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Conflicts of Interest

We have no conflicts of interest to report.

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ABSTRACT

Objective: To investigate the efficacy of virtual reality (VR)- and gaming-based interventions for improving upper extremity function post-stroke, and to examine demographic and treatment-related factors that may moderate treatment response.

Data Sources: A comprehensive search was conducted within the PubMed, CINAHL/EBSCO, SCOPUS, Ovid MEDLINE and EMBASE databases for articles published between 2005 and 2019 (PROSPERO Registration number 95052).

Study Selection: Articles investigating gaming and VR methods of treatment for upper extremity weakness were collected with the following study inclusion criteria: 1) participants aged 18 or older with upper extremity deficits, 2) randomized controlled trials or prospective study design, 3) Downs-Black rating score of >= 18, and 4) outcome measure was the Wolf Motor Functioning Test (WMFT), the Fugl-Meyer (FM) or the Action Research Arm Test (ARAT).

Data Extraction: Thirty-eight articles met inclusion criteria. The primary outcome was proportional improvement on the WMFT, FM, or ARAT. The following individual or treatment factors were extracted: VR/gaming dose, total treatment dose, chronicity (> or < 6 months), severity of motor impairment, and presence of a gaming component.

Data analysis: Random effects meta-analysis models were utilized to quantify 1) the proportional recovery that occurs following VR/gaming, 2) the comparative treatment effect of

VR/gaming versus conventional physiotherapy, and 3) whether the benefit of virtual reality differed based on participant characteristics or elements of the treatment.

Results: On average, VR/gaming interventions produced an improvement of 28.5% of the maximal possible improvement. Dose and severity of motor impairment did not significantly influence rehabilitation outcomes. Treatment gains were significantly larger overall (10.8%) when the computerized training involved a gaming component versus just visual feedback. VR/gaming interventions showed a significant treatment advantage (10.4%) over active control treatments.

Conclusions: Overall, VR/gaming-based upper extremity rehabilitation post-stroke appears to be more effective than conventional methods. Further in-depth study of variables impacting improvement, such as individual motor presentation, treatment dose, and the relationship between the two, are needed.

Key Words: stroke, virtual reality, upper extremity, paresis

List of Abbreviations:

ARAT	Action Research Arm Test
WMFT	Wolf Motor Functioning Test
ICC	Intraclass Correlation Coefficient
VR	Virtual Reality
MAd R	Meta-Analysis with Mean Differences

Post	Post-test score
Pre	Pre-test score
Max	Best possible score on measure
RCT	Randomized Controlled Trial
PROSPERO	International Prospective Register of Systematic Reviews

Stroke has been identified as one of the leading causes of disability across the globe with estimates of over 17 million people experiencing a stroke each year worldwide and approximately 795,000 per year in the United States [1, 2, 3]. Additionally, mortality rates from stroke have decreased over the years due to improved medical interventions [4]. This has inevitably caused an increase in the number of people who now require targeted treatments for motor deficits that impact participation in everyday life activities [5, 6, 7, 8]. In addition, many individuals with stroke report several barriers to full engagement in rehabilitation, such as fatigue, low motivation, depression, lack of social support, and cost [9-11]. In the past two decades, researchers and clinicians have turned to virtual reality (VR) and gaming approaches to rehabilitation in an effort to address cost while increasing engagement [12].

VR for rehabilitation has been broadly defined over the past 2 decades of research and generally refers to the interaction of the user with a computer or mobile device simulation that “appears and feels similar to real-word objects and events” [13]. There are inherent differences between VR and conventional approaches. VR systems may delivery multi-sensory feedback (e.g., enhanced auditory and/or visual feedback) that is unavailable during traditional motor practice [14, 15], yet they oftentimes limit potentially beneficial tactile feedback because the person often acts on virtual objects [16-18]. Gaming-based VR interventions also inherently harness the concurrent benefits of task variability [19] and behaviorally-relevant training [20] by requiring a person to switch rapidly between motor movements in order to successfully navigate the virtual world. These differences warrant direct comparison of VR and conventional training approaches.

The level of interaction and immersion varies across VR systems. Some VR systems include a game element that has challenges, has an overall theme/objective (e.g., defend the net), and awards points for performance; others only include visual/auditory performance feedback during specific prompted exercises (e.g., shoulder abduction) [12]. Given the growing adoption of heterogeneous VR and gaming technologies for rehabilitation, it is important to establish how, and for whom, they can be most effectively applied in clinical practice. A recent meta-analysis of virtual reality interventions for stroke rehabilitation, shows initial promise of VR approaches [12]. Virtual reality-based and gaming-based interventions were shown to be approximately equally effective to other dose-matched modalities of upper extremity practice, and to provide a vehicle for further enhancing outcomes through additional practice [12]. Prior work emphatically states that more research is necessary and highlights heterogeneous findings between individual studies [12]. Person-specific factors (e.g., acute versus chronic hemiparesis, severity of hemiparesis, etc.) may account for some of the outcomes variability. Dosing may also play a role. Finally, elements of the training itself, for example the extent to which the system can engage an individual through gaming (versus only providing visual feedback), may influence outcomes. Accordingly, a recent initiative in the field of rehabilitation seeks to identify therapeutic “ingredients” that may moderate the effectiveness of interventions that on the surface may appear similar (i.e., utilize VR technology), but may vary substantially in their implementation and individual therapeutic components [21].

A thorough 2017 meta-analysis by Laver and colleagues examined how some of the aforementioned factors individually influenced outcomes (age, chronicity, higher versus lower dose, custom vs consumer-based system)[12]. However, at the time of that review, there were relatively few randomized controlled trials to include in each comparison. Accordingly, though some trends were observed in their data, none of these factors was found to show a statistically significant effect on outcomes.

This meta-analysis seeks to expand upon the prior work of Laver and colleagues by examining treatment factors that may account for the varying efficacy of virtual reality rehabilitation. To this end, this work includes an updated search and broader inclusion criteria to allow inclusion of 38 (versus 22) upper extremity studies. It also seeks to quantify the effectiveness of VR rehabilitation using an outcome metric (observed improvement as a fraction of the maximum possible improvement) that is both easy for clinicians to understand and addresses known sources of analytic bias/ measurement error [22].

METHODS

Design

This review was a meta-analysis of studies to examine the effectiveness of VR- and game-based interventions for upper extremity hemiparesis post-stroke. It followed PRISMA collaboration recommendations and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) #95052, accessible at [https://www.crd.york.ac.uk/prospero/].

Identification and Selection of Studies

The authors consulted with a professional librarian to review PubMed, CINAHL/EBSCO, SCOPUS, Ovid MEDLINE and EMBASE electronic databases for articles published from January of 2005 to May of 2019. The following search terms characterized the population: stroke, infarction, hemiparesis. The following keywords characterized the intervention: "upper extremity," arm, "upper limb", gaming, game, "virtual reality." The keyword "motor" was utilized to describe the outcome of interest. The full search strategy is detailed in Web Supplement 1. Articles were first screened for relevance via title/abstract review. Additional articles were identified by cross-referencing relevant review articles.

Inclusion criteria required that studies were prospective studies (including single group, cross-over, or randomized clinical/controlled trials) in stroke rehabilitation, were written in English, involved adult participants age 18 and up, had greater than 5 participants, were focused on upper limb rehabilitation exclusively, and used either the Wolf Motor Functioning Test (WMFT) [23], the Fugl-Meyer [24] or the Action Research Arm Test (ARAT) [25] as the primary outcome measure. For the purposes of this study, a stroke was defined as "rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours, with no apparent cause other than that of vascular origin'' [26].

Author, institution, year of publication, and journal name were then masked for articles meeting inclusion criteria prior to determining whether they met exclusion criteria. Articles scoring below 18/27 on the Downs-Black scale [27] were excluded outright due to overall poor quality (these failed to meet many of the reporting standards for clinical trials). Two independent reviewers utilized the Downs-Black rating scale [27] to assess each article's fitness for inclusion. When initial consensus was not reached between the two reviewers, the ratings were discussed amongst all co-authors until a consensus was reached. Intra-class correlation of initial ratings determined inter-rater reliability. Studies that focused the intervention on the lower limb, case reports with a sample size less than 6, or studies lacking the data elements necessary for meta-analysis (e.g., pre-treatment and post-treatment means and standard deviations) were also excluded.

Risk of Bias Assessment

Table 1 shows risk of bias of each study extracted from Downs-Black rating scale items [27] pertaining to method of selection, randomization, blinding of outcome assessors, and intent-to-treat analysis.

(Table 1)

Data Extraction

The intent of the authors was to utilize original study data for the meta-analysis. Authors of each original study were contacted via email and de-identified datasets were requested. The majority of the authors contacted did not respond and most that responded indicated that their dataset was not available. Therefore, it was necessary to utilize reported group averages to calculate a weighted treatment effect for each study. Proportional improvement was chosen as the dependent variable for the following reasons: 1) it has been used in systematic reviews of physical therapy interventions [28] to address ceiling effects [29] and eliminate a known source of analytic bias (greater overall improvement amongst those with greater impairment [30]), 2) it can reduce measurement error [31], 3) it enables comparing the magnitude of clinical change across studies that utilize different measures of motor function, 4) it is in keeping with prior work showing that the magnitude of clinical improvement is largely proportional to the initial deficit [32, 33], and 5) it is intuitive to clinicians. Proportional improvement was calculated using Formula 1.

$$(1)\ \%\Delta = (\text{Post-Pre})/(\text{Max-Pre})$$

Post is the mean score of the post-tests within a treatment group, Pre is the mean score of the pre-tests within a treatment group and Max is the best possible score (or normal performance in the case of the WMFT) [23] on any of the three measures used. In the case of a negative treatment change (worsening), the percent change was extracted according to Formula 2.

