
Keith R. Lohse, PhD; Catherine E. Lang, PT, PhD; Lara A. Boyd, PT, PhD

Background and Purpose—Neurophysiological models of rehabilitation and recovery suggest that a large volume of specific practice is required to induce the neuropsychological changes that underlie behavioral recovery. The primary objective of this meta-analysis was to explore the relationship between time scheduled for therapy and improvement in motor therapy for adults after stroke by (1) comparing high doses to low doses and (2) using metaregression to quantify the dose–response relationship further.

Methods—Databases were searched to find randomized controlled trials that were not dosage matched for total time scheduled for therapy. Regression models were used to predict improvement during therapy as a function of total time scheduled for therapy and years after stroke.

Results—Overall, treatment groups receiving more therapy improved beyond control groups that received less (g=0.35; 95% confidence interval, 0.26–0.45). Furthermore, increased time scheduled for therapy was a significant predictor of increased improvement by itself and when controlling for linear and quadratic effects of time after stroke.

Conclusions—There is a positive relationship between the time scheduled for therapy and therapy outcomes. These data suggest that large doses of therapy lead to clinically meaningful improvements, controlling for time after stroke. Currently, trials report time scheduled for therapy as a measure of therapy dose. Preferable measures of dose would be active time in therapy or repetitions of an exercise. (Stroke. 2014;45:2053-2058.)

Key Words: rehabilitation ■ stroke ■ therapy

Studies in experimental psychology, neuroscience, and rehabilitation science explore adaptations in neural tissue with respect to type, intensity, and frequency of a stimulus. Studies of experience-dependent synaptic plasticity in nonhuman animals1,2 and humans3 demonstrate that large quantities of practice lead to cortical reorganization and improved behavioral function. Similar studies link neural changes with recovery of function and learning in adults after stroke.4,5 These data indicate that increased practice leads to greater skill, as long as practice is challenging, progressive, and skill based.4,6 Meta-analyses7,8 also suggest a positive dose–response relationship.

Some define dose as the amount of time actively spent in practice6 or the number of repetitions of a movement.10,11 For this article, dose is defined as total time scheduled for therapy (eg, 3 hours/d×(10 days)=30 hours). Time scheduled for therapy may not accurately reflect actual practice time or the number of movement repetitions,12 so this measure is not ideal; however, time scheduled for therapy is the only consistently reported metric in rehabilitation research studies.

Response may be defined as improved function or reduced impairment. For this article, response was defined as a standardized effect size, Hedges’ g, which shows improved function or reduced impairment on a standardized, validated behavioral test. Effect sizes reported here were based on the primary or secondary outcomes of randomized controlled trials (RCTs) found through the systematic review.

Our objective was to quantify the magnitude of functional improvement gained by increasing therapeutic time after stroke. Our meta-analysis builds on work addressing dose–response in a binary manner: Is more therapy better than less therapy?7–9 To meet this objective, we purposely included articles with different types of therapy interventions because it is unclear at this time how the type of therapy provided affects responses.13,14 By reviewing RCTs with different therapy times for treatment and control groups, we modeled the effect of increased time scheduled for therapy on standardized measures of recovery. We tested linear and quadratic effects of therapy time while controlling for linear and quadratic effects of years from the initial stroke to the beginning of the RCT. We chose this approach because it is unlikely that any effects are linear. We hypothesized that increased therapy time would positively affect outcomes,15 whereas time after stroke might negatively affect outcomes.15

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.114.004695/-/DC1.
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Methods

The population of interest was adults after stroke (Population, Intervention, Comparison, and Outcome model).16 Interventions were therapies without exogenous stimulation. Comparison groups included RCTs where the treatment and control groups received different amounts of time scheduled for therapy. In some studies,15–16 each group received the same therapy in different dosages. In other studies,20–22 groups received different types of therapy in different dosages. Outcomes were restricted to validated behavioral measures of function or impairment. In 2 cases,23,24 no appropriate parametric statistics for the primary outcome were presented, thus we used a secondary outcome.

Search Strategy

Manual and electronic searches identified relevant literature. Searches were conducted from the earliest available date in Medline, PSYCInfo, PubMed, and Google Scholar to April 9, 2013. Search terms included “stroke” or “stroke rehab$” in combination with 1 of the terms “dose,” “intens$,” “constraint$,” or “gait.” Filters limited articles to RCTs (otherwise, random and control were search terms). Bibliographies of retrieved trials and review articles were searched.

Study Selection

An initial 832 titles were identified. After screening titles and abstracts and removing duplicates, 138 articles were assessed (Appendix I in the online-only Data Supplement). Details of the interventions and the time scheduled for therapy in the treatment and control groups were extracted. Exclusion criteria were (1) lack of randomization with a control, (2) studied children (age, <18 years), (3) >30% participants with neurological disorders other than stroke, (4) therapy in combination with a pharmaceutical treatment or electric stimulation, (5) dose-matched treatment and control conditions, and (F) unpublished or not translated into English. Thirty-seven trials remained (Table I in the online-only Data Supplement) and were included in the assessment of study quality,13–15,42 The Physiotherapy Evidence Database Scale was used to rate methodological quality (www.pedro.org.au).

