER$exp.MAX)
sd(MASTER$exp.MAX)
range(MASTER$exp.MAX)

#Descriptives of tenh.50 (delta time for the 50% calculation in 10hours increments)
mean(MASTER$tenh.50)
sd(MASTER$tenh.50)
range(MASTER$tenh.50)

#Descriptives of the duration of treatment in treatment groups:
mean(MASTER$exp.dur)
sd(MASTER$exp.dur)
range(MASTER$exp.dur)

#Descriptives of the duration of treatment in control groups:
mean(MASTER$ctrl.dur)
sd(MASTER$ctrl.dur)
range(MASTER$ctrl.dur)

#Descriptives of years post-stroke in treatment groups:
exp.yrs.ps<-MASTER$exp.ps/365
mean(exp.yrs.ps)
sd(exp.yrs.ps)
range(exp.yrs.ps)

#Descriptives of years post-stroke in control groups:
ctrl.yrs.ps<-MASTER$ctrl.ps/365
```

```
mean(ctrl.yrs.ps)
sd(ctrl.yrs.ps)
range(ctrl.yrs.ps)

#Descriptives of AVERAGE years post-stroke (averaging across treatment and control:
mean(MASTER$yrs.ps)
sd(MASTER$yrs.ps)
range(MASTER$yrs.ps)

#Calculation of the quadratic predictor variables
MASTER$square.ps<-MASTER$yrs.ps**2
MASTER$time.sq<-MASTER$tenh.50**2

############################
##META REGRESSION MODELS##
############################

##50% time calculation
#Simple linear effect of time post-stroke
ModelA<-rma(g, v, mods=~yrs.ps,data=MASTER, method="ML", weighted = FALSE)
ModelA
qqnorm(ModelA, main="Mixed-Effects Model")

#Simple linear effect of time scheduled for therapy
ModelB<-rma(g, v, mods=~tenh.50, data=MASTER,method="ML", weighted=FALSE)
ModelB
qqnorm(ModelB, main="Mixed-Effects Model")

#Linear and quadratic effects of time post-stroke
ModelC<-rma(g, v, mods=~yrs.ps+square.ps,data=MASTER, method="ML",weighted=FALSE)
ModelC
qqnorm(ModelC, main="Mixed-Effects Model")

#Linear and quadtratic effects of time scheduled for therapy
ModelD<-rma(g, v, mods=~tenh.50+time.sq, method="ML", data=MASTER)
ModelD

#Linear effects of time for therapy controlling for time post-stroke
ModelE<-rma(g, v, mods=~yrs.ps+square.ps+tenh.50,data=MASTER, method="ML",
weighted=FALSE)
ModelE
qqnorm(ModelE, main="Mixed-Effects Model")

#Linear effects of time for therapy plus interaction with yrs.PS
```

```
ModelF<-rma(g, v, mods=~yrs.ps+square.ps+yrs.ps*tenh.50,data=MASTER, method="ML",
weighted=FALSE)
ModelF
qqnorm(ModelF, main="Mixed-Effects Model")

#Linear effects of time for therapy plus interaction with square.PS
ModelG<-rma(g, v, mods=~yrs.ps*tenh.50+square.ps*tenh.50,data=MASTER, method="ML",
weighted=FALSE)
ModelG
qqnorm(ModelG, main="Mixed-Effects Model")

#Linear and quadratic effects of time controlling for time post-stroke
ModelH<-rma(g, v, mods=~yrs.ps+square.ps+tenh.50+time.sq,data=MASTER, method="ML",
weighted=FALSE)
ModelH
qqnorm(ModelH, main="Mixed-Effects Model")

#Linear and quadratic effects of time scheduled for therapy and the interaction
#of time-sq and square.ps
ModelI<-rma(g, v, mods=~yrs.ps+tenh.50+square.ps*time.sq,data=MASTER, method="ML",
weighted=FALSE)
ModelI
qqnorm(ModelI,main="Mixed-Effects Model")


#####################################################################
##Max Time and Min Time Calculations: Detailed in the Appendix ###########
#####################################################################

#####################################################################
#MAX TIME calculation (100% of constraint time is counted as therapy time)
#Modeling the effects of time post stroke on the effect size
#Creating a quadratic predictor for MAX time:
MASTER$MAX.sq<-MASTER$tenh.MAX**2
MASTER$MAX.sq