(2) $\%\Delta = [\text{Post-Pre}]/\text{Pre}$

For the sensitivity analysis regarding whether the benefit of virtual reality differed based on participant characteristics or elements of the study protocol, the acute versus chronic status of the study population (< or > 6 months post-stroke), severity of motor impairment, mean hours of treatment, mean total hours of study-related intervention, and whether gaming was included in the intervention were extracted from each study. The information extracted is summarized in Table 2.

(Table 2)

Data Analysis

A random effects meta-analysis model was used for all analyses [34] using the MAd R package to explore heterogeneity in the effect of VR by study-level characteristics. As some of the studies included in this review were identified as prone to bias, these analyses were repeated after excluding articles that did not meet at least 3 of the methodological standards from Table 1.

RESULTS

Flow of studies through the review

A total of 58,323 articles were identified from the initial search. After removing duplicates and screening title, year, and abstract, 71 articles were assessed for eligibility using the Downs-Black rating scale [27] which resulted in 11 exclusions. From the remaining 60 articles, another 22 were removed due to insufficient data for meta-analysis (e.g., missing means and/or standard deviations), leaving 38 articles for analysis (Figure 1). There was generally good agreement between the raters in overall score on the Downs-Black rating scale (ICC=0.775) amongst the included articles. The data extracted from the individual articles is presented in Table 3.

(Figure 1)

(Table 3)

Treatment effects of VR/gaming interventions

To facilitate inclusion of prospective studies, we initially examined the magnitude of improvement from the VR/gaming groups from all studies.[35-72] The estimated percent possible improvement across all studies was 28.45% (95% confidence interval of 24.40% to 32.49%). Figure 2 presents a forest plot summarizing the effects. The estimated I^2 value is 38.60% and Q value is 63.51 (p=0.001), reflecting significant heterogeneity between studies. A funnel plot is shown in Supplemental Figure 1.

(Figure 2)

(Supplemental Figure 1)

We explored if any of the following factors influenced response to VR/gaming interventions: 1) intervention type (gaming vs. feedback only), 2) VR/gaming dose, 3) total dose, 4) chronicity, and 5) stroke severity. Each comparison was considered separately and the results are presented in Table 4. Unsurprisingly, the percent possible improvement observed in chronic stroke studies was less than that found in acute stroke studies (difference = 12.82%, p = 0.003). Virtual interventions that included gaming tended to be more effective than those delivering feedback only (difference = 10.82%, p = 0.003).

(Table 4)

Comparative treatment effects of VR/gaming interventions versus conventional rehabilitation

To determine the comparative efficacy of VR/gaming interventions, and whether the comparative efficacy depended on any of the aforementioned characteristics, the 29 multi-arm studies with an active comparator were analyzed. The active comparator arm varied across studies. A few only stated "conventional/traditional occupational therapy" with no further description of activities included [49, 54, 65]. Some included a comparator treatment based on task-oriented rehabilitation or task-related practice theories [35, 39, 42]. Most studies included a description of “traditional rehabilitation” that was based on recovery models such as Bobath and Neurodevelopmental Treatment (NDT) and included a variety of stretching, strengthening, and ADL-focused activities [42, 43, 46, 51, 52, 55, 56, 60, 61, 67, 70]. Overall, VR/gaming interventions produced larger proportional recovery than conventional rehabilitation (difference = 10.4%, confidence interval: 5.65%-15.14%). The estimated I^2 value is 0.00% and the Q value is 23.17 (p=0.534; Supplemental Figure 2). Figure 3 shows a forest plot summarizing the comparative effectiveness of VR/gaming to conventional rehabilitation. Again, we examined whether heterogeneity in comparative treatment effects could be explained by any of the following factors: 1) intervention type (gaming vs. visual feedback only), 2) VR/gaming dose, 3) total dose, 4) stroke severity, and 5) chronicity. None of the above treatment variables significantly influenced the *comparative* treatment effect (Table 5).

(Figure 3)

(Table 5)

(Supplemental Figure 2)

Influence of bias

When excluding articles with a higher risk of bias, the treatment effect sizes were similar. This suggests that the results of this meta-analysis are unlikely to be influenced by study bias (Web Supplement 2- Supplemental Tables 1 and 2 and Supplemental Figures 3-6).

Analysis of Follow-up Data

Follow-up data was not included in the meta-analysis because it was only recorded in half of the studies and there was substantial heterogeneity in the follow-up intervention (2 to 26 weeks) amongst those studies. When examined descriptively, the 19 studies with follow-up data showed complete retention of most treatment gains obtained via VR rehabilitation (median increase in proportional recovery of 3.63% over the follow-up period with a range of -14.28% to 23.45%).

DISCUSSION

The objective of this meta-analysis was to determine the impact of gaming and virtual reality-based interventions for improving upper extremity function post-stroke. The observed percent possible improvement for the VR/gaming groups across all studies was almost 29%, which is consistent with other upper extremity studies [73, 74]. Studies within both the acute and chronic stroke population showed a positive effect of VR/gaming rehabilitation on motor function, with significantly greater motor recovery occurring in acute/sub-acute (<6 month) stroke studies, a time period in which rehabilitation-induced improvements co-occur with spontaneous recovery. It is well established that the majority of motor recovery occurs within the first few months (i.e., 3 to 6 months) [75-78]. However, this meta-analysis shows that substantial recovery is still possible within the chronic phase post-stroke (Figure 2) and is typically well-maintained over time. Cauraugh and Summers [79] have attributed continued recovery of upper extremity motor functioning in chronic stroke patients to neuroplasticity. Specifically, these authors suggest that a) “motor neuron disinhibition” allows for use of spared pathways of the damaged region, b) ipsilateral pathways begin to be utilized and c) “upregulation of descending premotorneuron commands onto propriospinal neurons” play a large role in recovery with chronic stroke patients [79].

When VR/gaming interventions were compared to conventional rehabilitation approaches, the literature significantly favored VR/gaming. The comparative treatment effect was small, with the observed difference in percent possible change between VR/gaming and conventional treatment groups under 11%, which is estimated at roughly half of the minimally clinically important difference for a typical participant on the outcome measures employed. The difference between VR/gaming and conventional treatment groups equates to 38% of the typical treatment response to VR/gaming. Recent studies [80, 81] have suggested that gaming interventions, in particular, are superior to traditional treatment as they can increase motivation via goal orientation and extrinsic rewards. This idea is supported by our finding that gaming interventions produced significantly greater treatment effects than virtual reality interventions that lacked a gaming aspect. By eliminating the need for task set-up, gaming interventions also enable rapid alternation in task demands and complexity, a therapeutic factor that has been associated with superior retention of gains [82]. This amount of meaningful clinical change and long-term maintenance of clinical gains lends excellent support for VR/gaming-based approaches over conventional approaches in clinical settings (physical therapy, occupational therapy). Additionally, more repetitions of movement can be achieved. Although the literature remains equivocal as to whether higher intensity (repetitions per time) improves outcomes, [83, 84] it is likely that some degree of repetition is necessary to facilitate motor learning, particularly when paired with implicit feedback (i.e., knowledge of results) [85]. Finally, it is possible that use of an avatar can prime the motor system to respond more favorably to motor training, similar to mirror training or action-observation therapies [86-88]. In sum, VR gaming is a viable, cost-efficient rehabilitation option that conveys some slight advantages over more conventional approaches.

Contrary to expectation, interventions incorporating higher doses did not yield significantly greater treatment effects on average. It should be noted that the absence of studies involving very high doses might produce a restricted-range challenge for this analysis. With regard to dose, recent meta-analyses of the effect of constraint-induced movement therapy after stroke suggest that severity of the post-stroke symptoms often serves as a confounder when studying the effects of dose [89]. Across interventions, the effects of dose on treatment outcomes have been mixed [84, 90-9581-85]. This inconsistency may be due to the markedly variable patterns of dose-response trajectories between individuals, with some showing a plateau in function prior to the end of treatment, while the majority showed positive improvement trajectories at the end of treatment of varying slope (suggesting that they would continue to benefit from different amounts of additional therapy) [95]. Thus, the effects of dose are likely multifactorial and further studies are required to allow for a better understanding of the circumstances under which increasing the dose conveys benefit.

Study Limitations

This meta-analysis has a few limitations. The authors reached out to the corresponding authors of the articles included in the study, and none volunteered raw data. Many of these studies were conducted outside of the United States which, at times, made communication difficult (e.g., e-mails did not go through due to foreign government prohibitions). Without raw data for analysis, the analysis was limited to what was reported in the original publications. As a result, the authors had to rely on summary statistics for analysis, and participant-level effects could not be examined. The methodological rigor of the majority of studies was low to moderate. Additionally, all the studies included within this article did not collect the same endpoints or outcomes. To address this constraint, percent possible improvement served as a common measure for inclusion of all studies in the meta-analysis.