Quantitative Analysis

Mean, SD, and sample sizes for the treatment and control groups were entered into a spreadsheet. Standardized effect sizes (Hedges’ g) and variances (V) were calculated.13 Effect sizes were computed from the terminal difference between treatment and control or the difference in improvement between treatment and control, divided by the SD within groups. Subtraction was arranged so that effects favoring the treatment group were positive. Effect-size measures were analyzed using the metafor package54 in R (cran.r-project.org; Table II in the online-only Data Supplement). A funnel plot was constructed. There were 3 studies with large effect sizes and low levels of precision.38,39,51 These studies were removed, leaving 34 studies for inclusion in the quantitative analysis (Appendix II in the online-only Data Supplement).

Custom scripts (Appendix III in the online-only Data Supplement) tested a random-effects model for the overall effect of increased therapy dosage. The analysis was broken into 2 parts. Part 1 was congruent with previous analyses,13,14 calculating a summary effect size for groups who received more therapy when compared with groups who received less. Part 2 elaborated on this analysis using metaregression models to quantify the dose–response relationship controlling for other factors. Four studies were omitted from regression models because of missing data9,23,30,47 (see the NAs in Table II in the online-only Data Supplement); regression was based on 30 studies. Time after stroke (Yrs.PS) was the average years from hospital admission to the onset of the intervention. Total time scheduled for therapy was calculated for the treatment and control groups based on descriptions in the text. Regression models then used the difference between groups in total time scheduled for therapy (ΔTime).

Constraint time in constraint-induced movement therapy creates a problem for calculating ΔTime because it is not clear how time under constraint should be counted as time scheduled for therapy. To address this problem, we coded 3 different ΔTimes for constraint-induced movement therapy studies. In the MIN time calculation, 0% of constraint time counted as time scheduled for therapy. In the 50% time calculation, 50% of constraint time counted as time scheduled. In the MAX time calculation, 100% of constraint time counted as time scheduled. The results of the 50% time calculation are presented here because we assume that some, but not all, of constraint time was spent using the affected limb (details of all analyses are presented in Appendix II in the online-only Data Supplement).

Results

Comparing High Dose to Low Dose: There Is an Overall Benefit of Increased Time in Therapy

Across studies, there was a benefit for treatment groups receiving more therapy, (g=0.35; 95% confidence interval, 0.26–0.45; Figure 1), which was significant, Z = 7.21,
Quantifying Dose: Increased Scheduled Therapy Predicts Greater Recovery

To look at the linear effect of ΔTime, a series of models was tested. Model 1 tested the simple effect of ΔTime (in 10-hour units) as a predictor of effect size. This model was significant, \( Q(1) = 5.40, P = 0.02 \), and the parameter estimate of ΔTime was \( b = 0.037; 95\% \) confidence interval, 0.01 to 0.07; \( P = 0.02 \). Model 2 tested the linear and quadratic effects of Yrs.PS. Model 2 was not significant, \( Q(2) = 1.44, P = 0.49 \), and the parameter estimates of Yrs.PS \( (b = 0.100; 95\% \) confidence interval, \(-0.34 \) to \(0.54; P = 0.65\) \) and Yrs.PS\(^2\) \((b = -0.010; 95\% \) confidence interval, \(-0.11 \) to \(0.08; P = 0.85\) \) were not significant individually. Model 3, shown in Table 1, included the linear and quadratic effects of Yrs.PS with the linear effect of ΔTime. The omnibus test of moderators was nonsignificant, \( Q(3) = 6.73, P = 0.08 \), but the effect of ΔTime was significant. The test of residual homogeneity was not significant, \( Q(26) = 20.51, P = 0.77 \).

Controlling for a Nonlinear Effect of ΔTime

Model 4 (Table 2) included linear and quadratic effects of both Yrs.PS and ΔTime. Overall, the test of moderators was nonsignificant, \( Q(4) = 8.21, P = 0.08 \). The test of residual homogeneity was not significant, \( Q(25) = 14.89, P = 0.94 \).

The linear effect of ΔTime was significant \((P = 0.04)\) and ΔTime\(^2\) approached significance \((P = 0.09)\). The predicted effect sizes \((g)\) of models 3 and 4 are shown in Figure 3. The nonsignificant effect of ΔTime\(^2\) suggests that the basic effect of ΔTime is positive and for every additional 10 hours scheduled for therapy, the effect of ΔTime may become less positive. However, statistical power is an issue with this many moderators, so this effect should be interpreted with caution.
data imply that providers of rehabilitation services should consider multiple ways to increase therapy time, both within and outside formal sessions. Furthermore, there was no interaction between time after stroke and time scheduled for therapy. The lack of an interaction suggests that the benefit of large increases in therapy is similar across a range of post-stroke times regardless of whether a client is several months or several years after stroke (poststroke times ranged from 0.003 to 5.38 years).

Importantly, there are complications to this effect. For instance, if started too early, intensive therapy may hinder the rate of recovery\textsuperscript{20} or have no benefit over less intense therapies.\textsuperscript{18} Also, too many hours of therapy may not be tolerable for participants, leading to dropouts.\textsuperscript{21} These nonlinearities are important considerations for clinicians, which are not captured in the current analysis. As more data are added at different time points, these complexities in the dose–response relationship can be modeled more reliably.