##Regression models for MAX time.
Model1<-rma(g, v, mods=~yrs.ps,data=MASTER, method="ML", weighted=FALSE)
Model1

Model2<-rma(g, v, mods=~yrs.ps+square.ps,data=MASTER, method="ML", weighted=FALSE)
Model2

Model16<-rma(g, v, mods=~tenh.MAX,data=MASTER, method="ML", weighted=FALSE)
```

```
Model16

Model3<-rma(g, v, mods=~yrs.ps+square.ps+tenh.MAX,data=MASTER, method="ML",
weighted=FALSE)
Model3

Model4<-rma(g, v, mods=~yrs.ps+square.ps+yrs.ps*tenh.MAX,data=MASTER, method="ML",
weighted=FALSE)
Model4

Model5<-rma(g, v, mods=~yrs.ps+yrs.ps*tenh.MAX+square.ps*tenh.MAX,data=MASTER,
method="ML", weighted=FALSE)
Model5

Model6<-rma(g, v, mods=~yrs.ps+square.ps+tenh.MAX+MAX.sq,data=MASTER, method="ML",
weighted=FALSE)
Model6

Model13<-rma(g, v, mods=~yrs.ps+tenh.MAX+square.ps*MAX.sq,data=MASTER, method="ML",
weighted=FALSE)
Model13

#################################################################
#MIN TIME calculation (0% of contraint time is counted as therapy time)
#################################################################

#Calculating a random effects model for the overall effect of therapy (i.e., intercept only)
#Descriptive statistics time scheduled for therapy in the treatment and control groups
summary(MASTER$exp.MIN)
sd(MASTER$exp.MIN, na.rm=T)

summary(MASTER$ctrl.time)
sd(MASTER$ctrl.time, na.rm=T)

#Modeling the effects of time post stroke on the effect size
#Creating a quadratic predictor for MIN time:
MASTER$MIN.sq<-MASTER$tenh.MIN**2

##Models using the MIN time calculation
Model7<-rma(g, v, mods=~yrs.ps,data=MASTER, method="ML", weighted=FALSE)
Model7

Model8<-rma(g, v, mods=~yrs.ps+square.ps,data=MASTER, method="ML", weighted=FALSE)
Model8
```

```
Model15<-rma(g, v, mods=~tenh.MIN,data=MASTER, method="ML", weighted=FALSE)
Model15

Model9<-rma(g, v, mods=~yrs.ps+square.ps+tenh.MIN,data=MASTER, method="ML",
weighted=FALSE)
Model9

Model10<-rma(g, v, mods=~yrs.ps+square.ps+yrs.ps*tenh.MIN,data=MASTER, method="ML",
weighted=FALSE)
Model10

Model11<-rma(g, v, mods=~yrs.ps*tenh.MIN+square.ps*tenh.MIN,data=MASTER,
method="ML", weighted=FALSE)
Model11

Model12<-rma(g, v, mods=~yrs.ps+square.ps+tenh.MIN+MIN.sq,data=MASTER, method="ML",
weighted=FALSE)
Model12

