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EFFICACY OF MEMORY REHABILITATION THERAPY: A META-ANALYSIS OF TBI AND STROKE COGNITIVE REHABILITATION LITERATURE

by

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THESIS APPROVAL PAGE

This is to certify that the thesis prepared by Madison A. Elliott, entitled Efficacy of Memory Rehabilitation Therapy: A Meta-analysis of TBI and stroke cognitive rehabilitation literature, has been approved by this thesis committee as satisfactory completion of the thesis requirement for the degree of Master of Arts in Clinical Psychology.

Chair, Thesis Committee	5/1/13 Date
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ABSTRACT

Efficacy of Memory Rehabilitation Therapy

Madison Elliott

This meta-analysis evaluated 26 studies of memory retraining and recovery that were published between the years 1985 and 2013. The primary purpose of this meta-analysis was to determine the overall effect size (ES) in these studies. The study assessed the significance of the overall ES and determined which of several covariates in these studies predict the obtained ESs. Results indicated a significant average ES (r = .51) in the treatment intervention conditions. There was also a significant average ES (r = .31) in the control conditions, in which participants did not receive any treatment. The largest treatment ESs occurred in studies of stroke patients, and the smallest ESs occurred in studies of patients with traumatic brain injury (TBI). Results showed that memory rehabilitation was an effective therapeutic intervention. However, the results also indicated that significant memory improvement occurred spontaneously over time.

Keywords: memory, working memory, cognitive rehabilitation, neurorehabilitation, remediation, TBI, stroke, meta-analysis

Table of Contents

LIST OF FIGURES

Introduction to Brain Injury

The incidence of Traumatic Brain Injury (TBI) and stroke is on the rise worldwide. The Centers for Disease Control and Prevention (CDC) report that in 2011 an estimated 1.7 million individuals suffered a brain injury. Even more striking is their report that Traumatic Brain Injury (TBI) contributes to 30.5% of all injury-related deaths in the USA alone (CDC, 2012). Males are twice as likely as females to sustain a brain injury, and persons aged 75 or older are the most susceptible population. The majority of TBIs are caused by falls, vehicle crashes, and other assaults. War zone blasts are the most common cause of TBI in military personnel. Sports-related head injuries are becoming increasingly common in the USA. The CDC originally cited that approximately 300,000 sports-related TBIs occur each year, however, other reports estimate that the figure may be closer to 2 million (Langlois et al., 2006; Collins et al., 2003). Formal terms like ‘Mild’, ‘Moderate’ and ‘Severe’ Brain Injury simply describe the level of neurological insult but they do not take into account other persistent physiological, psychological factors and family issues that can greatly influence a person’s recovery. The Brain Injury Association of America (BIAA) emphasizes that any injury to the brain can pose a serious medical threat. Even so-called ‘Mild’ brain injuries can create debilitating after-effects like memory difficulties, sleep disturbance, attention difficulties, decreased speed of thinking, emotional volatility, and balance problems (BIAA, 2012).

Because of their prevalence and range of severity, TBI and stroke are exceptionally expensive problems. Lifetime costs associated with all TBIs in the USA are upwards of $60 billion per year (Langlois et al., 2006). A recent comprehensive study by Mar et al. (2011) about the impact of brain damage revealed that TBI and stroke are primary causes of long-term disability, and that individuals being treated for strokes are responsible for two to four percent of health costs across industrialized countries.

Health professionals consider TBI to be one of the most debilitating injuries (Langlois et al. 2006; Englander et al. 1992). TBI-related productivity loss is fourteen times worse than productivity loss after spinal cord injuries, and at least 5.3 million US citizens live with a permanent TBI- or stroke-related disability. Clinicians face major difficulties when identifying cognitive impairments caused by brain injury or stroke. Because it can take so long to identify these problems, reintegration into the workplace and daily social life is often impossible for individuals who have sustained a neurological injury (Mar et al., 2011).

