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

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Abstract

Background and Purpose—Neurophysiological models of rehabilitation and recovery suggest that a large volume of specific practice is required to induce the neuroplastic 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 post-stroke by (1) comparing high-doses to low-doses and (2) using meta-regression to further quantify the dose-response relationship.

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 post-stroke.

Results—Overall, treatment groups receiving more therapy improved beyond control groups that received less, g = 0.35, 95% CI = [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 post-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 post-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.

Key Terms

Stroke; Rehabilitation; Dose; Therapy

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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 animals[1,2] and humans[3] demonstrate that large quantities of practice lead to cortical reorganization and improved behavioural function. Similar studies link neural changes with recovery of function and learning in adults post-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-analyses[7,8] also suggest a positive dose-response relationship.

Some define dose as the amount of time actively spent in practice[9], or the number of repetitions of a movement[10,11]. For this paper, dose is defined as total time scheduled for therapy (e.g., 3 hrs/day * (10 days) = 30 hrs). Time scheduled for therapy may not accurately reflect actual practice time nor the number of movement repetitions (see Lang et al.[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 paper response was defined as a standardized effect-size, Hedges' g, which shows improved function or reduced impairment on a standardized, validated behavioural 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 papers 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[7,8] whereas time post-stroke might negatively affect outcomes[15].

Methods

The population of interest was adults post-stroke (PICO model: Population, Intervention, Comparison, Outcome[16]). Interventions were therapies without exogenous stimulation. Comparison groups included randomized controlled trials where the treatment and control groups received different amounts of time scheduled for therapy. In some (e.g.[17–19]), each group received the same therapy in different dosages. In others, groups received different types of therapy (e.g.[20–22]) in different dosages. Outcomes were restricted to validated behavioural measures of function or impairment. In two 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 9th, 2013. Search terms included "stroke" or "stroke rehab$" in combination with one of the terms "dose", "intens$", "constrain$", or "gait". Filters limited papers to randomized controlled trials (otherwise, "random" and "control" were search terms). Bibliographies of retrieved trials and review papers were searched.

Study Selection

An initial 832 titles were identified. After screening titles and abstracts, and removing duplicates, 138 papers were assessed (see Supplemental Appendix I). Details of the interventions and the time scheduled for therapy in the treatment and control groups was extracted. Exclusion criteria were: (a) lack of randomization with a control, (b) studied children (<18 years old), (c) >30% participants with neurological disorders other than stroke, (d) therapy in combination with a pharmaceutical treatment or electrical stimulation, (e) dose matched treatment and control conditions, and (f) unpublished or not translated into English. Thirty-seven trials remained (see Supplemental Table I) and were included in the assessment of study quality[13,17–52]. The Physiotherapy Evidence Database Scale was used to rate methodological quality (PEDro; www.pedro.org.au).

Quantitative Analysis

Means, standard deviations, and sample sizes for the treatment and control groups were entered into a spreadsheet. Standardized effect-sizes (Hedges' g) and variances (V_g) were calculated[53]. Effect sizes were computed from the terminal difference between treatment and control or the difference in improvement between treatment and control, divided by the standard deviation within groups. Subtraction was arranged so that effects favoring the treatment group were positive. Effect-size measures were analyzed using the "metafor" package[54] in R (cran.r-project.org; Supplemental Table II). A funnel plot was constructed. There were three 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 (Supplemental Appendix II).

Custom scripts (Supplemental Appendix 3) tested a random-effects model for the overall effect of increased therapy dosage. The analysis was broken into two parts. Part one was congruent with previous analyses[7,8], calculating a summary effect-size for groups who received more therapy compared to groups who received less. Part two elaborated on this analysis by using meta-regression models to quantify the dose-response relationship controlling for other factors. Four studies were omitted from regression models due to missing data[19, 23, 30, 47] (see the "NAs" in Supplemental Table II); regression was based on 30 studies. Time post-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 CIMT 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 three different ΔTimes for CIMT 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, as we assume that some, but not all, of constraint time was spent using the affected limb. (Details of all analyses are presented in Supplemental Appendix II.)