Model14<-rma(g, v, mods=~yrs.ps+tenh.MIN+square.ps*MIN.sq,data=MASTER, method="ML",
weighted=FALSE)
Model14
```

Supplemental References

1. Burgar, CH, Lum, PS, Scremin, AME, Garber, SL, Van der Loos, HFM, Kenney, D, et al. Robot-assisted upper-limb therapy in acute rehabilitation setting following stroke: Department of Veterans Affairs multisite clinical trial. Journal of Rehabilitation Research & Development. 2011;48:445-458.

2. Cooke, EV, Tallis, RC, Clark, A, Pomeroy, VM. Efficacy of functional strength training on restoration of lower-limb motor function early after stroke: Phase I randomized control trial. Neurorehabilitation and Neural Repair. 2010;24:88-96.

3. Dean, CM, Richards, CL, Malouin, F. Task-related circuit training improves performance of locomotor tasks in chronic stroke: A randomized, controlled pilot trial. Archives of Physical Medicine and Rehabilitation. 2000;81:409-417.

4. Di Lauro, A, Pellegrino, L, Savastano, G, Ferraro, C, Fusco, M, Balzarano, F, et al. A randomized trial on the efficacy of intensive rehabilitation in the acute phase of ischemic stroke. Journal of Neurology. 2003;250:1206-1208.

5. Donaldson, C, Tallis, R, Miller, S, Sunderland, A, Lemon, R, Pomeroy, V. Effects of conventional physical therapy and functional strength training on upper limb motor recovery after stroke: A randomized phase II study. Neurorehabilitation and Neural Repair. 2009;23:389-397.

6. Dromerick, AW, Edwards, DF, & Hahn, M. Does the application of constraint-induced movement therapy during acute rehabilitation reduce arm impairment after ischemic stroke? Stroke. 2000;31:2984-2988.

7. Dromerick, AW, Lang, CE, Birkenmeier, RL, Wagner, JM, Miller, JP, Videen, TO, et al. Very early constraint-induced movement during stroke rehabilitation (VECTORS): A single-center RCT. Neurology. 2009;73:195-201.

8. Duncan, P, Studenski, S, Richards, L, Gollub, S, Lai, SM, Reker, D, et al. Randomized clinical trial of therapeutic exercise in subacute stroke. Stroke. 2003;34:2173-2180.

9. Duncan, PW, Sullivan, KJ, Behrman, AL, Azen, SP, Wu, SS, Nadeau, SE, et al. Body-weight supported treadmill rehabilitation after stroke. New England Journal of Medicine. 2011;364:2026-2036.

10. Fang, Y, Chen, X, Li, H, Lin, J, Huang, R, Zeng, J. A study on additional early physiotherapy after stroke and factors affecting functional recovery. Clinical Rehabilitation. 2003;17:608-617.

11. Feys, HM, De Weerdt, WD, Selz, BE, Cox Steck, GA, Spichiger, R, Vereeck, LE, et al. Effect of a therapeutic intervention for the hemiplegic upper limb in the acute phase after stroke: A single-blind, randomized, controlled multicenter trial. Stroke. 1998;29:785-792.

12. The Glasgow Augmented Physiotherapy Study (GAPS) group. Can augmented physiotherapy input enhance recovery of mobility after stroke? A randomized clinical trial. Clinical Rehabilitation. 2004;18:529-537.

13. Green, J, Forster, A, Bogle, S, Young, J. Physiotherapy for patients with mobility problems more than 1 year after stroke; A randomised controlled trial. Lancet. 2002;359:199-203.

14. Hesse, S, Welz, A, Werner, C, Quentin, B, Wissel, J. Comparison of an intermittent high-intensity vs continuous low intensity physiotherapy service over 12 months in community dwelling people with stroke: A randomized trial. Clinical Rehabilitation. 2011;25:146-156.

15. Hunter, SM, Hammett, L, Ball, S, Smith, N, Anderson, C, Clark, A, et al. Dose-response study of mobilisation and tactile stimulation therapy for the upper extremity early after stroke: A phase I trial. Neurorehabilitation and Neural Repair. 2011;25:314-322.

16. Kuys, SS, Brauer, SG, Ada, L. Higher-intensity treadmill walking during rehabilitation after stroke in feasible and not detrimental to walking pattern or quality: A pilot randomized trial. Clinical Rehabilitation. 2011;25:316-326.

17. Kwakkel, G, Wagenaar, RC, Twisk, JWR, Lankhorst, GJ, Koestier, JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: A randomised trial. Lancet. 1999;354:191-196.

18. Langhammer, B, Stanghelle, JK. Exercise on a treadmill or walking outdoors? A randomized controlled trial comparing effectiveness of two walking exercise programmes later after stroke. Clinical Rehabilitation. 2010;24:46-54.