Recovery after stroke is clearly a multidimensional problem, but it is reassuring to establish that time scheduled for therapy significantly predicted functional outcomes across studies. Our results also agree with experimental work in which dose was tightly controlled.\textsuperscript{55–57} In those studies, the correlation between dose (measured in repetitions) and outcome was moderate ($r=0.5–0.6$). In comparison, our meta-analysis is limited using time scheduled for therapy as a predictor when ideally we could use active time in movement practice or movement repetitions. However, in the existing literature, the only consistently reported metric was time scheduled for therapy. Within our own data set, 23.5% of studies (8 of 34 RCTs) provided a more certain/more detailed measure than time scheduled for therapy. These studies specified active time in therapy (such as time spent walking) or gave descriptive statistics about how much therapy time was fulfilled by participants (which may include active time plus rests, demonstrations, instructions, etc., but is still a more detailed measure than time scheduled). Thus, we recommend future RCTs report active time or repetitions of an exercise for a more accurate representation of the dose of therapy received.

With 30 studies in the metaregression, we rapidly lost power to detect additional effects and interactions. Additional studies need to be included in the data set to test additional predictors (eg, stroke severity), higher order effects (eg, cubic effects), or interactions. Although the metadata approach is powerful, dose–response relationships are likely more complex than what we present here. Additional work can address this issue. We are currently conducting a systematic review that will result in a larger database of RCTs. These data will be analyzed with respect to terminal improvements and retention at long-term follow-up (the current analysis is limited by only studying terminal effects) for treatment and control groups, separately. This approach allows the modeling of dosage effects for studies with different durations, intensities, and frequencies of treatment in more homogeneous treatment groups. Furthermore, the current metadata and other experimental data\textsuperscript{55–57} warrant larger experimental studies to explore dose–response effects.

**Discussion**

This meta-analysis agrees with previous work,\textsuperscript{7,3} suggesting a small overall benefit of augmented time in therapy (ie, more is better). The review of Kwakkel et al\textsuperscript{7} found smaller benefits of therapy dose ($\approx 0.20$ for measures of activities of daily living and walking speed) than our overall $g=0.35$, which is likely because of differences in the methods for inclusion and analysis. It is difficult to compare our results directly with the review of Langhorne et al\textsuperscript{8} because those authors measured odds ratios and weighted mean differences rather than standardized effect sizes. However, those authors also found what they described as modest effects of increased therapy. Our analysis goes further to suggest reliable dose–response relationships between the time scheduled for therapy and improvement on clinical measures of function and impairment. In our analysis, neither the linear nor quadratic effects of time after stroke were significant. However, there was a significant positive effect of time scheduled for therapy on outcomes (model 1) even when controlling for time after stroke (model 3). Our evidence also suggests the potential for a nonlinear effect of time scheduled for therapy when controlling for the linear effect (model 4).

We interpret these results as strong evidence of a positive relationship between dose and response. We were able to see a positive dose–response relationship across studies rehabilitating different impairments and functions, using different interventions, and measuring outcomes with different tools. All of these factors are potential sources of noise that could mask the dose–response relationship. Thus, we interpret these effects as evidence that time in therapy is a robust predictor of recovery across different types of therapy. Our

![Figure 3. Predicted effect size ($\hat{g}$) as a function of years after stroke (x axis) and select values of additional time scheduled for therapy (separate lines). A. Model 3 includes the linear effect of time scheduled for therapy. B. Model 4 includes the linear and the quadratic effects of time scheduled for therapy. The dashed black line (+0 hours) represents the predicted effect size when no additional time is scheduled for therapy between treatment and control groups.](http://stroke.ahajournals.org/ Downloaded from)

The lack of an interaction suggests that the benefit of large increases in therapy is similar across a range of post-stroke times regardless of whether a client is several months or several years after stroke (poststroke times ranged from 0.003 to 5.38 years).
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Disclosures
None.

References


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/content/45/7/e136.full.pdf

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http://stroke.ahajournals.org/content/suppl/2014/05/27/STROKEAHA.114.004695.DC1

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The publish-ahead-of-print version used the term “Hedges’s g” when it should have read “Hedges’ g.” The publisher apologizes for the error.

This has been corrected in the online and print versions of the article.
SUPPLEMENTAL MATERIAL:

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

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

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

<table>
<thead>
<tr>
<th>Trial 1-37</th>
<th>Treatment Intervention</th>
<th>Control Intervention</th>
<th>Time Scheduled for Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Burgar et al., 2011</strong></td>
<td>Robot assisted therapy at a high dose.</td>
<td>Robot assisted therapy at a low dose.</td>
<td>15.8 hrs / 21 days</td>
</tr>
<tr>
<td><strong>Cooke et al., 2010</strong></td>
<td>Functional strength training combined with conventional therapy.</td>
<td>Conventional therapy alone.</td>
<td>23.5 hrs / 42 days</td>
</tr>
<tr>
<td><strong>Dean et al., 2000</strong></td>
<td>Lower-limb focused rehabilitation.</td>
<td>Upper-limb therapy.</td>
<td>12 hrs / 28 days</td>
</tr>
<tr>
<td><strong>Di Lauro et al., 2003</strong></td>
<td>Intensive rehabilitation therapy.</td>
<td>Conventional therapy.</td>
<td>28 hrs / 14 days</td>
</tr>
<tr>
<td><strong>Donaldson et al., 2009</strong></td>
<td>Functional strength training combined with conventional therapy.</td>
<td>Conventional therapy alone.</td>
<td>17.7 hrs / 42 days</td>
</tr>
<tr>
<td><strong>Dromerick et al., 2000</strong></td>
<td>CIMT, constraint for 6 hours per day.</td>
<td>Standard occupational therapy combined with a circuit training program.</td>
<td>62 hrs / 14 days</td>
</tr>
<tr>
<td><strong>Dromerick et al., 2009</strong></td>
<td>CIMT, constraint for 90% of waking hours</td>
<td>ADL retraining and UE bilateral training.</td>
<td>80.4 hrs / 14 days</td>
</tr>
<tr>
<td><strong>Duncan et al., 2003</strong></td>
<td>In-home program of thirty-six sessions.</td>
<td>Usual care prescribed by physician.</td>
<td>50.6 hrs / 84 days</td>
</tr>
<tr>
<td><strong>Duncan et al., 2011</strong></td>
<td>Thirty-six sessions of body-weight supported treadmill therapy.</td>
<td>No therapy (deferred treatment).</td>
<td>54 hrs / 98 days</td>
</tr>
<tr>
<td><strong>Fang et al., 2003</strong></td>
<td>Additional conventional therapy.</td>
<td>No professional rehabilitation therapy during the intervention.</td>
<td>15 hrs / 28 days</td>
</tr>
<tr>
<td><strong>Feys et al., 1998</strong></td>
<td>Targeted UE therapy.</td>
<td>Sham short wave therapy on the shoulder.</td>
<td>15 hrs / 42 days</td>
</tr>
<tr>
<td><strong>GAPS Group, 2004</strong></td>
<td>Additional conventional therapy.</td>
<td>Conventional therapy alone.</td>
<td>34 hrs / 4 weeks</td>
</tr>
<tr>
<td><strong>Green et al., 2002</strong></td>
<td>Community physiotherapy</td>
<td>No intervention.</td>
<td>NA***</td>
</tr>
<tr>
<td><strong>Hesse et al., 2011</strong></td>
<td>Intermittent high-intensity therapy.</td>
<td>Continuous low-intensity therapy.</td>
<td>120 hrs / 365 days</td>
</tr>
<tr>
<td><strong>Hunter et al., 2011</strong></td>
<td>Conventional therapy plus mobilisation and tactile stimulation.</td>
<td>Conventional therapy alone.</td>
<td>8.7 hrs / 14 days</td>
</tr>
<tr>
<td><strong>Kuys et al., 2011</strong></td>
<td>High intensity treadmill therapy in addition to conventional therapy.</td>
<td>Conventional therapy alone.</td>
<td>51.0 hrs / 42 days</td>
</tr>
<tr>
<td><strong>Kwakkel et al., 1999</strong></td>
<td>Rehabilitation program with an emphasis on leg training.</td>
<td>Conventional therapy plus immobilization with an inflatable pressure splint.</td>
<td>117.2 hrs / 70 days</td>
</tr>
<tr>
<td><strong>Langhammer et al., 2010</strong></td>
<td>Conventional therapy plus treadmill training.</td>
<td>Conventional therapy plus outdoor walking.</td>
<td>49.5 hrs / 15.9 days</td>
</tr>
<tr>
<td><strong>Lin et al., 2007</strong></td>
<td>Modified CIMT, constraint for 6 hours per day.</td>
<td>Conventional rehabilitation.</td>
<td>75 hrs / 21 days</td>
</tr>
<tr>
<td><strong>Luft et al., 2008</strong></td>
<td>Progressive treadmill therapy.</td>
<td>Comparable time in supervised stretching.</td>
<td>52 hrs / 168 days</td>
</tr>
<tr>
<td><strong>Page et al., 2004</strong></td>
<td>Modified CIMT, constraint for 5 hours a day.</td>
<td>Control patients received no therapy during the 10-140 hrs / 70 days</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Control Intervention</td>
<td>Therapy Time</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Page et al., 2005</td>
<td>Modified CIMT, constraint for 5 hours per day.</td>
<td>Conventional therapy for the affected arm.</td>
<td>140 hrs / 70 days</td>
</tr>
<tr>
<td>Page et al., 2008</td>
<td>Modified CIMT, constraint for 5 hours per day.</td>