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% CI = [0.26, 0.45] (Figure 1), which was significant, Z_{obs} = 7.21, p < 0.001. The random-effects model had a τ^2 = 0.01 (which is the maximum-likelihood estimate of between-study variance), I^2 = 16.34 (which is the % of total variability due to heterogeneity), and H^2 = 1.20 (the ratio of total variability to sampling variability). The test for heterogeneity was not significant, $Q(33) = 37.34$, $p = 0.28$. Thus, there was an overall benefit for more time scheduled for therapy compared to less.

Descriptive statistics for the regression models

For the 30 studies included in the regression models, there were 1,750 total participants. The median number of participants in treatment groups was n = 21.5 and in control groups n = 19.5. In treatment groups time post-stroke was 1.01 ±1.49 yrs, [0.003, 5.14], shown as M ±SD [Min, Max]. In control groups time post-stroke was 1.02 ±1.63 yrs, [0.003, 5.38]. The duration of therapy in treatment groups was 49.56 ±68.12 days, [14, 365]. The duration of therapy in control groups was virtually identical, 49.60 ±68.10 days, [14, 365], as most studies were matched for treatment duration (see Supplemental Table I). Matching studies on treatment duration means that differences in total therapy time result from changes in the frequency and intensity of therapy for a given duration. Time scheduled for therapy in treatment groups was 57.41 ±44.88 hrs, [4.0, 160.8]. Time scheduled for therapy in control groups was 24.08 ±30.39 hrs, [0.0, 140.0]. The average ΔTime was 33.33 ±36.20 hrs, [−6.50, 160.80]. Observed effect-sizes as a function of ΔTime and Yrs.PS are shown in Figure 2.

Quantifying dose: Increased scheduled therapy predicts greater recovery

In order to look at the linear effect of ΔTime, a series of models was tested. Model 1 tested the simple effect of ΔTime (in 10 hr units) as a predictor of effect size. This model was significant, Q(1) = 5.40, p = .02 and the parameter estimate of ΔTime was b = 0.037, 95% CI = [0.01, 0.07], p = .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% 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, 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 non-significant, $Q(3) = 6.73$, $p = .08$, but the effect of ΔTime was significant. The test of residual homogeneity was not significant, $Q(26) = 20.51$, $p = .77$.

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 non-significant, Q(4) = 8.21, p = .08. The test of residual homogeneity was not significant, Q(25) = 14.89, p = .94.

The linear effect of ΔTime was significant (p = .04) and $\Delta Time^2$ approached significance (p = .09). The predicted effect-sizes ($\hat{g}$) of Models 3 and 4 are shown in Figure 3. The non-significant effect of $\Delta Time^2$ suggests that the basic effect of ΔTime is positive and for every additional 10 hrs 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.