Conclusions

Overall, gaming and VR methods of treatment are effective, closing on average 28.45% of the gap between baseline function and normal motor ability. VR/gaming interventions were more effective than active treatment controls, but the comparative treatment effect was small. Interventions employing a gaming component are more effective overall than those that merely deliver feedback. Future research should involve large-scale randomized controlled studies with high methodological rigor [96] that examine both upper extremity motor function and impact on daily life (e.g., arm use, quality of life, participation). Further, the authors recommend utilizing the data-capture capabilities of these systems for longitudinal investigations that shed light on individual factors related to dose-response. Finally, we recommend future studies examine cost-effectiveness, the relationship between individual motor presentation, the treatment doe required to attain maximum possible improvement, and methods for implementation of gaming/VR treatments.

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Suppliers:

a. Meta-Analysis with Mean Differences (MAd R; Version 0.8-2.1).

b. Statistical Package for the Social Sciences (SPSS; Version 20).

Figure Legends

Figure 1: Flow chart of article selection and exclusion.

Figure 2: Forest plot summarizing the treatment change for the VR/gaming arms of each study. The square icons represent the percent possible improvement estimates extracted from each study. Those with larger squares were weighted more strongly in the calculation of the overall treatment effect. Those located to the right of the vertical dashed line had larger treatment effects. The horizontal lines reflect the 95% confidence interval for the treatment change.

Figure 3: Forest plot summarizing the comparative effectiveness of VR/gaming versus conventional rehabilitation. The square icons represent the difference in percent possible improvement between the VR/gaming and control groups. Those located to the right of the vertical dashed line had larger treatment effects for the VR/gaming groups than the control group. Those with larger squares were weighted more strongly in the calculation of the overall treatment effect. The horizontal lines reflect the 95% confidence interval for the treatment change.

Table 1. Quality standards fulfillment and risk of bias for all articles included in the meta-analysis

Author	Year	Representative Sample	Random group assignment	Blinded outcome assessor	Intent-to-treat analysis
Adie et al.	2016	+	+	+	+
Ballester et al.	2016	+	+	+	-
Boone et al.*	2019	+	-	-	-
Borstad et al.	2018	+	-	+	+
Brunner et al.	2017	+	+	+	-
da Silva Cameirao et al.	2011	+	+	+	-
Chen et al.	2015	-	+	+	-
Choi et al.	2016	+	+	+	+
Colomer et al.*	2016	-	-	+	+
Combs et al.*	2012	-	-	-	+
Connelly et al.*	2010	+	-	+	-
Crosbie et al.	2012	+	+	+	-
Givon et al.	2016	-	+	+	+
Jang et al.	2005	-	+	+	+
Jo et al.*	2012	-	-	+	-
dos Santos Junior et al.	2019	+	+	+	-
Kiper et al.*	2011	-	-	+	+
Kiper et al.*	2014	-	-	-	+
Kipper et al.	2018	+	+	+	+
Kong et al.	2016	-	+	+	+
Kwon et al.*	2013	-	+	+	-
Lee et al.	2014	+	+	+	+
Levin et al.	2012	+	+	+	+
Oh et al.	2019	+	+	+	-
Park et al.	2016	-	+	+	+
Piron et al.	2009	-	+	+	+
Piron et al.	2010	-	+	+	+
Rand et al.	2016	+	+	+	+
Reinthal et al.*	2012	-	-	+	-
Saposnik et al.	2016	+	+	+	+
Shin et al.	2014	+	+	+	-
Shiri et al. *	2012	+	-	-	+
Sin et al.	2013	+	+	+	-
Thielbar et al.	2014	+	+	+	-
Tsoupikova et al.*	2015	+	-	-	-
Turolla et al.*	2013	-	+	-	-
Wang et al.	2017	+	+	+	+
Weber et al.*	2019	-	-	-	-

+ : quality standard met - : quality standard not met
*higher risk of bias (≥2/4 standards not met)

Table 2
Relevant variables extracted from and calculated for each included study

Variable	Variable Type	Description
Severity	Dichotomous	
Mild		Fugl-Meyer Score > 40
Moderate		Fugl-Meyer Score <40
Chronicity	Categorical	
Acute/Subacute		< 6 months post-stroke
Chronic		> 6 months post-stroke
Mixed		Mixed chronicity
N	Continuous	Study sample size, all participants
nVR	Continuous	VR group sample size
VR Dose	Continuous-calculated	Total number of minutes of VR treatment
Total Dose	Continuous-calculated	The number of hours of treatment plus additional hours of other forms of therapy provided to the treatment group.
x̄preVR	Continuous	Mean of primary UE motor function outcome forVR group pre-treatment
SDpreVR	Continuous	VR treatment group standard deviation pre-treatment
x̄postVR	Continous	Mean of primary UE motor function outcome for VR group post-treatment
SDpostVR	Continuous	VR treatment group standard deviation post-treatment
x̄ΔVR	Continuous-calculated	Mean change on primary UE motor function outcome (post-pre) for VR treatment group
nControl	Continuous	Control/Comparison group sample size
Dose-matching	Dichotomous	Was the control group treatment dosage matched to the VR group? (yes/no)
x̄preControl	Continuous	Mean of primary UE motor function outcome for control group pre-treatment
SDpreControl	Continuous	Control group standard deviation pre-treatment
x̄postControl	Continuous	Mean of primary UE motor function outcome for control

		group post-treatment
SDpostControl	Continuous	Control group standard deviation post-treatment
x̄ΔControl	Continuous-calculated	Mean change on primary UE motor function outcome (post-pre) for Control group

Table 3: Summary of the characteristics of the studies included in the meta-analysis

Authors	Year	n	Chronicity	Gaming	Dose VR (hrs)	Mean (SD) VR T0	Mean (SD) Control T0	Mean (SD) VR Post	Mean (SD) Control Post	Total Dose (hrs)	% possible improvement
Adie et al. [35]	2017	117	Acute	Yes	31.5	41.2 (15.9)	41 (16.6)	47.6 (14.2)	50 (13.6)	42	41
Ballester et al. [36]	2016	12	Chronic	Yes	15	32.33 (16.09)	36.89 (12.29)	38.33 (17.30)	43.22 (12.6)	15	18
Boone et al. [37]	2019	10	Chronic	Yes	24	34.5 (10.6)		42.7 (10.4)		36	26
Borstad et al. [38]	2018	16	Chronic	Yes	30	22.4 (9.3)		28.1 (11.4)		135	38
Brunner et al. [39]	2017	112	Acute	Yes	16	25.8 (18.13)	24.2 (18.6)	37.7 (19.5)	38.14 (18.8)	16	38
da Silva Cameirao et al. [40]	2011	8	Acute	No	12	37.9 (12.1)	24.4 (11.4)	62 (30.8)	55.6 (22.1)	12	86
Chen et al. [41]	2015	24	Mixed*	Yes	10	37.1 (19.2)	27 (6.9)	52.1 (11.4)	27.94 (4.5)	11	52
Choi et al. [42]	2016	24	--*	Yes	5	24.5 (22.2)	21.5 (20.6)	43.58 (--)	21.73 (--)	10	45
Colomer et al. [43]	2016	30	Chronic	No	22.5	53.9 (15.7)		48.1 (15.7)		45	11
Combs et al. [44]	2012	9	Chronic	Yes	9	6.2 (54.8)		6.9 (42.8)		9	-15
Connelly et al. [45]	2010	14	Chronic	No	18	38.4 (4.5)		43.1 (4.6)		18	17
Crosbie et al. [46]	2012	18	Chronic	No	--	51.3 (8.2)	47.3 (18.1)	52.8 (6.9)	29.89 (18.9)	5.6	26
Givon et al. [47]	2016	24	Chronic	Yes	14.6	28.5 (23.2)	21.9 (22.4)	28.4 (23.1)	23.7 (24)	14.6	-0.35
Jang et al. [48]	2005	6	Chronic	Yes	30	51 (3.2)	52.6 (2.0)	58 (2.8)	55 (1.7)	20	47

Jo et al. [49]	2012	15	--*	Yes	20	40.1 (22.4)	44.5 (13.6)	36.4 (21.1)	42.8 (13.1)	20	10
dos Santos Junior et al. [50]	2019	11	Chronic	Yes	10.64	38.9 (23.2)	30.8 (	43.8 (23.7)	33.8 (24.7)	10.64	18
Kiper et al. [51]	2011	80	Chronic	No	20	39.1 (17)	44.8 (17.4)	48.9 (15.2)	46.4 (17.1)	20	36
Kiper et al. [52]	2014	23	Chronic	No	40	43.0 (14.7)	46.3 (17.5)	49.8 (12.5)	49.5 (16.2)	40	29
Kiper et al. [53]	2018	68	Chronic	No	20	37.99 (17.76)	43.15 (17.21)	47.71 (15.74)	46.29 (17.25)	40	35
Kong et al. [54]	2016	32	Acute	Yes	12	14.6 (12.6)	18 (14.4)	32.8 (18.2)	25.62 (17.8)	12	35
Kwon et al. [55]	2012	13	Acute	Yes	10	60.31 (5.41)	56.38 (10.83)	62.92 (3.45)	56.86 (4.54)	23.3	46
Lee et al. [56]	2014	12	Chronic	No	10	16.33 (8.33)	19.83 (10.63)	20.33 (9.94)	21.83 (11.27)	30	8
Levin et el. [57]	2012	6	Chronic	Yes	6.75	40.1 (13.6)	42.3 (13.6)	47.3 (11.9)	44.9 (11.7)	6.75	27
Oh et al. [58]	2019	17	Chronic	No	9	37.6 (	36.5 (17.8)	39.5 (15.1)	38.6 (18.5)	9	7
Park et al. [59]	2016	15	Chronic	Yes	10	49.3 (1.2)	48.9 (1.4)	54.4 (1.9)	53.1 (2.4)	10	30
Piron et al. [60]	2009	18	Chronic	No	30	48.5 (7.8)	47.3 (4.6)	53.6 (7.7)	49.5 (4.8)	20	29
Piron et al. [61]	2010	27	Chronic	No	20	42.4 (11.3)	43.9 (9.7)	49.7 (10.1)	46.5 (9.7)	20	30
Rand et al. [62]	2016	13	Chronic	Yes	30	32.1 (18.8)	43.8 (16.8)	36 (19.3)	46.1 (16.7)	18.8	16
Reinthal et al. [63]	2012	16	Mixed*	Yes	8.3	41 (39)		30 (39)		8.3	28
Saposnik et al. [64]	2016	59	Acute	Yes	10	91.9 (122.3)	68.4 (101.2)	64.1 (104)	39.8 (35.5)	10	32
Shin et al. [65]	2014	9	Acute	Yes	3.3	39.4 (10.7)	34.4 (12.4)	51.1 (7.8)	40.7 (9.8)	1.6	44