<td>Conventional therapy for the affected arm.</td>
<td>140 hrs / 70 days</td>
</tr>
<tr>
<td>Partridge et al., 2000</td>
<td>Conventional therapy at a high-dose.</td>
<td>Conventional therapy at a low-dose.</td>
<td>30 hrs / 42 days</td>
</tr>
<tr>
<td>Rydewik et al., 2006</td>
<td>Combined active and passive treatment with a Stimulo device.</td>
<td>No therapy (deferred treatment).</td>
<td>9 hrs / 42 days</td>
</tr>
<tr>
<td>Smania et al., 2012</td>
<td>Modified CIMT, constraint for 12 hours a day.</td>
<td>Conventional therapy for the affected arm.</td>
<td>80 hrs / 14 days</td>
</tr>
<tr>
<td>Sonoda et al., 2004</td>
<td>Combined PT/OT therapy seven days per week.</td>
<td>Combined PT/OT therapy five days per week.</td>
<td>46.7 hrs / 35 days</td>
</tr>
<tr>
<td>Tanaka et al., 2012</td>
<td>Robot-assisted gait training using Gaitmaster 4.</td>
<td>No therapy (deferred treatment).</td>
<td>4 hrs / 35 days</td>
</tr>
<tr>
<td>Taub et al., 2006</td>
<td>CIMT, constraint for 90% of waking hours.</td>
<td>A program of fitness training, cognitive exercises, and relaxation exercises.</td>
<td>116 hrs / 14 days</td>
</tr>
<tr>
<td>Treger et al., 2012</td>
<td>Modified CIMT, constraint for 4 hours per day.</td>
<td>Conventional therapy.</td>
<td>30 hrs / 14 days</td>
</tr>
<tr>
<td>Wade et al., 1992</td>
<td>Conventional therapy</td>
<td>No therapy (deferred treatment).</td>
<td>NA***</td>
</tr>
<tr>
<td>Weinstein et al., 2004</td>
<td>Functional task practice and strength training plus conventional therapy.</td>
<td>Conventional therapy alone.</td>
<td>40 hrs / 28 days</td>
</tr>
<tr>
<td>Wolf et al., 2006</td>
<td>CIMT, constraint for 90% of waking hours.</td>
<td>No therapy (deferred treatment).</td>
<td>160.8 hrs / 14 days</td>
</tr>
<tr>
<td>Wu et al., 2007</td>
<td>CIMT, constraint for 6 hours per day.</td>
<td>Conventional therapy.</td>
<td>75 hrs / 21 days</td>
</tr>
<tr>
<td>Yang et al., 2005</td>
<td>Conventional therapy plus additional walking training.</td>
<td>Conventional therapy alone.</td>
<td>10.5 hrs / 21 days</td>
</tr>
<tr>
<td>Yang et al., 2007</td>
<td>Experimental dual-task therapy.</td>
<td>No therapy.</td>
<td>6 hrs / 28 days</td>
</tr>
<tr>
<td>Yavuzer et al., 2006</td>
<td>Conventional therapy plus additional balance training.</td>
<td>Conventional therapy alone.</td>
<td>143.8 hrs / 56 days</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Trial1–37</th>
<th>Outcome</th>
<th>Time Post-Stroke (yrs)</th>
<th>Δ Time (hrs)</th>
<th>Treat. M (SD)</th>
<th>Treat. N</th>
<th>Ctrl. M (SD)</th>
<th>Ctrl. N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgar et al., 2011</td>
<td>FMA</td>
<td>0.046</td>
<td>7.20</td>
<td>14.40 (14.84)</td>
<td>17</td>
<td>6.80 (8.28)</td>
<td>19</td>
</tr>
<tr>
<td>Cooke et al., 2010</td>
<td>Gait speed</td>
<td>0.097</td>
<td>14.30</td>
<td>0.42 (0.39)</td>
<td>36</td>
<td>0.3 (0.35)</td>
<td>31</td>
</tr>
<tr>
<td>Dean et al., 2000</td>
<td>6MWT</td>
<td>1.800</td>
<td>12.00</td>
<td>42.1* (127.75)</td>
<td>5</td>
<td>7.7* (156.89)</td>
<td>4</td>
</tr>
<tr>
<td>Di Lauro et al., 2003</td>
<td>BI</td>
<td>0.003</td>
<td>17.50</td>
<td>1.8* (2.00)</td>
<td>26</td>
<td>1.7* (2.60)</td>
<td>27</td>
</tr>
<tr>
<td>Donaldson et al., 2011</td>
<td>ARAT</td>
<td>0.048</td>
<td>14.89</td>
<td>19.5* (15.05)</td>
<td>10</td>
<td>11.5* (13.51)</td>
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<tr>
<td>Dromerick et al., 2000</td>
<td>ARAT</td>
<td>0.016</td>
<td>42.00</td>
<td>52.80 (5.90)</td>
<td>11</td>
<td>44.30 (11.10)</td>
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<tr>
<td>Dromerick et al., 2009</td>
<td>ARAT</td>
<td>0.026</td>
<td>60.40</td>
<td>33.93 (16.64)</td>
<td>16</td>
<td>36.20 (16.69)</td>
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<tr>
<td>Duncan et al., 2003</td>
<td>FMA</td>
<td>0.207</td>
<td>21.02</td>
<td>2.74* (3.05)</td>
<td>44</td>
<td>1.76* (3.87)</td>
<td>48</td>
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<tr>
<td>Duncan et al., 2011</td>
<td>Gait speed</td>
<td>.176</td>
<td>54.00</td>
<td>0.23* (0.2)</td>
<td>139</td>
<td>0.13* (0.14)</td>
<td>143</td>
</tr>
<tr>
<td>Fang et al., 2003</td>
<td>FMA</td>
<td>NA</td>
<td>15.00</td>
<td>9.39* (18.98)</td>
<td>50</td>
<td>5.67* (21.65)</td>
<td>78</td>
</tr>
<tr>
<td>Feys et al., 1998</td>
<td>BFMT</td>
<td>0.062</td>
<td>15.00</td>
<td>2.93 (0.73)</td>
<td>50</td>
<td>2.77 (0.84)</td>
<td>50</td>
</tr>
<tr>
<td>GAPS Group, 2004</td>
<td>MI</td>
<td>0.102</td>
<td>13.00</td>
<td>119 (46.00)</td>
<td>34</td>