Cognitive Rehabilitation of Memory

The field of Cognitive Rehabilitation Therapy (CRT) for brain injury and stroke is a diverse field with numerous treatment and theoretical models. Treatments can be process-specific, aimed at improving overall performance of a given activity, skill-based, motor-based, or restricted to a certain area of cognition like attention, language, executive function, or memory. Overall goals of treatment and treatment implementation are as varied as the treatments themselves (Katz et al., 2006).

One reason that rehabilitation is such a broad field derives from the unique nature of every brain injury. Because the human brain integrates so many complex forms of information, there are many consequences of an injury that can determine the nature of cognitive and behavioral affect. In the case of memory impairment, long-term, short-term, and/or working memory can be affected. Rehabilitation tasks and their outcome measures are often developed to improve or evaluate function within a specific type of memory (Cicerone et al., 2000). Memory impairment is commonly reported after brain injury or stroke, and individuals who experience trauma localized in the temporal lobes, hippocampus and amygdala are particularly susceptible to memory impairment. However, the area of brain injury is not the sole determinant of memory problems; many factors contribute to each person's unique outcome post- brain injury (BIAA, 2012). To explain the varying nature of TBI, Kay (2003) and McCrea et al. (2013) propose integrated, multi-factorial neuropsychological models of brain injury outcome, including determining factors like neurological health, psychological health, physiological health, and their interactions with individual subjective or objective cognitive functions.

Various memory treatment strategies have been proven efficacious, such as the internet-based tasks used in Bergquist et al. (2009). Other forms of computerized training (Lundqvuist, et al., 2010), awareness questionnaires (Livengood, et al., 2010), and motive, or incentive-based tasks (McCauley, et al., 2009) have also demonstrated efficacy. Relatively few articles have been published that document successful pharmaceutical treatments (Kim, et al., 2006).

The typical rehabilitation efficacy study evaluates memory differences for a control group versus experimental group, pre- and post- intervention design. Outcome measures vary greatly, and include neuropsychological batteries, motor-function tests, brain imaging, and various self-report instruments. Observer versions of the self-report measures can be given to participants' family members, professional supervisors, or close friends to obtain a more diverse understanding of their daily behavioral functioning (BIAA, 2012).

Although there are published reports of potentially effective treatments, there is no conclusive evidence of an effective standardized treatment program for memory dysfunction. Most treatments produce improvement in memory functioning but any one does not seem to work better than others (Dou et al., 2005). There is little research to document enduring improvement over time for any treatment modality. There is some evidence however, for treatment efficacy that exceeds the level of improvement that occurs with the passage of time (Rohling et al., 2005).

Memory Rehabilitation Efficacy

CRT after TBI and stroke has been the topic of a number of major reviews evaluating effectiveness. Park & Ingles, (2001); Robey (1998); Cicerone et al. (2000); Cicerone et al. (2005); and Rohling, Faust, Beverly, & Demakis (2009) published such work. In their extensive review, Cicerone et al. (2000; 2005) evaluated 118 studies about CRT, classifying them first in terms of methodological quality, and then summarizing the consistent findings. The highest ranked studies were those including randomized control trials (RCTs) (I), followed by studies including non-randomized control prospective or retrospective case-controls (II). The lowest ranked studies were those not including control groups, or those that used data from case studies of single subjects (III). The study also categorized the research into various domains: attention, vision, perception, apraxia, language and communication, working memory, executive functioning, problem solving and awareness, and comprehensive holistic cognitive rehabilitation. Some of the cognitive rehabilitation domains, for example, attention training, visual-spatial training, and language based interventions produced larger treatment effects than others (Cicerone et al., 2000; Cicerone et al., 2005). These authors generally provide support for the benefit of CRT for TBI and stroke.

More recently, however, Rohling et al. (2009) performed a quantitative meta-analysis of a select, well-controlled, literature set that derived from Cicerone et al. (2000), and Cicerone et al. (2005). Rohling et al. (2009) concluded that there was “modest qualitative support” for the claim about rehabilitation efficacy made in original paper by Cicerone et al. (2000; 2005). Rohling et al. (2009) found sufficient evidence that attention training after TBI, and language and visual-spatial training for symptoms of stroke were effective. The authors concluded that out of five major treatment-effectiveness findings in Cicerone et al. (2005), their meta-analysis results supported three: attention-training, language-based training, and visual-spatial training.