Shiri et al. [66]	2012	6	Chronic	No	7.5	35.5 (12.07)		43.17 (13.55)		7	25
Sin et al. [67]	2013	35	Chronic	Yes	9	26.06 (15.81)	32.29 (20.43)	47.72 (15.34)	34.59 (20.72)	18	54
Thielbar et al. [68]	2014	7	Chronic	Yes	18	48.7 (9.6)	41.9 (1.9)	50.4 (10.4)	43.6 (8.1)	18	10
Tsoupikova et al. [69]	2015	6	Chronic	Yes	18	40.7 (9.2)		41.7 (9.3)		18	4
Turolla et al. [70]	2013	263	Mixed*	No	20	41.7 (16.1)	41.1 (17.6)	48.2 (15.2)	44.1 (17.3)	40	27
Wang et al. [71]	2017	13	Acute	Yes	15	4.58 (0.80)	5 (0.87)	3.29 (0.82)	4.24 (0.57)	30	43
Weber et al. [72]	2019	10	Chronic	No	6	21.7 (8.68)		22.8 (9.19)			6

n = number of participants in the VR group; T0 = baseline; Post = post-treatment; Dose VR = number of hours participants were engaged in VR; * not included in analysis of that variable; -- missing information; means and standard deviations are reported for the relevant outcome measure (Fugl-Meyer, Wolf Motor Function Test, Action Research Arm Test).

Table 4
Estimated effects and 95% confidence intervals of each study-level covariate on percent possible improvement from the random effects meta-regression on gaming/VR articles.

Effect	Estimate	95% CI	p-value
Gaming	10.82	(3.78, 17.86)	0.003*
Dose VR	-0.06	(-0.72, 0.59)	0.851
Dose Total	0.08	(-0.17, 0.33)	0.528
Chronic	-12.82	(-21.16, -4.47)	0.003*
Mild	3.23	(-4.95, 11.41)	0.439

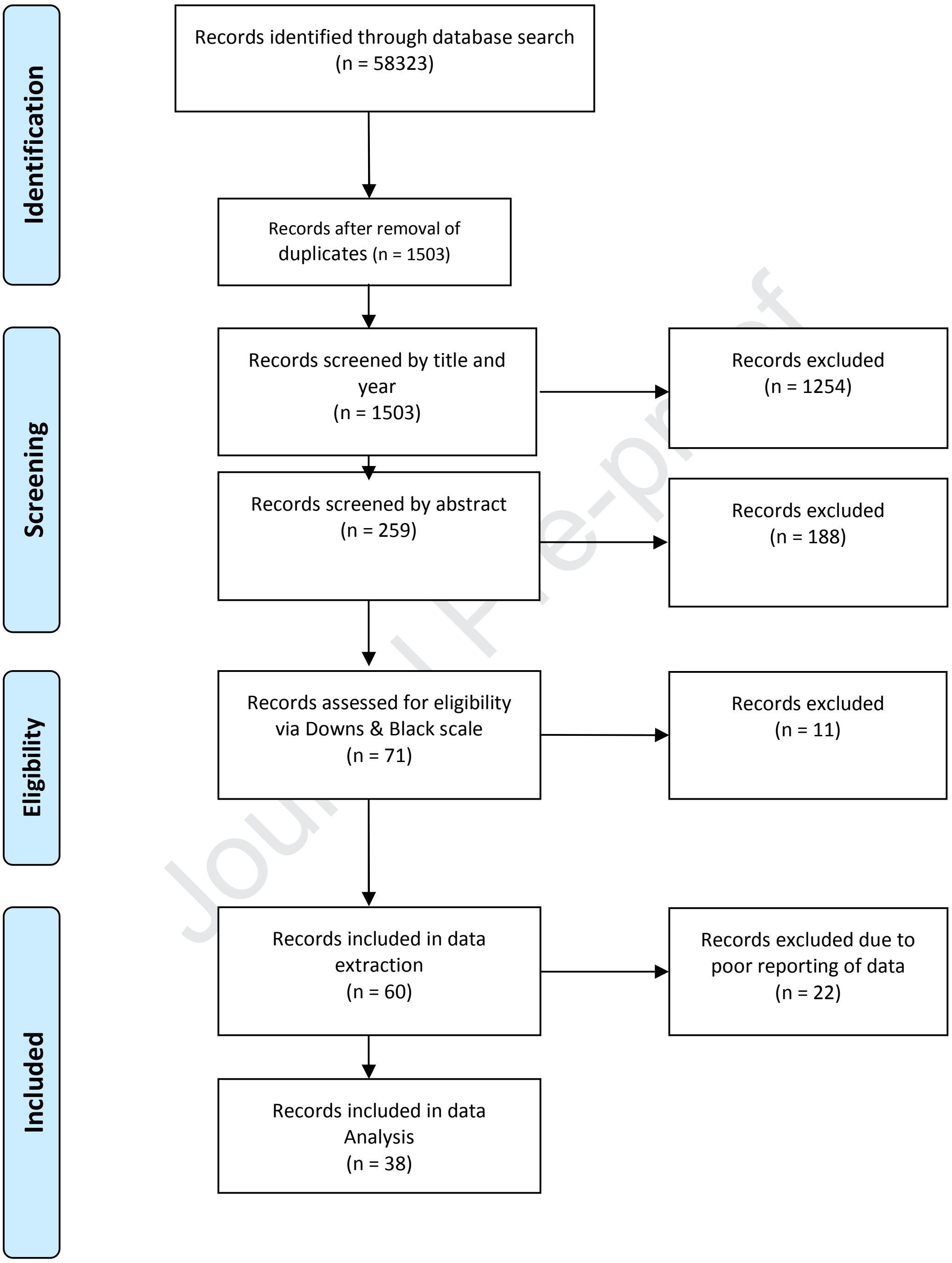
*$p < 0.05$
CI = confidence interval

Table 5
Estimated effects and 95% confidence intervals of each study-level covariate on the effect of intervention on percent possible improvement from random effects meta-regression on the comparative treatment effects of VR/gaming groups v. control groups.

Effect	N	Estimate	95% CI	p-value
Gaming	28	-8.80	(-19.33, 1.72)	0.101
Dose VR	28	-0.26	(-1.07, 0.54)	0.522
Dose Total	28	0.12	(-0.29, 0.53)	0.574
Chronic	26	3.26	(-7.08, 13.61)	0.537
Mild	28	-0.52	(-10.29, 9.25)	0.917