19. Lin, K-C, Wu, C-Y, Wei, T-H, Gung, C, Lee, C-Y, Liu, J-S. Effects of modified constraint induced movement therapy on reach to grasp movements and functional performance after chronics stroke: A randomized controlled study. Clinical Rehabilitation. 2007;21:1075-1086.

20. Luft, AR, Macko, RF, Forrester, LW, Villagra, F, Ivey, F., Sorkin, JD, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: A randomized controlled trial. Stroke. 2008;39:3341-3350.

21. Page, SJ, Sisto, S, Levine, P, McGrath, RE. Efficacy of a modified constraint-induced movement therapy in chronic stroke: A single-blinded randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2004;85:14-18.

22. Page, SJ, Levine, P, Leonard, AC. Modified constraint-induced therapy in acute stroke: A randomized controlled pilot study. Neurorehabilitation and Neural Repair. 2005;19:27-32.

23. Page, SJ, Levine, P, Leonard, AC, Szaflarski, JP, Kissela, BM. Modified constraint-induced therapy in chronic stroke: Results of a single-blinded randomized controlled trial. Physical Therapy. 2008;88:333-340.

24. Partridge, C, MacKenzie, M, Edwards, S, Reid, A, Jayawardena, S, Guck, N, et al. Is dosage of physiotherapy a critical factor in deciding patterns of recovery from stroke: A pragmatic randomized controlled trial. Physiotherapy Research International. 2000;5:230-240.

25. Rydwyk, E, Eliasson, S, Akner, G. The effect of exercise of the affected foot in stroke patients - a randomized controlled pilot trial. Clinical Rehabilitation. 2006;20:645-655.

26. Smania, N, Gandolfi, M, Paolucci, S, Iosa, M, Ianes, P, Recchia, S, et al. Reduced-intensity modified constraint induced movement therapy versus conventional therapy for upper extremity rehabilitation after stroke: A multicenter trial. Neurorehabilitation & Neural Repair. 2012;26:1035-1045.

27. Sonoda, S, Saitoh, E, Nagai, S, Kawakita, M, Kanada, Y. Full-time integrated treatment program, a new system for stroke rehabilitation in Japan. American Journal of Physical Medicine & Rehabilitation. 2004;83:88-93.

28. Tanaka, N, Saitou, H, Takao, T, Iizuka, N, Okuno, J, Yano, H, et al. Effects of gait rehabilitation with a footpad type locomotion interface in patients with chronic post-stroke hemiparesis: A pilot study. Clinical Rehabilitation. 2012;26:686-695.

29. Taub, E, Uswatte, G, Kay King, D, Morris, D, Crago, JE, Chatterjee, A. A placebo-controlled trial of constraint-induced movement therapy for upper extremity after stroke. Stroke. 2006;37:1045-1049.

30. Treger, I, Aidinof, L, Lehrer, H, Kalichman, L. Modified constraint-induced movement therapy improved upper limb function in subacute poststroke patients: A small-scale clinical trial. Top Stroke Rehabil. 2012;19:287-293.

31. Wade, DT, Collen, FM, Robb, GF, Warlow, CP. Physiotherapy intervention late after stroke and mobility. BMJ. 1992;304:609-613.

32. Winstein, CJ, Rose, DK, Tan, SM, Lewthwaite, R, Chui, HC, Azen, SP. A randomized controlled comparison of upper-extremity rehabilitation strategies in acute stroke: A pilot study of immediate and long-term outcomes. Archives of Physical Medicine and Rehabilitation. 2004;85:620-628.

33. Wolf, SL, Winstein, CJ, Miller, JP, Taub, E, Uswatte, G, Morris, D, et al. Effect of constraint induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. JAMA. 2006;296:2095-2104.

34. Wu, C-Y, Chen, C-L, Tang, SF, Lin, K-C, Huang, Y-Y. Kinematic and clinical analyses of upper-extremity movements after constraint-induced movement therapy in patients with stroke: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2007;88:964-970.

35. Yang, Y-R, Yen, J-G, Wang, R-Y, Yen-L-L, Lieu, F-K. Gait outcomes after additional backward walking training in patients with stroke: A randomized controlled trial. Clinical Rehabilitation. 2005;19:264-273.

36. Yang, Y-R, Wang, R-Y, Chen, Y-C, Kao, M-J. Dual task exercise improves walking ability in chronic stroke: A randomized controlled trial. Archives of Physical Medicine and Rehabilitation. 2007;88:1236-1240.

37. Yavuzer, G, Eser, F, Karakus, D, Karaoglan, B, Stam, HJ. The effects of balance training on gait late after stroke: A randomized control trial. Clinical Rehabilitation. 2006;20:960-969.