Rohling et al. (2009) cautioned readers that Cicerone et al. (2005) made two claims prematurely, because authors did not adequately estimate retest effects from studies with uncontrolled designs. One of the two major claims Rohling et al. (2009) questioned was the efficacy of memory rehabilitation. Although their data showed a moderate effect size (ES) for memory rehabilitation, it was not significant. Additionally, very few of the 115 articles evaluated in Rohling et al. (2009) involved memory rehabilitation, so it is difficult to derive any conclusive evidence about the overall efficacy of memory rehabilitation.

The present study builds upon the previously inconclusive results about memory rehabilitation. Many neuro-rehabilitation techniques have changed and advanced since the Rohling et al. (2009) meta-analysis. However, their methodology for meta-analytic research in this area is exemplary. Therefore, the methods for the current study were adapted from Rohling et al. (2009). These procedures include using the most recent publications, the most rigorous and careful methods of the four major reviews listed, and replicating the Rohling et al. (2009) selection criteria. The same meta-analytic procedures were used to identify variables predicting effect sizes in the current set of published studies. The present work reviewed studies published through 2013 about memory rehabilitation in participants who had suffered a TBI or stroke.

Meta-Analysis and Effect Size Measures

A meta-analytic review is a study of published studies. Generally, the purpose of a meta-analysis is to examine the overall effect of a specific variable in published literature. Meta-analyses use published research as a unit of measure to evaluate central tendency and variability of the ESs across the sample of chosen studies. In most cases, ESs are determined as a measure of the amount of variance the effect controls in a given experiment, and the meta-analysis calculates the extent to which the variable of interest (i.e. working memory recovery) controls significant portions of the variance in the study sample. By usual standards, the overall effect of the variable is considered reliable if the average ES is significantly different from zero. A typical meta-analysis reduces the relevant statistical information in each published study to standard units of ES, and then evaluates whether the ESs co-vary with any of several other variables that describe the conditions of the original experiments.

METHODS

Sample of Studies

Studies were identified using combinations of the search terms: “working memory”, “rehabilitation”, “remediation”, “memory”, “training”, “brain injury”, “TBI” and “stroke” in the following research databases: Medline, Pub Med, PsycINFO, PsycArticles, and Google Scholar. Based on Rohling et al.’s (2009) criteria, excluded studies 1) did not contain a memory-rehabilitative intervention; 2) merely describe treatment approaches or theories; 3) were review articles; 4) present unspecified or unmeasured interventions; 5) lack a diagnosis or assessment of TBI or stroke; 6) were case studies of a single participant with no empirical data; 7) were non-peer reviewed articles; 8) were included exclusively-pharmacological interventions; and 9) were articles not written in English. Rohling, et al. (2009) mention that single papers may include multiple analyzable studies, with “unique non-overlapping samples of participants”. Within the present sample, twelve papers included two analyzable study groups. In total, twenty six published memory rehabilitation studies met selection standards and could be used for the analysis. Fourteen of the studies compared a treatment intervention condition to a control group. The other twelve studies contained a treatment intervention, but no control condition.

Procedural Analysis

Meta-Analytic procedures using the MIX 2.0 for Microsoft Excel meta-analysis software package were used to evaluate the effect sizes (ESs) computed from the available statistics in each published study. These ESs (calculated as the Pearson's *r*) were subsequently analyzed to determine whether or not the average ESs were significantly different from zero.

ESs from control conditions estimated how much memory improvement was not attributable to an experimental intervention, but instead attributable to the passage of time and non-specific neuroplasticity. ESs from intervention conditions were subsequently analyzed, and used to estimate how much memory improvement could be attributed to a cognitive rehabilitation effort. The final analytic procedure compared the first (control analysis) to the second (intervention analysis) in order to determine whether cognitive rehabilitation interventions yield significantly larger ESs compared to control conditions, where no intervention has taken place.