CI = confidence interval

Figure 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2

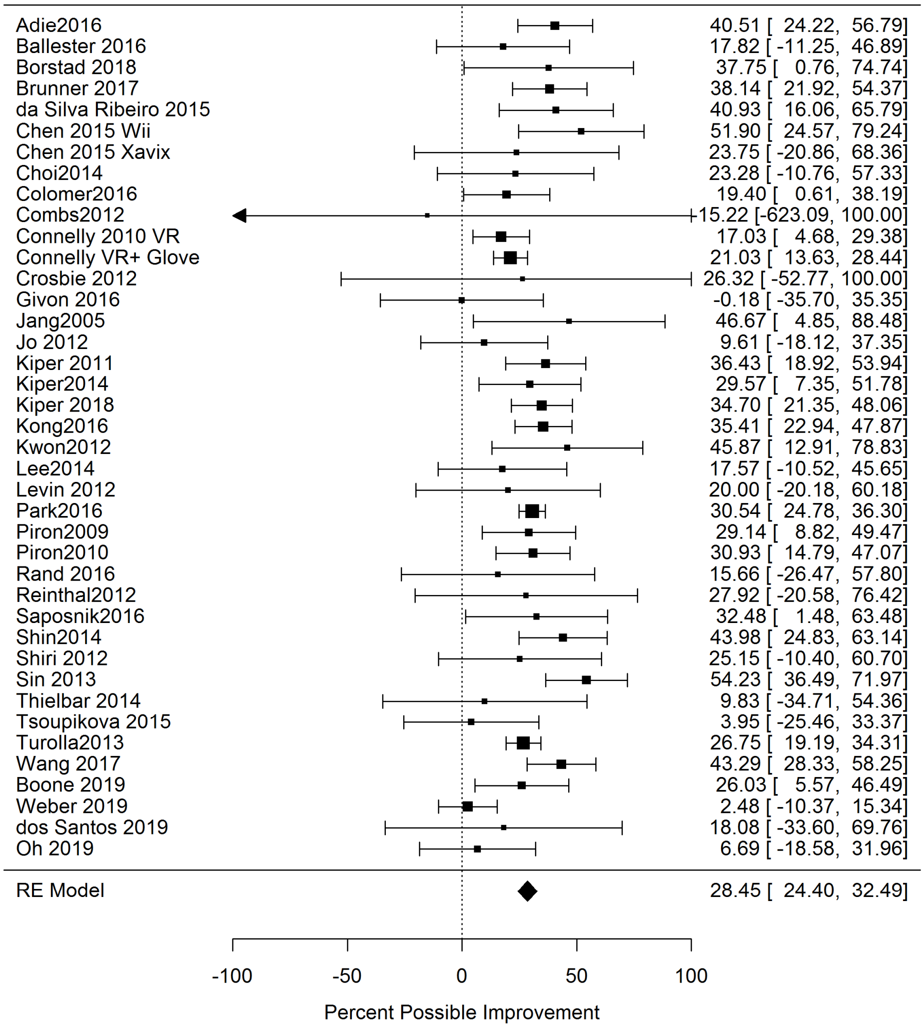
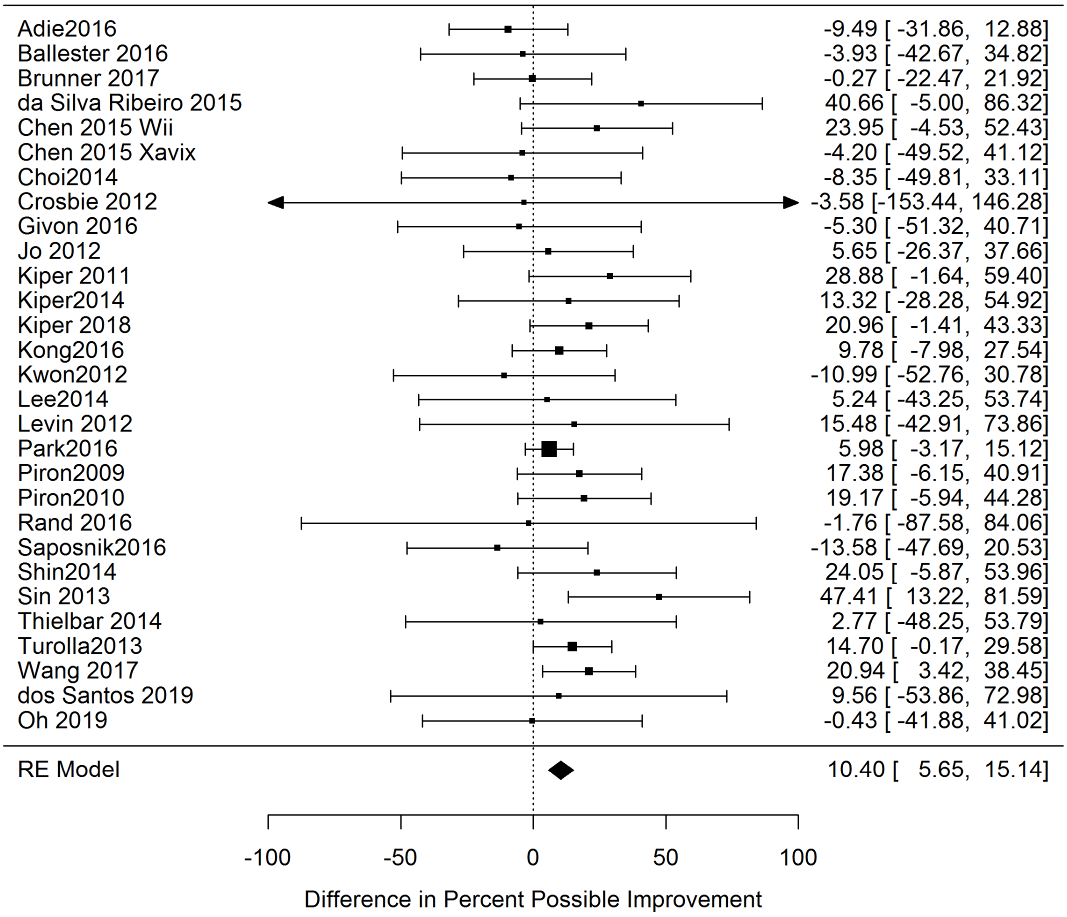

Adie2016 40.51 [24.22, 56.79]
Ballester 2016 17.82 [-11.25, 46.89]
Borstad 2018 37.75 [0.76, 74.74]
Brunner 2017 38.14 [21.92, 54.37]
da Silva Ribeiro 2015 40.93 [16.06, 65.79]
Chen 2015 Wii 51.90 [24.57, 79.24]
Chen 2015 Xavix 23.75 [-20.86, 68.36]
Choi2014 23.28 [-10.76, 57.33]
Colomer2016 19.40 [0.61, 38.19]
Combs2012 -15.22 [-623.09, 100.00]
Connelly 2010 VR 17.03 [4.68, 29.38]
Connelly VR+ Glove 21.03 [13.63, 28.44]
Crosbie 2012 26.32 [-52.77, 100.00]
Givon 2016 -0.18 [-35.70, 35.35]
Jang2005 46.67 [4.85, 88.48]
Jo 2012 9.61 [-18.12, 37.35]
Kiper 2011 36.43 [18.92, 53.94]
Kiper2014 29.57 [7.35, 51.78]
Kiper 2018 34.70 [21.35, 48.06]
Kong2016 35.41 [22.94, 47.87]
Kwon2012 45.87 [12.91, 78.83]
Lee2014 17.57 [-10.52, 45.65]
Levin 2012 20.00 [-20.18, 60.18]
Park2016 30.54 [24.78, 36.30]
Piron2009 29.14 [8.82, 49.47]
Piron2010 30.93 [14.79, 47.07]
Rand 2016 15.66 [-26.47, 57.80]
Reinthal2012 27.92 [-20.58, 76.42]
Saposnik2016 32.48 [1.48, 63.48]
Shin2014 43.98 [24.83, 63.14]
Shiri 2012 25.15 [-10.40, 60.70]
Sin 2013 54.23 [36.49, 71.97]
Thielbar 2014 9.83 [-34.71, 54.36]
Tsoupikova 2015 3.95 [-25.46, 33.37]
Turolla2013 26.75 [19.19, 34.31]
Wang 2017 43.29 [28.33, 58.25]
Boone 2019 26.03 [5.57, 46.49]
Weber 2019 2.48 [-10.37, 15.34]
dos Santos 2019 18.08 [-33.60, 69.76]
Oh 2019 6.69 [-18.58, 31.96]
RE Model 28.45 [24.40, 32.49]
-100
-50
0
50
100
Percent Possible Improvement

Figure 3


Adie2016 -9.49 [-31.86, 12.88]
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Brunner 2017 -0.27 [-22.47, 21.92]
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Chen 2015 Wii 23.95 [-4.53, 52.43]
Chen 2015 Xavix -4.20 [-49.52, 41.12]
Choi2014 -8.35 [-49.81, 33.11]
Crosbie 2012 -3.58 [-153.44, 146.28]
Givon 2016 -5.30 [-51.32, 40.71]
Jo 2012 5.65 [-26.37, 37.66]
Kiper 2011 28.88 [-1.64, 59.40]
Kiper2014 13.32 [-28.28, 54.92]
Kiper 2018 20.96 [-1.41, 43.33]
Kong2016 9.78 [-7.98, 27.54]
Kwon2012 -10.99 [-52.76, 30.78]
Lee2014 5.24 [-43.25, 53.74]
Levin 2012 15.48 [-42.91, 73.86]
Park2016 5.98 [-3.17, 15.12]
Piron2009 17.38 [-6.15, 40.91]
Piron2010 19.17 [-5.94, 44.28]
Rand 2016 -1.76 [-87.58, 84.06]
Saposnik2016 -13.58 [-47.69, 20.53]
Shin2014 24.05 [-5.87, 53.96]
Sin 2013 47.41 [13.22, 81.59]
Thielbar 2014 2.77 [-48.25, 53.79]
Turolla2013 14.70 [-0.17, 29.58]
Wang 2017 20.94 [3.42, 38.45]
dos Santos 2019 9.56 [-53.86, 72.98]
Oh 2019 -0.43 [-41.88, 41.02]
RE Model 10.40 [5.65, 15.14]
-100
-50
0
50
100
Difference in Percent Possible Improvement

Supplement 1: Search Strategy and Search Terms for Each Database Used in the Meta-Analysis

Database: Scopus

Date of Search: 04/30/2019

Number of Results Returned: 191

Search Terms and Strategy: (TITLE-ABS-KEY ("video game" OR "video games" OR gaming OR game OR games OR "virtual reality" OR wii OR "Nintendo Wii" OR "Wii based movement therapy" OR "virtual rehabilitation") AND TITLE-ABS-KEY (stroke OR strokes OR infarction OR infarctions) AND TITLE-ABS-KEY (hemiparesis OR paresis) AND TITLE-ABS-KEY ("Upper extremity" OR "Upper limb" OR shoulder OR arm OR elbow OR forearm OR hand OR wrist OR fingers OR thumb)) AND PUBYEAR > 2004 AND PUBYEAR < 2020 AND (LIMIT-TO (LANGUAGE , "English"))