<td>111 (45.00)</td>
<td>35</td>
</tr>
<tr>
<td>Green et al., 2002</td>
<td>Gait speed**</td>
<td>&gt;1.00</td>
<td>NA</td>
<td>25.50 (12.60)</td>
<td>78</td>
<td>24.90 (13.80)</td>
<td>77</td>
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<td>RMI</td>
<td>0.299</td>
<td>55.00</td>
<td>12.20 (1.70)</td>
<td>25</td>
<td>11.30 (2.70)</td>
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</tr>
<tr>
<td>Hunter et al., 2011</td>
<td>MI</td>
<td>0.075</td>
<td>8.70</td>
<td>17 <em>(22.41)</em></td>
<td>19</td>
<td>12.4* (25.73)*</td>
<td>19</td>
</tr>
<tr>
<td>Kuys et al., 2011</td>
<td>6MWT</td>
<td>0.138</td>
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<td>107.00* (134.58)</td>
<td>13</td>
<td>60.00* (155.21)</td>
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<tr>
<td>Kwakkel et al., 1999</td>
<td>Gait speed**</td>
<td>0.020</td>
<td>43.67</td>
<td>0.65 (0.46)</td>
<td>26</td>
<td>0.37 (0.41)</td>
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<tr>
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<td>6MWT</td>
<td>1.052</td>
<td>-6.48</td>
<td>320.00 (153.80)</td>
<td>18</td>
<td>310.00 (164.40)</td>
<td>16</td>
</tr>
<tr>
<td>Lin et al., 2007</td>
<td>FIM</td>
<td>1.357</td>
<td>45</td>
<td>113.06 (10.55)</td>
<td>17</td>
<td>105.67 (15.85)</td>
<td>15</td>
</tr>
<tr>
<td>Luft et al., 2008</td>
<td>Gait speed</td>
<td>4.461</td>
<td>52.00</td>
<td>1.11 (0.30)</td>
<td>37</td>
<td>0.88 (0.28)</td>
<td>34</td>
</tr>
<tr>
<td>Page et al., 2004 RM</td>
<td>FMA</td>
<td>2.463</td>
<td>140</td>
<td>18.40* (7.41)</td>
<td>7</td>
<td>-2.90* (7.10)</td>
<td>6</td>
</tr>
<tr>
<td>Page et al., 2005 RM</td>
<td>FMA</td>
<td>0.012</td>
<td>125</td>
<td>52.60 (3.04)</td>
<td>5</td>
<td>39.40 (6.99)</td>
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</tr>
<tr>
<td>Page et al., 2008</td>
<td>ARAT</td>
<td>3.316</td>
<td>125</td>
<td>40.54 (8.18)</td>
<td>13</td>
<td>29.17 (10.00)</td>
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<tr>
<td>Partridge et al., 2000</td>
<td>POR</td>
<td>NA</td>
<td>15.00</td>
<td>9.50 (4.80)</td>
<td>52</td>
<td>9.8 (4.60)</td>
<td>56</td>
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<td>6MWT</td>
<td>4.007</td>
<td>9.00</td>
<td>46.40* (71.50)</td>
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<td>21.80*</td>
<td>6</td>
</tr>
<tr>
<td>Year</td>
<td>Author et al.</td>
<td>Test</td>
<td>M</td>
<td>Time</td>
<td>Time Difference</td>
<td>n</td>
<td>p</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>------</td>
<td>---</td>
<td>------</td>
<td>-----------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2006</td>
<td>Smania et al., 2012</td>
<td>WMFT</td>
<td>0.842</td>
<td>60.00 C</td>
<td>3.62 (0.78)</td>
<td>30</td>
<td>2.92 (0.86)</td>
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<td>97.10 (26.20)</td>
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<td>2012</td>
<td>Tanaka et al., Gait speed</td>
<td>4.964</td>
<td>4.00</td>
<td>0.12* (0.44)</td>
<td>7</td>
<td>0.02* (0.16)</td>
<td></td>
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<tr>
<td>2006</td>
<td>Taub et al., WMFT</td>
<td>4.450</td>
<td>56.00 C</td>
<td>2.30* (2.33)</td>
<td>21</td>
<td>-0.50* (3.58)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>Treger et al., MFT</td>
<td>0.086</td>
<td>20.00 C</td>
<td>5.40* (3.40)</td>
<td>9</td>
<td>3.50 (2.20)</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Wade et al., 10MWT</td>
<td>4.631</td>
<td>NA</td>
<td>3.90* (27.06)</td>
<td>49</td>
<td>-6.40 (37.91)</td>
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<tr>
<td>2004</td>
<td>Weinstein et al., FMA</td>
<td>0.044</td>
<td>20.00</td>
<td>17.35* (17.98)</td>
<td>40</td>
<td>9.05* (22.31)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Wolf et al., WMFT</td>
<td>0.503</td>
<td>160.80 C</td>
<td>0.58* (1.37)</td>
<td>98</td>
<td>0.08* (1.37)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Wu et al., FMA</td>
<td>1.006</td>
<td>45.00 C</td>
<td>46.75 (11.58)</td>
<td>24</td>
<td>44.78 (13.08)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Yang et al., Gait speed</td>
<td>0.525</td>
<td>4.50</td>
<td>33.43 (5.20)</td>
<td>13</td>
<td>29.62 (16.35)</td>
<td></td>
</tr>
<tr>
<td>2007RM</td>
<td>Yang et al., Gait speed</td>
<td>4.380</td>
<td>6.00</td>
<td>29.74* (19.01)</td>
<td>13</td>
<td>-12.84* (24.71)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Yavuzer et al., Gait speed</td>
<td>0.682</td>
<td>3.75</td>
<td>0.08 (0.20)</td>
<td>22</td>
<td>0.01 (0.20)</td>
<td></td>
</tr>
</tbody>
</table>