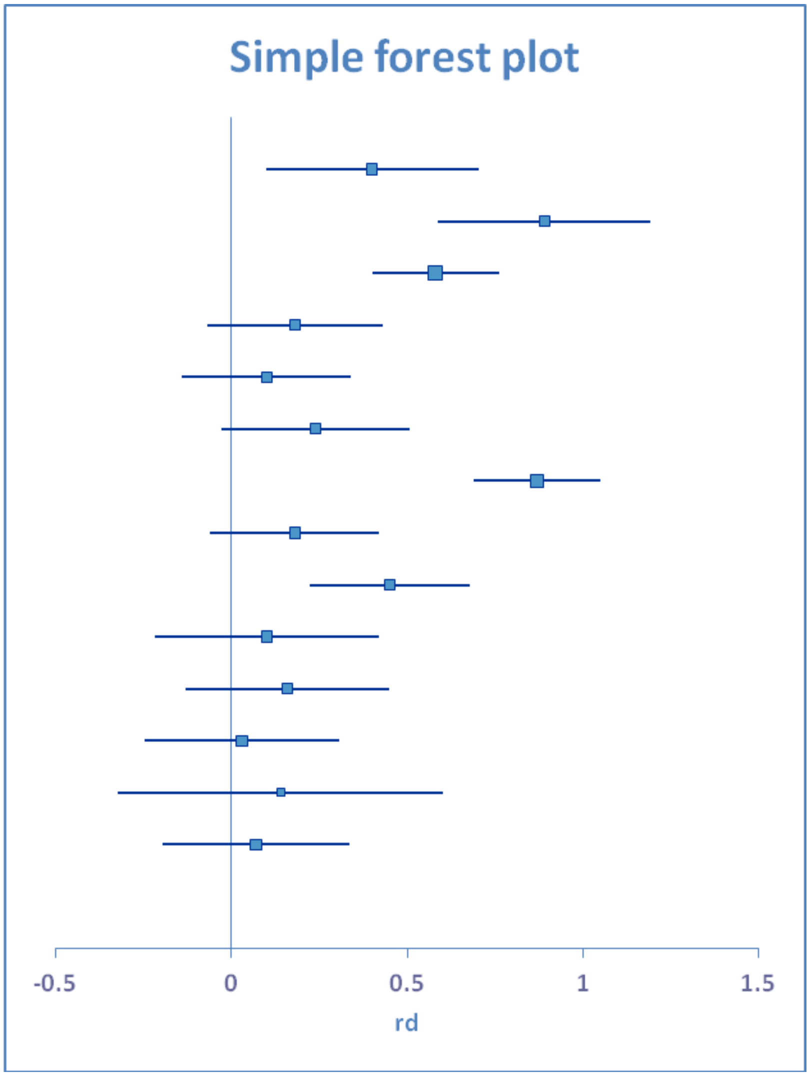
The Q statistic was calculated to evaluate the significance of the overall effect size and to assess the significance of the difference between the treatment ES once the control ES is removed. The Q statistic was also calculated initially to assess the homogeneity of the ESs across the various studies. Begg's Test statistics were calculated to assess whether or not sample sizes affected the reported ESs. The degree of dissemination bias, i.e. the extent to which the published studies overestimate the size of the effect was also examined using a funnel plot. Covariates of the ESs, including the average age of the patients, ratio of males to females in the sample, year of publication, type of brain injury, type of intervention, and sample size, were also evaluated.

RESULTS

Control Conditions Analysis

The average effect size for this condition of $r = .31$ was significant ($Z = 10.00$ $p < .05$) which indicated a moderate and significant improvement in memory, which was not attributable to a rehabilitation intervention. Figure 1 is a forest plot displaying the ESs for all included studies. The plot displays the ES and 95% confidence interval for each included study. The extent to which the horizontal lines overlap is an indication of the homogeneity of the ESs across studies. This visual representation of the data demonstrates that the studies were generally homogenous in their reported ESs, with two possible outliers. The outliers may be due to different methodology or publication bias, as suggested by Control Group Q statistic and selectivity funnel plot results.