Database: Ovid MEDLINE

Date of Search: 04/30/2019

Number of Results Returned: 96

Search Terms and Strategy:

#	**Searches**
1	Video Games/
2	virtual reality/
3	(video game or video games or gaming or game or games or virtual reality or Wii or Nintendo Wii or Wii based movement therapy or virtual rehabilitation).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	or/1-3
5	exp Stroke/
6	Stroke Rehabilitation/
7	(Stroke or strokes or infarction or infarctions).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	or/5-7
9	Paresis/
10	(Hemiparesis or paresis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11	or/9-10
12	exp Upper Extremity/
13	(Upper extremity or Upper limb or Shoulder or Arm or Elbow or Forearm or Hand or Wrist or Fingers or Thumb).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14	or/12-13
15	and/4,8,11,14
16	remove duplicates from 15
17	limit 16 to (english language and yr="2005 - 2019")

Database: CINAHL EBSCO

Date of Search: 04/30/2019

Number of Results Returned: 39

Search Terms and Strategy:

#	Query
S13	S3 AND S8 AND S9 AND S12
S12	S10 OR S11
S11	Upper extremity OR Upper limb OR Shoulder OR Arm OR Elbow OR Forearm OR Hand OR Wrist OR Fingers OR Thumb
S10	(MH "Upper Extremity") OR (MH "Arm") OR (MH "Axilla") OR (MH "Elbow") OR (MH "Forearm") OR (MH "Hand") OR (MH "Fingers") OR (MH "Wrist") OR (MH "Shoulder")
S9	Hemiparesis OR paresis
S8	S4 OR S5 OR S6 OR S7
S7	Stroke OR strokes OR infarction OR infarctions
S6	(MH "Stroke Patients")
S5	(MH "Infarction")
S4	(MH "Stroke") OR (MH "Stroke, Lacunar")
S3	S1 OR S2
S2	video game OR video games OR gaming OR game OR games OR virtual reality OR Wii OR Nintendo Wii OR Wii based movement therapy OR virtual rehabilitation
S1	(MH "Video Games") OR (MH "Exergames") OR (MH "Virtual Reality")

Web Supplement 2

When repeating the same analyses after excluding articles at highest risk of bias, the effect sizes were similar. The analyses performed on just those studies at lower risk of bias are reported below.

Effects of bias on treatment effects of VR/gaming interventions for lower bias studies

VR/gaming interventions produced an estimated improvement of 31.78% of the maximum possible improvement on tests of upper extremity function. The forest plot summarizing these effects is shown in Supplemental Figure 3.

The estimated I^2 value is 39.72%, which means that approximately 40% of the variability is due to study heterogeneity. The Q value of 43.14 (p=0.019) indicates significant heterogeneity (Supplemental Figure 4).

The estimated percent possible improvement for studies that included chronic participants was less than those that include acute participants only (difference = -9.64%, p =0.066; Supplemental Table 1).

Supplemental Table 1: Results of the sensitivity analysis examining how population- and intervention-related factors influence the overall treatment response to VR/gaming. **"**Estimate" refers to the regression coefficient of the linear model. For dichotomous variables (i.e., Gaming, Chronic, Mild), “Estimate” reflects the difference between categories (e.g., chronic versus acute). “Difference” reflects the Difference in Estimates between the full sample and the lower bias studies. * Indicates p<.05 in the full analysis.

Effect	Estimate	95% CI	p-value
Gaming	12.88	(2.28, 23.48)	0.017*
Dose VR	0.24	(-0.54, 1.02)	0.550*
Dose Total	0.15	(-0.13, 0.43)	0.295
Chronic	-9.64	(-19.91, 0.64)	0.066*
Mild	0.83	(-10.56, 12.21)	0.887

Effects of bias on comparative treatment effects of VR/gaming interventions versus conventional rehabilitation for lower bias studies

For this analysis, the subset of multi-arm studies with an active comparator that were rated at lower risk of bias was analyzed. Overall, the estimated effect of VR/gaming compared to conventional rehabilitation on percent possible improvement across all studies was 9.90%, with 95% confidence interval of (4.64%, 15.17%). A forest plot summarizing the effects is below (Supplemental Figure 5).

The estimated I^2 value is 0.00%, which means that approximately 0% of the variability is due to study heterogeneity (Supplemental Figure 6).

As with the full sample, the comparative treatment effect did not appear to be strongly influenced by characteristics of the study participants or factors related to the intervention (Supplemental Table 2).

Supplemental Table 2: Results of the sensitivity analysis examining how population- and intervention-related factors influence the comparative efficacy of VR/gaming versus an active comparator intervention. Estimate refers to the regression coefficient of the linear model. For dichotomous variables (i.e., Gaming, Chronic, Mild), "Estimate" reflects the difference between categories (e.g., chronic versus acute). "Difference" reflects the Difference in Estimates between the full sample and the lower bias studies. * Indicates p<.05 in the full analysis.

Effect	Estimate	95% CI	p-value
Gaming	-9.72	(-23.99, 4.56)	0.182
Dose VR	-0.39	(-1.28, 0.49)	0.380
Dose Total	0.07	(-0.46, 0.59)	0.807
Chronic	1.91	(-8.77, 12.59)	0.726

Mild	-2.72	(-13.36, 7.92)	0.617

Figure Legends:

Supplemental Figure 1: Funnel plot of the pre- to post-treatment response for the VR/gaming groups (n=36).

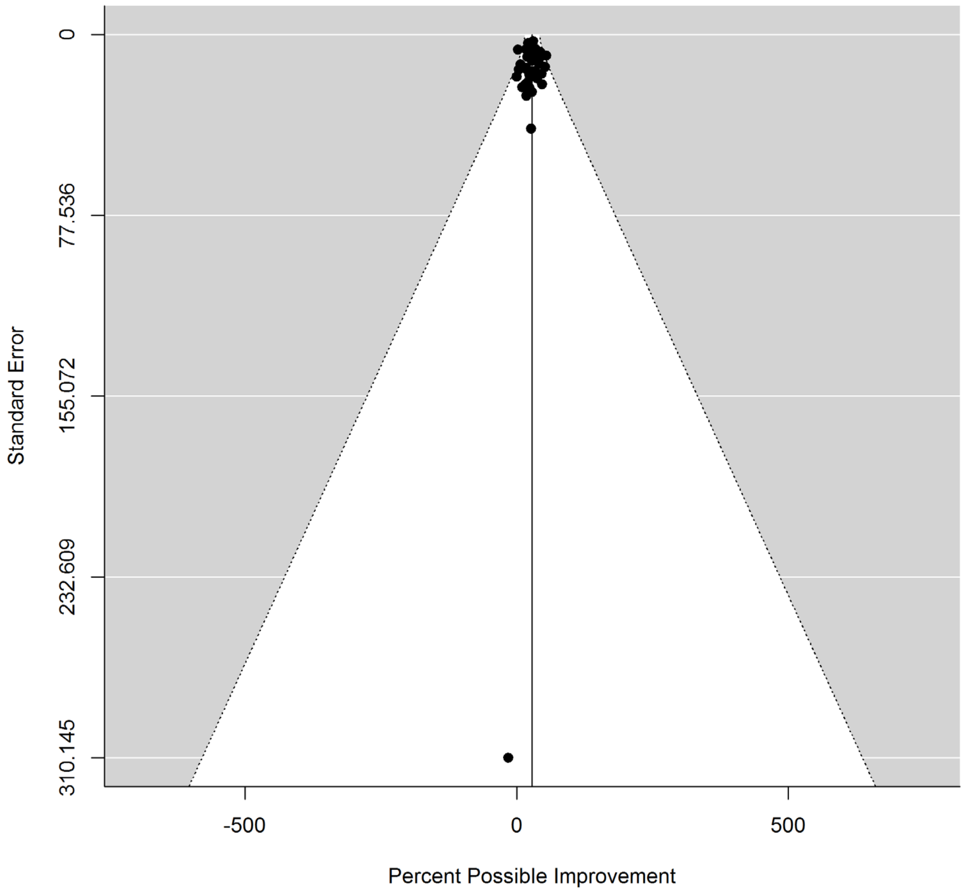
Supplemental Figure 2: Funnel plot of the comparative treatment effect (difference in the percent possible improvement between treatment and control groups) in the 27 studies with a control group.