Discussion

This meta-analysis agrees with previous work[7,8] suggesting a small overall benefit of augmented time in therapy (i.e., more is better). Kwakkel's review[7] found smaller benefits of therapy dose (~0.20 for measures of ADL and walking speed) than our overall g = 0.35, which is likely due to differences in the methods for inclusion and analysis. It is difficult to compare our results directly to Langhorne's review[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 post-stroke were significant. However, there was a significant positive effect of time scheduled for therapy on outcomes (Model 1) even when controlling for time post-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, employing 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 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 post-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 post-stroke (post-stroke 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[20] or have no benefit over less intense therapies[18]. Also, too many hours of therapy may not be tolerable for participants, leading to drop-outs[22]. These nonlinearities are important considerations for clinicians that 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 following 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[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 by 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 dataset, 23.5% of studies (8 out 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 meta-regression, we rapidly lost power to detect additional effects and interactions. Additional studies need to be included in the dataset to test additional predictors (e.g., stroke severity), higher order effects (e.g., cubic effects), or interactions. While the meta-data approach is powerful, dose-response relationships are likely more complex than what we present here. Future 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-ups (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 meta-data and other experimental data[55–57] warrant larger experimental studies to explore dose-response effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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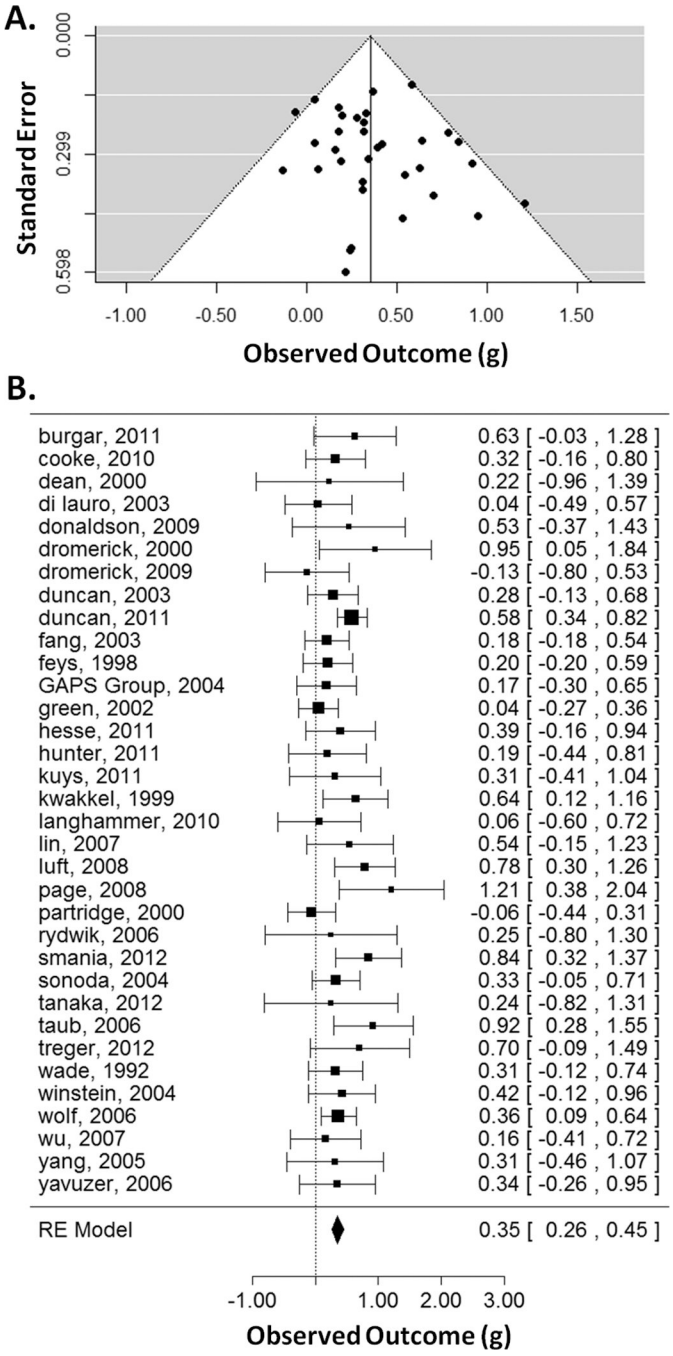

Figure 1.

Funnel plot (A) showing effect-sizes (g) as a function of precision (standard error). Asymmetry was not significant. Forest plot (B) showing the effect-sizes and 95% confidence intervals for each study and the summary effect-size from the random-effects model. Positive values show a difference in favor of increased time scheduled for therapy. RE=random effects.