Figure 1. Forest Plot of ESs in Control Group Studies

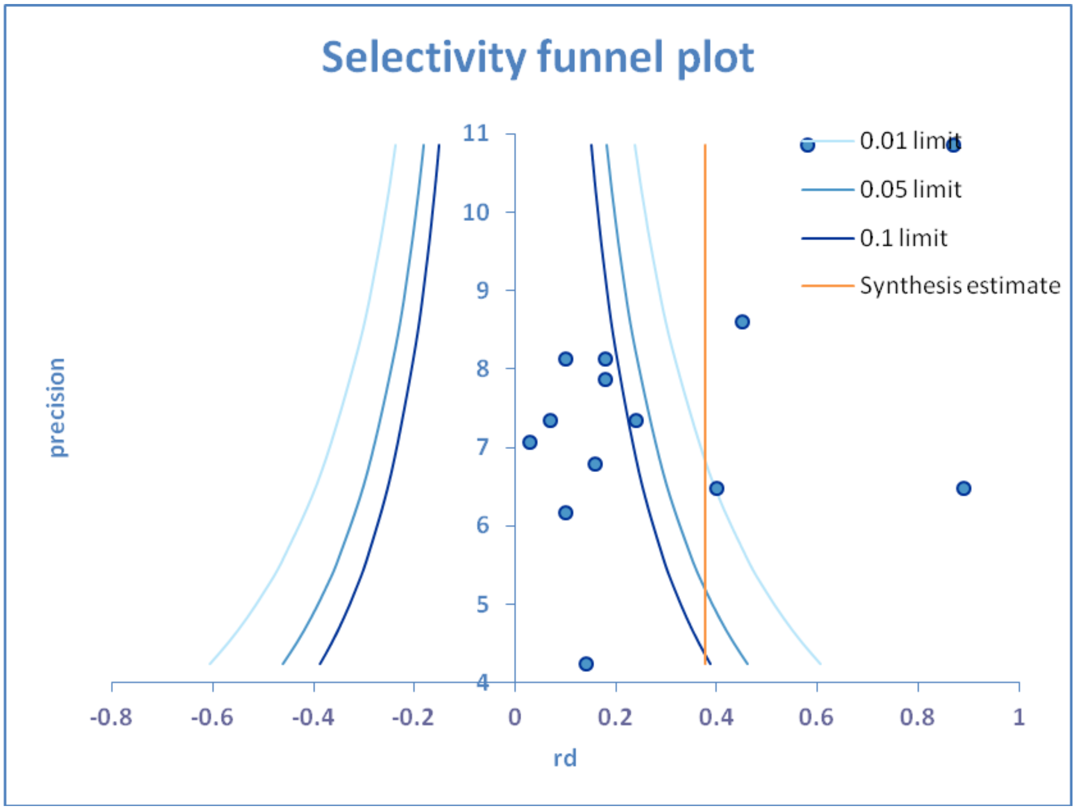


A significant Q statistic (73.259, $p = 0.00$) also indicates that the studies included are not homogenous. The I^2 statistic estimates the percentage of within-study variance among the studies due to non-random factors. The I^2 statistic 82.25% also suggests heterogeneity among the ESs. It is important to note that when k<20, as in the present analysis, both the Q and I^2 tests should be interpreted with caution (Higgens et al., 2003). Nevertheless, this statistic suggests that it may be worthwhile to explore characteristics of the various experiments that may have contributed to the inconsistency of methods used among the control studies.

Begg's Test statistics were computed to determine whether publication bias is present in the sample of studies used for analysis. Smaller samples with fewer degrees of freedom often produce inflated ESs, and may indicate the existence of unpublished studies with lower ESs. The Begg's statistics computed on these data was not significant (p = .46), indicating the presence of publication bias among the chosen studies.

Funnel plots are used to illustrate dissemination bias. If there is little or no dissemination bias, a funnel plot will show all the dots distributed randomly around the synthesis estimate line, and they will also fall between the confidence interval funnel lines on each side of the plot. The funnel plot from the present analysis, depicted in Figure 2 below, indicates the presence of dissemination bias in control condition studies. This also means that there is a possibility of unpublished studies with lower ESs existing, and reinforces the Begg's test results, that published studies contain inflated ESs which are possibly overestimating the effect of recovery without an intervention condition.