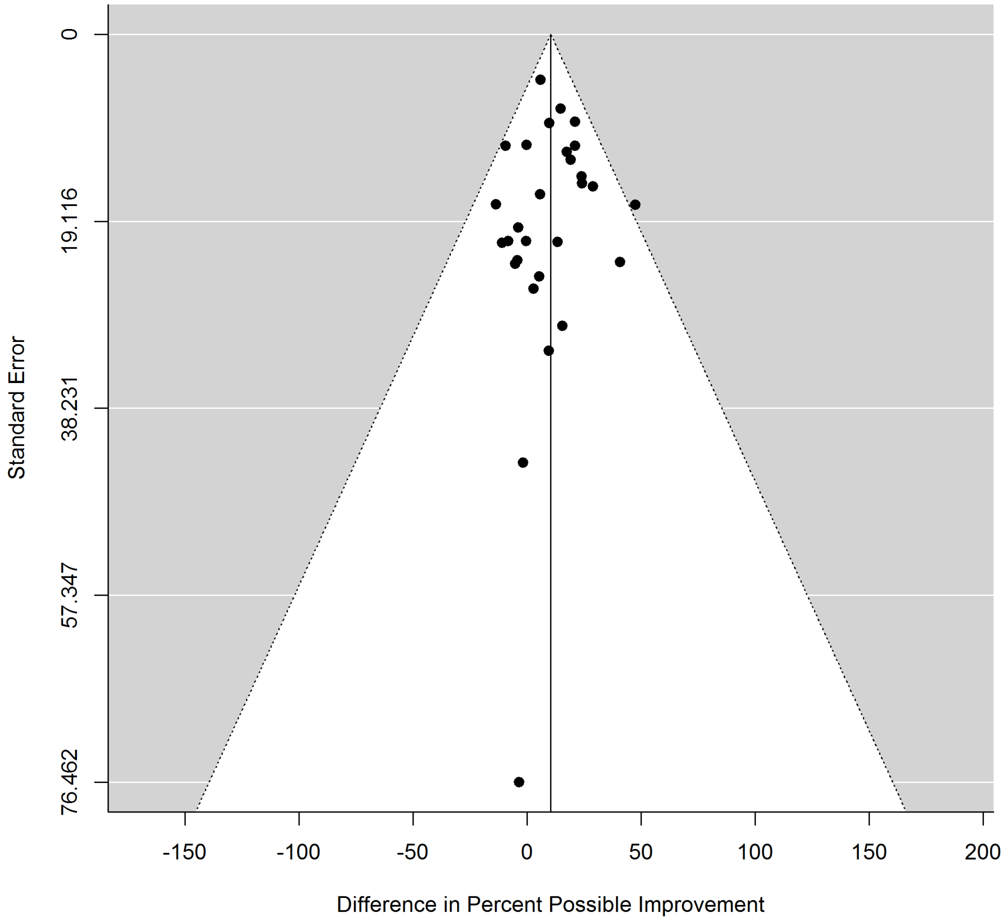
Supplemental Figure 3: Forest plot summarizing the treatment response following VR/gaming interventions.

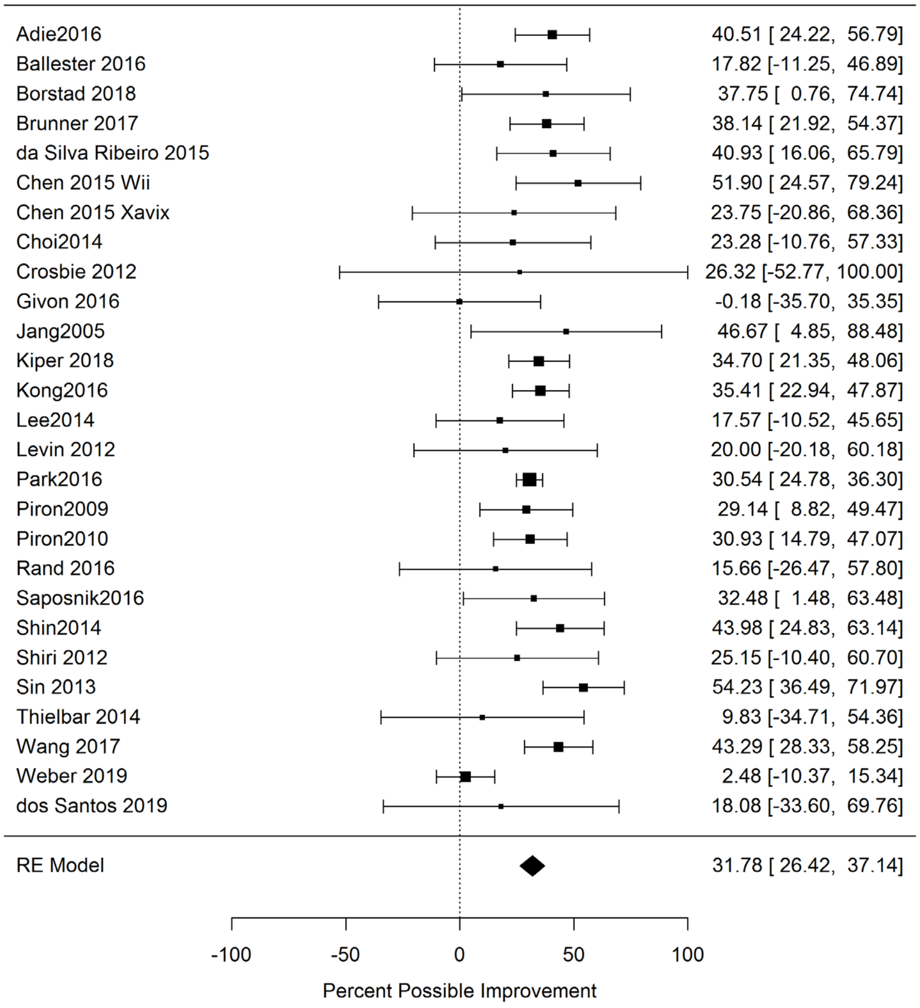
Supplemental Figure 4: Funnel plot of the effects of VR/gaming interventions on upper extremity function amongst studies at lowest risk of bias. The Y axis reflects the standard error, while the X axis reflects the mean percent possible improvement for each study.

Supplemental Figure 5: Forest plot of VR/gaming versus an active comparator for studies at lower risk of bias. Studies with larger squares are weighted higher in the overall estimate. The X-axis indicates the difference in percent possible improvement between VR/gaming and the active comparator. Squares to the right of 0 indicate that VR/gaming was more effective than the active comparator.

Supplemental Figure 6: Funnel plot of the comparative treatment effect amongst studies at lowest risk of bias. The Y axis reflects the standard error, while the X axis reflects the difference in mean percent possible improvement between VR/gaming and active comparator groups for each study.


0
77.536
155.072
232.609
310.145
Standard Error
-500
0
500
Percent Possible Improvement