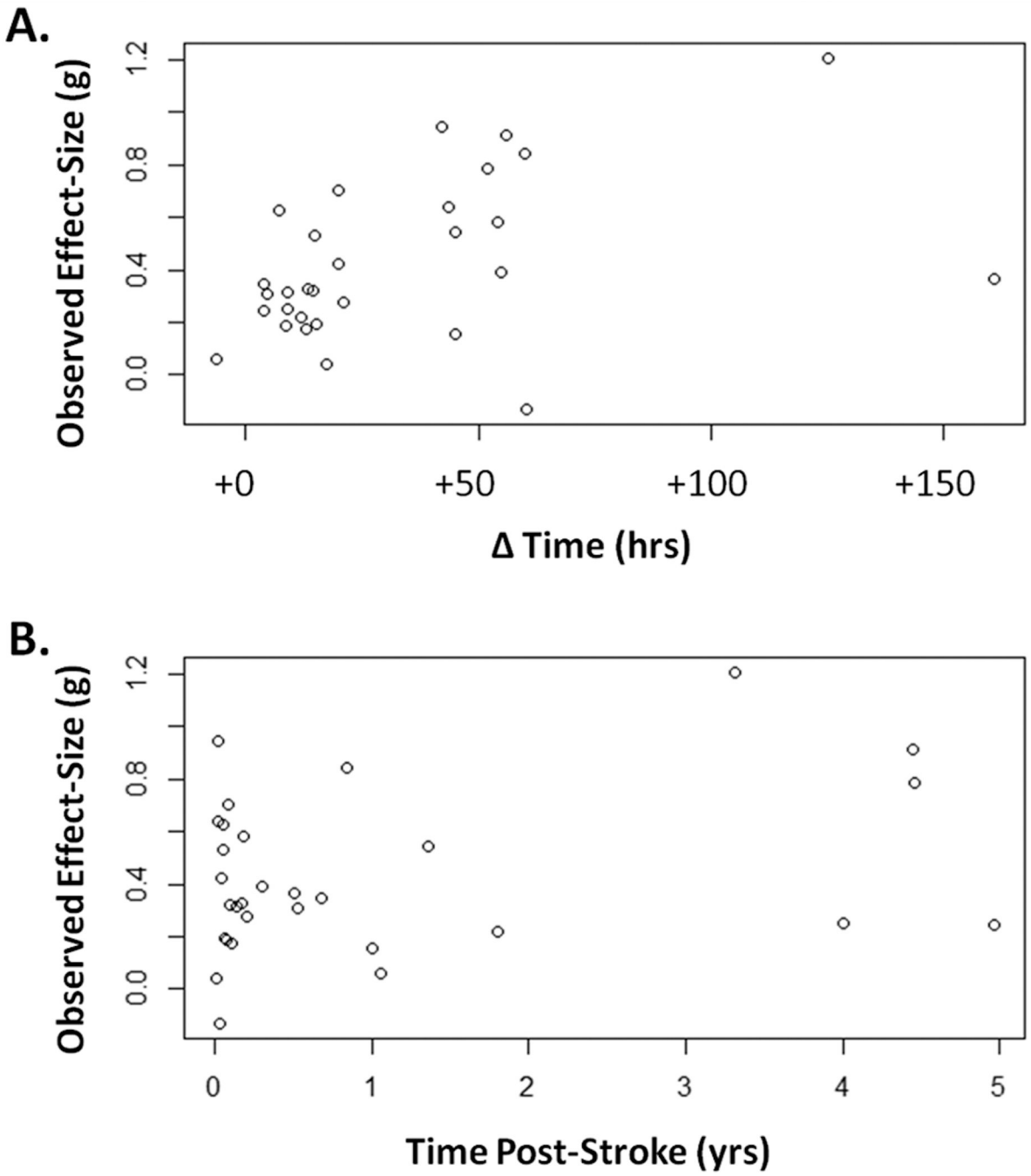

Figure 2.

Observed effect-size (g) for each study as a function of additional time scheduled for therapy (A) and as a function of years post-stroke (B).