Figure 2. Funnel Plot for Control Group Studies

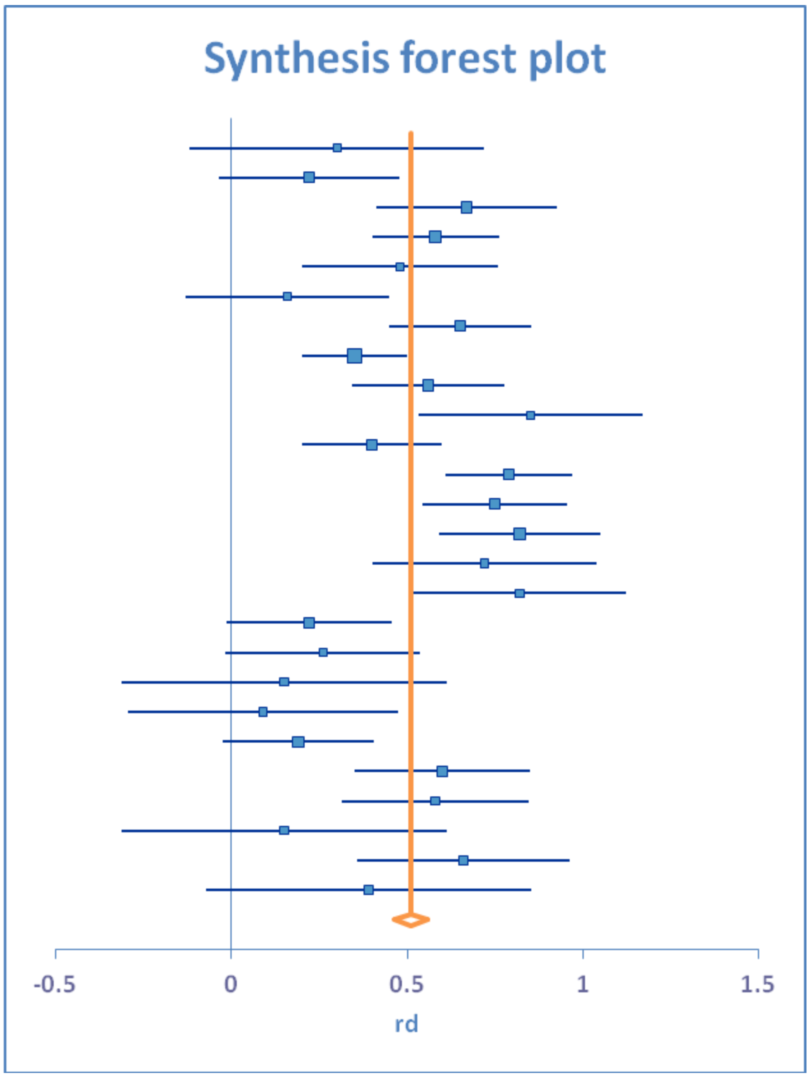


Intervention Conditions Analysis

. The average effect size for this group of studies was r = .51 (Z = 20.62, $p < .05$) which was significantly different from zero. The confidence interval for the overall ES (.462 - .558), did not include the average ES for the control studies (r = .31). The results therefore indicated that overall, a moderate and significant improvement in memory was apparent in the cognitive measures used in these studies. This change in memory function cannot be attributed solely to the passage of time.

Figure 3 is a forest plot for the intervention condition studies. The visual representation of the data here demonstrates that the combination of intervention and control studies were more heterogeneous in their reported ESs. These outliers may be due to different methodology or publication bias, as suggested by the Intervention Group Q statistic and selectivity funnel plot results.