0
19.116
38.231
57.347
76.462
Standard Error
-150
-100
-50
0
50
100
150
200
Difference in Percent Possible Improvement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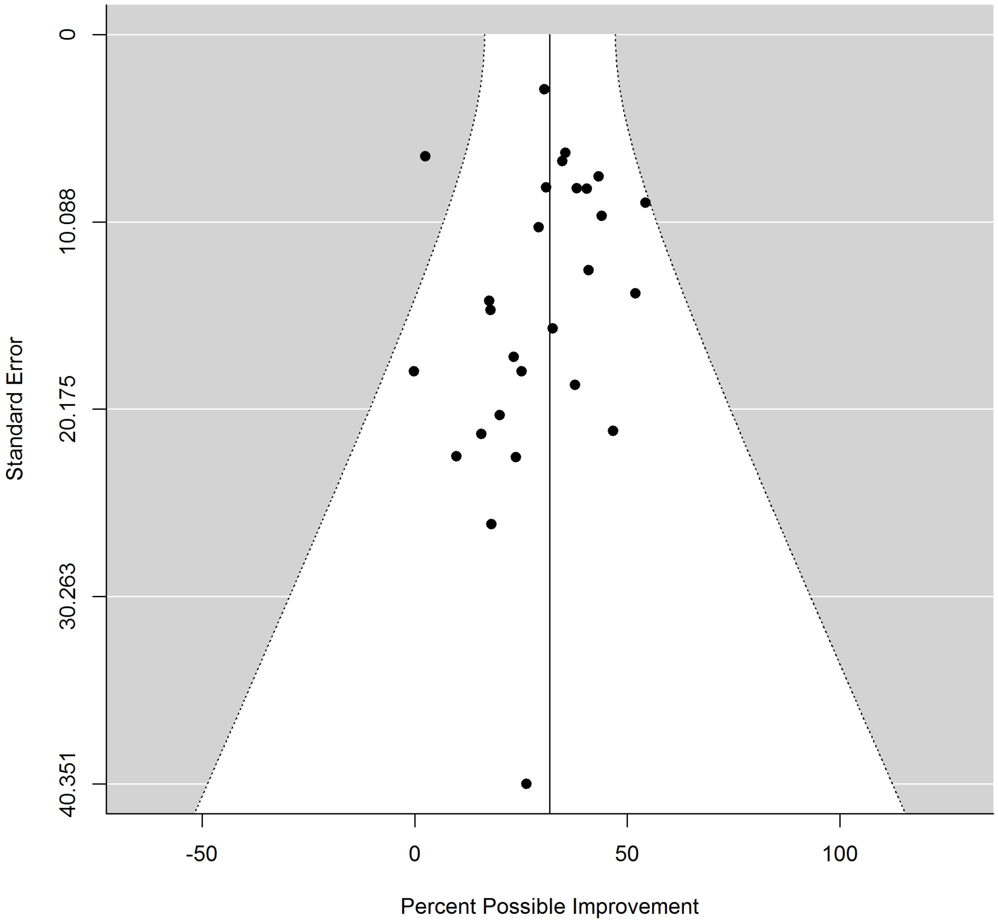
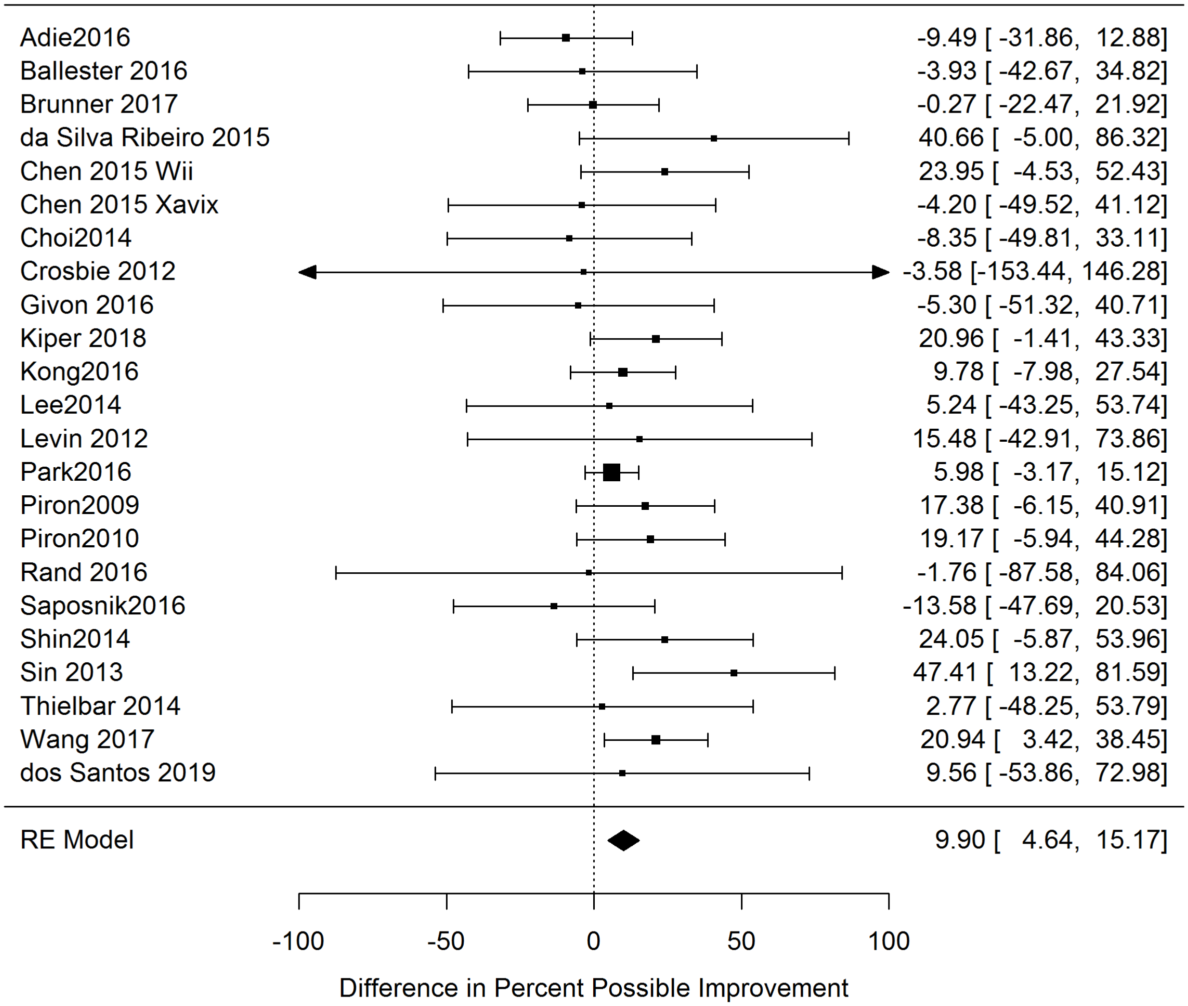
Ballester 2016 17.82 [-11.25, 46.89]
Borstad 2018 37.75 [0.76, 74.74]
Brunner 2017 38.14 [21.92, 54.37]
da Silva Ribeiro 2015 40.93 [16.06, 65.79]
Chen 2015 Wii 51.90 [24.57, 79.24]
Chen 2015 Xavix 23.75 [-20.86, 68.36]
Choi2014 23.28 [-10.76, 57.33]
Crosbie 2012 26.32 [-52.77, 100.00]
Givon 2016 -0.18 [-35.70, 35.35]
Jang2005 46.67 [4.85, 88.48]
Kiper 2018 34.70 [21.35, 48.06]
Kong2016 35.41 [22.94, 47.87]
Lee2014 17.57 [-10.52, 45.65]
Levin 2012 20.00 [-20.18, 60.18]
Park2016 30.54 [24.78, 36.30]
Piron2009 29.14 [8.82, 49.47]
Piron2010 30.93 [14.79, 47.07]
Rand 2016 15.66 [-26.47, 57.80]
Saposnik2016 32.48 [1.48, 63.48]
Shin2014 43.98 [24.83, 63.14]
Shiri 2012 25.15 [-10.40, 60.70]
Sin 2013 54.23 [36.49, 71.97]
Thielbar 2014 9.83 [-34.71, 54.36]
Wang 2017 43.29 [28.33, 58.25]
Weber 2019 2.48 [-10.37, 15.34]
dos Santos 2019 18.08 [-33.60, 69.76]
RE Model 31.78 [26.42, 37.14]
-100
-50
0
50
100
Percent Possible Improvement


Standard Error
0
10.088
20.175
30.263
40.351
-50
0
50
100
Percent Possible Improvement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Ballester 2016 -3.93 [-42.67, 34.82]
Brunner 2017 -0.27 [-22.47, 21.92]
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Chen 2015 Wii 23.95 [-4.53, 52.43]
Chen 2015 Xavix -4.20 [-49.52, 41.12]
Choi2014 -8.35 [-49.81, 33.11]
Crosbie 2012 -3.58 [-153.44, 146.28]
Givon 2016 -5.30 [-51.32, 40.71]
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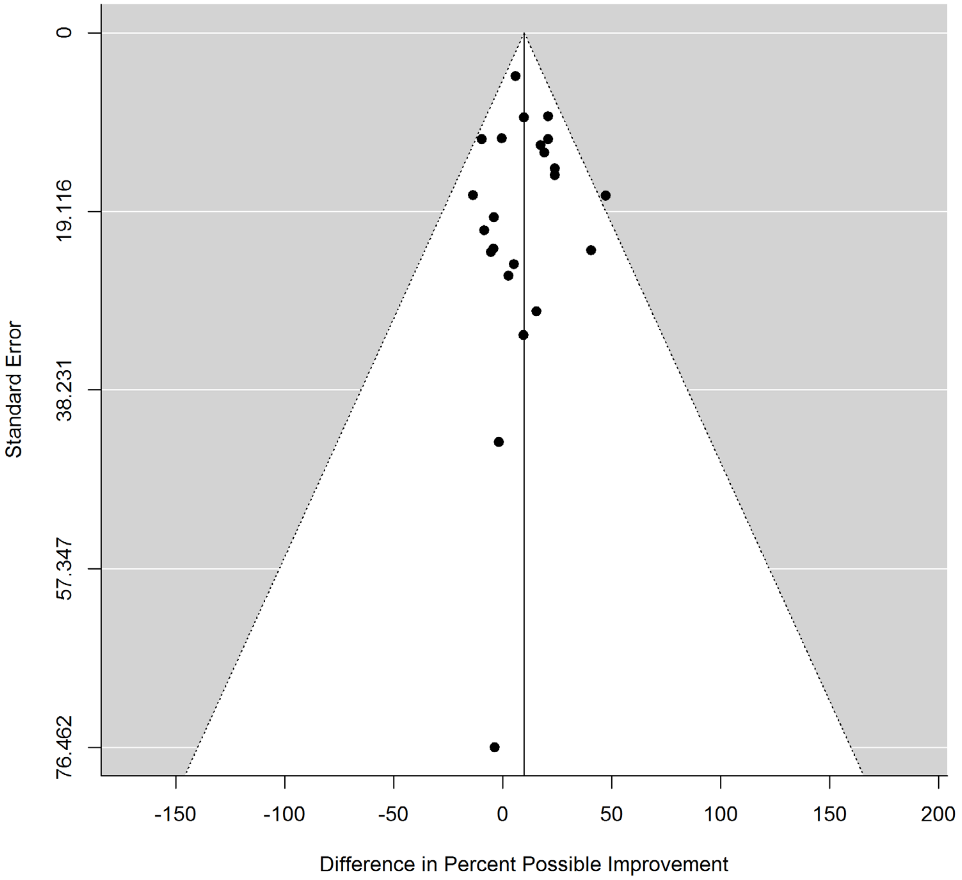
Piron2009 17.38 [-6.15, 40.91]
Piron2010 19.17 [-5.94, 44.28]
Rand 2016 -1.76 [-87.58, 84.06]
Saposnik2016 -13.58 [-47.69, 20.53]
Shin2014 24.05 [-5.87, 53.96]
Sin 2013 47.41 [13.22, 81.59]
Thielbar 2014 2.77 [-48.25, 53.79]
Wang 2017 20.94 [3.42, 38.45]
dos Santos 2019 9.56 [-53.86, 72.98]
RE Model 9.90 [4.64, 15.17]
-100
-50
0
50
100
Difference in Percent Possible Improvement


Standard Error
0
19.116
38.231
57.347
76.462
-150
-100
-50
0
50
100
150
200
Difference in Percent Possible Improvement