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.

Quality 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.

<table>
<thead>
<tr>
<th>Author*</th>
<th>Year</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
<th>C9</th>
<th>C10</th>
<th>C11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgar</td>
<td>2011</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cooke</td>
<td>2010</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dean</td>
<td>2000</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Di Lauro</td>
<td>2003</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Donaldson</td>
<td>2009</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dromerick</td>
<td>2000</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dromerick</td>
<td>2009</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Duncan</td>
<td>2003</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Duncan</td>
<td>2011</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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\textsuperscript{1-37}. Three of these studies (Page et al., 2004\textsuperscript{21}; Page et al., 2005\textsuperscript{22}; and Yang et al., 2007\textsuperscript{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).

![Funnel plot](image.png)

**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 (\(\Delta\)Time) 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., $\Delta T_{\text{MAX}}$) and quadratic (e.g., $\Delta T_{\text{MAX}}^2$) 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.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ctrl. Time</th>
<th>$\Delta T_{\text{MIN}}$</th>
<th>$\Delta T_{\text{50%}}$</th>
<th>$\Delta T_{\text{MAX}}$</th>
<th>Change</th>
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<td>Burgar et al., 2011</td>
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<td>7.2</td>
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<td>Dean et al., 2000</td>
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<td>84</td>
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<td>7</td>
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<td>20</td>
<td>10</td>
<td>60.40</td>
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<td>29.64</td>
<td>21.02</td>
<td>21.02</td>
<td>21.02</td>
</tr>
<tr>
<td>9</td>
<td>Duncan et al., 2011</td>
<td>0</td>
<td>54</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>Fees et al., 1998</td>
<td>0</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>GAPS Group, 2004</td>
<td>21</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>Hesse et al., 2011</td>
<td>65</td>
<td>55</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td>13</td>
<td>Hunter et al., 2011</td>
<td>0</td>
<td>8.7</td>
<td>8.7</td>
<td>8.7</td>
</tr>
<tr>
<td>14</td>
<td>Kuys et al., 2011</td>
<td>42</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>Kwakkel et al., 1999</td>
<td>73.5</td>
<td>43.67</td>
<td>43.67</td>
<td>43.67</td>
</tr>
<tr>
<td>16</td>
<td>Langhammer et al., 2010</td>
<td>55.95</td>
<td>-6.48</td>
<td>-6.48</td>
<td>-6.48</td>
</tr>
<tr>
<td>17</td>
<td>Lin et al., 2007</td>
<td>30</td>
<td>0</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>18</td>
<td>Luft et al., 2008</td>
<td>0</td>
<td>54</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>19</td>
<td>Page et al., 2008</td>
<td>15</td>
<td>0</td>
<td>125</td>
<td>250</td>
</tr>
<tr>
<td>20</td>
<td>Rydwik et al., 2006</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>21</td>
<td>Smania et al., 2012</td>
<td>20</td>
<td>0</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>22</td>
<td>Sonoda et al., 2004</td>
<td>33.33</td>
<td>13.40</td>
<td>13.40</td>
<td>13.40</td>
</tr>
<tr>
<td>23</td>
<td>Tanaka et al., 2012</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>Taub et al., 2006</td>
<td>60</td>
<td>0</td>
<td>56</td>
<td>112</td>
</tr>
<tr>
<td>25</td>
<td>Treger et al., 2012</td>
<td>10</td>
<td>0</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>26</td>
<td>Weinstein et al., 2004</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>Wolf et al., 2006</td>
<td>0</td>
<td>60</td>
<td>160.80</td>
<td>261.6</td>
</tr>
<tr>
<td>28</td>
<td>Wu et al., 2007</td>
<td>30</td>
<td>0</td>
<td>45</td>
<td>90</td>
</tr>
<tr>
<td>29</td>
<td>Yang et al., 2005</td>
<td>6</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>30</td>
<td>Yavuzer et al., 2006</td>
<td>140</td>
<td>3.75</td>
<td>3.75</td>
<td>3.75</td>
</tr>
</tbody>
</table>

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 (ΔTime\text_{MIN}, shown in Table All, and ΔTime^2\text{MIN}). Model 1 tested the simple effect of ΔTime\text{MIN} (in 10 hr units) and was not significant, Q(1) = 0.09, p = 0.76, and the parameter estimate of ΔTime\text{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 ΔTime\text{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 no effect of time post-stroke (p = 0.60), Yrs.PS^2 (p = 0.78), or ΔTime\text{MIN} (p = 0.54).