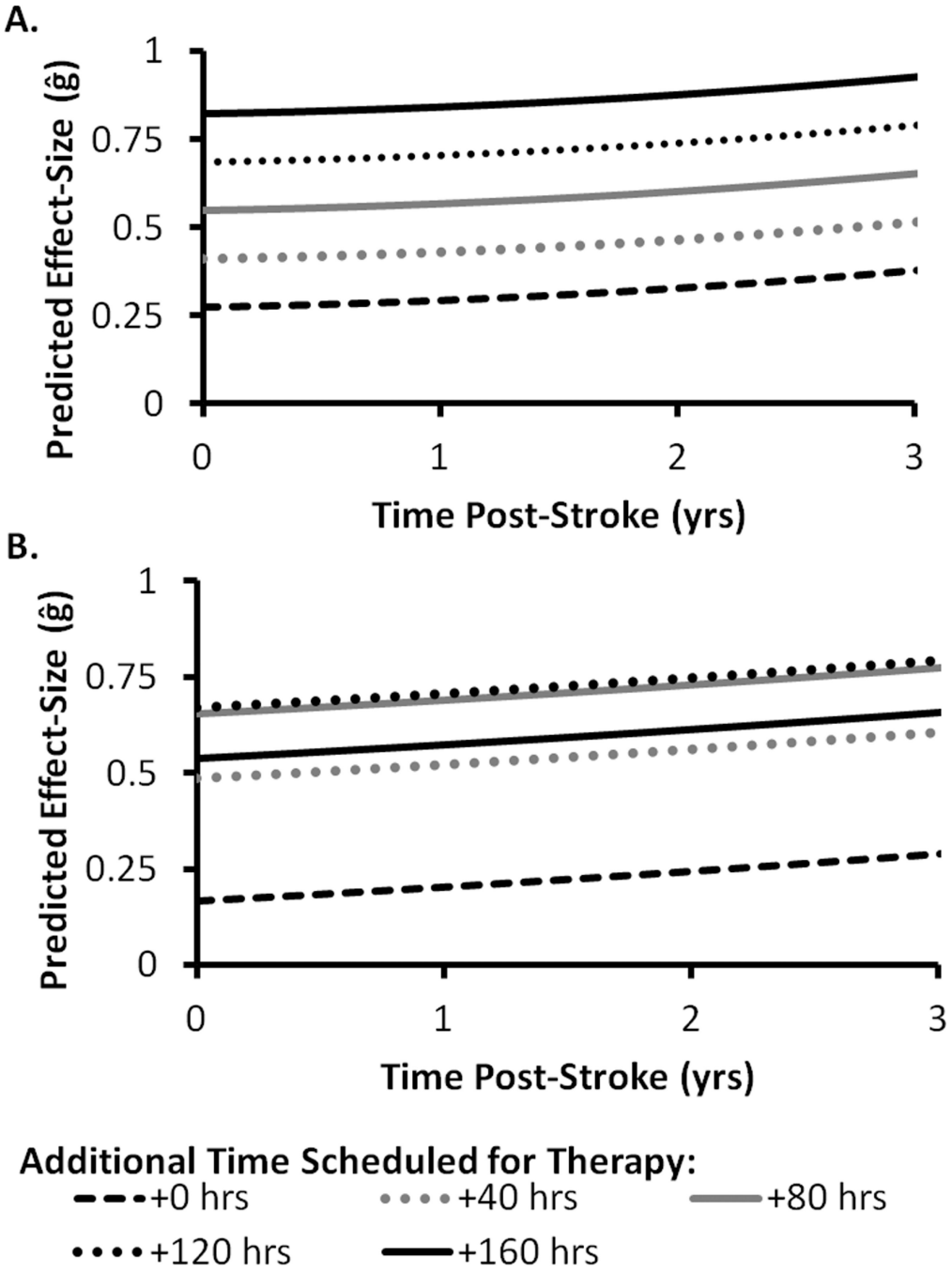

Figure 3.

Predicted effect-size (ĝ) as a function years post-stroke (x-axis) and select values of additional time scheduled for therapy (separate lines). Model 3 (A) includes the linear effect of time scheduled for therapy. Model 4 (B) includes the linear and quadratic effects of time scheduled for therapy. The dashed black line (+0 hrs) represents the predicted effect-size when no additional time is scheduled for therapy between treatment and control groups.

Table 1

Details of Regression Model 3.

	Parameter Estimate	95% Confidence Interval	Z-value	P-value
Intercept	0.2735	[0.09, 0.46]	2.85	.004
Yrs.PS (yrs)	0.0110	[−0.45, 0.47]	0.04	.963
$Yrs.PS^2$	0.0078	[−0.09, 0.11]	0.15	.879
ΔTime (10 hrs)	0.0344	[0.00, 0.07]	2.04	.041

Note. Parameter estimates for Yrs.PS in years and the estimates for ΔTime in 10-hour units. We tested the interaction of Yrs.PS and ΔTime, which was marginally significant ($p = 0.06$; $b = 0.027$), suggesting the effect of increased time in therapy was larger for later post-stroke times. This interaction was marginal and did not improve the fit of the model, so the main effects model is presented.

Table 2

Details of Regression Model 4.

	Parameter Estimate	95% Confidence Interval	Z-value	P-value
Intercept	0.1680	[−0.07, 0.41]	1.36	.172
Yrs.PS (yrs)	0.0338	[−0.43, 0.49]	0.14	.885
$Yrs.PS^2$	0.0022	[−0.10, 0.10]	0.04	.966
ΔTime (10 hrs)	0.0983	[0.01, 0.19]	2.07	.038
$\Delta Time^2$	−0.0047	[−0.01, 0.00]	−1.69	.089

Note. Parameter estimates for Yrs.PS in years and estimates for ΔTime in 10-hour units. We also tested the interaction of $Yrs.PS^2$ and $\Delta Time^2$, which was not significant ($p = 0.12$), so the main effects model is presented.