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

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>95% Confidence Interval</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.3200</td>
<td>[0.09, 0.55]</td>
<td>2.73</td>
</tr>
<tr>
<td>Yrs.PS (yrs)</td>
<td>0.1238</td>
<td>[-0.34, 0.58]</td>
<td>0.53</td>
</tr>
<tr>
<td>Yrs.PS^2</td>
<td>-0.0143</td>
<td>[-0.12, 0.09]</td>
<td>-0.27</td>
</tr>
<tr>
<td>ΔTime\text{MIN} (10 hrs)</td>
<td>0.0173</td>
<td>[-0.04, 0.07]</td>
<td>0.62</td>
</tr>
</tbody>
</table>

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

Model 4 further added the quadratic effect of ΔTime^2\text{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 ΔTime\text{MIN} (p = 0.56), and no effect of ΔTime^2\text{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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.4264</td>
<td>[-0.00, 0.85]</td>
<td>1.95</td>
<td>.051</td>
</tr>
<tr>
<td>Yrs.PS (yrs)</td>
<td>0.0281</td>
<td>[-0.59, 0.65]</td>
<td>0.09</td>
<td>.929</td>
</tr>
<tr>
<td>Yrs.PS²</td>
<td>0.0040</td>
<td>[-13, 0.14]</td>
<td>0.06</td>
<td>.952</td>
</tr>
<tr>
<td>ΔTime_MIN (10 hrs)</td>
<td>-0.1034</td>
<td>[-0.46, -0.25]</td>
<td>-0.58</td>
<td>.565</td>
</tr>
<tr>
<td>ΔTime²_MIN (10 hrs)</td>
<td>0.0209</td>
<td>[-0.04, 0.08]</td>
<td>0.72</td>
<td>.472</td>
</tr>
</tbody>
</table>

Note. The parameter estimates for Yrs.PS are in years and the estimates for ΔTime_MIN are in 10 hour units. An additional model included the interaction of ΔTime_MIN x Yrs.PS², 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 (ΔTime_MAX, shown above, and ΔTime²_MAX). Model 1 tested the simple effect of ΔTime_MAX and the model was significant, Q(1) = 5.17, p = 0.02, and the parameter estimate of ΔTime_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.PS² (b = -0.010, 95% CI = [-0.11, 0.09], p = 0.85), were not significant individually.

Model 3 added the linear effect of ΔTime_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 =.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 ΔTime_MAX (p = 0.05).

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.3007</td>
<td>[0.12, 0.48]</td>
<td>3.36</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yrs.PS (yrs)</td>
<td>-0.0257</td>
<td>[-0.51, 0.45]</td>
<td>-0.11</td>
<td>.916</td>
</tr>
<tr>
<td>Yrs.PS²</td>
<td>0.0150</td>
<td>[-0.09, 0.12]</td>
<td>0.28</td>
<td>.779</td>
</tr>
<tr>
<td>ΔTime_MAX (10 hrs)</td>
<td>0.0201</td>
<td>[-0.00, 0.04]</td>
<td>1.95</td>
<td>.051</td>
</tr>
</tbody>
</table>

Note. The parameter estimates for Yrs.PS are in years and the estimates for ΔTime_MAX are in 10 hour units. An additional model included the interaction of ΔTime_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 $\Delta \text{Time}_{\text{MAX}}^2$. Overall, the test of
moderators was not significant, $Q(4) = 7.017$, $p = .13$, and the test of residual heterogeneity was
not significant, $Q(25) = 17.09$, $p = .88$. 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 ($p = 0.96$), $\text{Yrs.PS}^2$ ($p = 0.82$), $\Delta \text{Time}_{\text{MAX}}$ ($p = 0.14$), nor an effect of $\Delta \text{Time}_{\text{MAX}}^2$ ($p = 0.36$).

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

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

Note. The parameter estimates for $\text{Yrs.PS}$ are in years and the estimates for $\Delta \text{Time}_{\text{MAX}}$ are in 10 hour units. An additional model included the interaction of $\Delta \text{Time}_{\text{MAX}}^2 \times \text{Yrs.PS}^2$. 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Min Time</th>
<th>50% Time</th>
<th>Max Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Yrs.PS}$</td>
<td>0.1238</td>
<td>0.0281</td>
<td>-0.0257</td>
</tr>
<tr>
<td>$\text{Yrs.PS}^2$</td>
<td>-0.0143</td>
<td>0.0040</td>
<td>0.0150</td>
</tr>
<tr>
<td>$\Delta \text{Time}$</td>
<td>0.0173</td>
<td>-0.1034</td>
<td>0.0201*</td>
</tr>
<tr>
<td>$\Delta \text{Time}^2$</td>
<td>NA</td>
<td>0.0209</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note. $\text{Yrs.PS}$ and $\text{Yrs.PS}^2$ are in units of years. $\Delta \text{Time}$ and $\Delta \text{Time}^2$ are in units of 10 hours. NA = not applicable because Model 3 did not contain $\Delta \text{Time}^2$. † 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.

<table>
<thead>
<tr>
<th>Calculation</th>
<th>Intercept</th>
<th>95% CI</th>
<th>Slope of ΔTime</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min Time</td>
<td>0.4132</td>
<td>[0.24, 0.58]***</td>
<td>0.0079</td>
<td>[-0.04, 0.06]</td>
</tr>
<tr>
<td>50% Time</td>
<td>0.3041</td>
<td>[0.13, 0.48]***</td>
<td>0.0365</td>
<td>[0.01, 0.07]*</td>
</tr>
<tr>
<td>Max Time</td>
<td>0.3210</td>
<td>[0.16, 0.48]***</td>
<td>0.0208</td>
<td>[0.00, 0.04]*</td>
</tr>
</tbody>
</table>

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)

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
cconfint(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
cconfint(nooutliers)

FEnooutliers<-rma(g,v,data=OUTLIERS, method="FE")
FEnooutliers
cconfint(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=" \	")
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 quadratic 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
```r
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