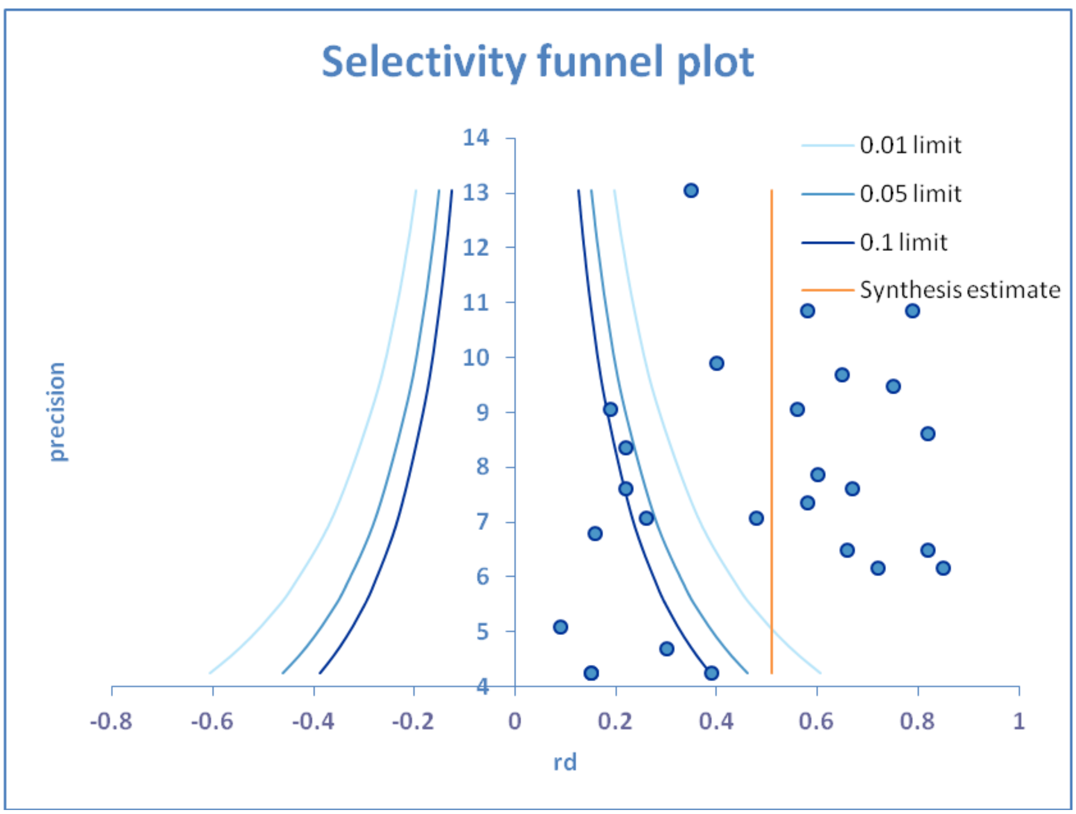
Figure 3. Forest plot of ESs in Intervention Group Studies



The significant Q statistic indicated significant heterogeneity of the ESs (Q=81.50, $p < .05$), presumably due to differences in study characteristics. The I^2 statistic of 69.31% indicates that there was somewhat less heterogeneity than the control conditions where $I^2 = 82.25\%$. These statistics should be considered more reliable for the intervention analysis (*k* = 26) according to sample size criteria in Higgens et al. (2003).

The Begg's test statistics computed on these data was not significant (*p* = .36), which showed that dissemination bias is present in the sample of studies used for the analysis. The intervention analysis funnel plot is displayed in Figure 4. The funnel plot is an additional indication of the presence of dissemination bias in intervention studies. This shows that, similar to published control studies, published intervention studies have inflated ESs, and may be overestimating the effect of recovery due to rehabilitation.

Figure 4. Funnel plot for Intervention Studies



Two of the study covariates predicted the ESs. The 95% confidence intervals computed on the ESs in the treatment type intervention group conditions indicated that studies of stroke rehabilitation produced significantly larger ESs compared to mixed brain injury and TBI studies. This is shown in Figure 5. Confidence intervals were also computed and presented in Figure 6 to determine ES differences between the intervention (experimental group) and control groups in studies that included both. The discrepancy between the confidence intervals in Figure 6 indicates a significant difference between the experimental and control group ESs. A separate analysis showed that working memory studies produced significantly higher effect sizes relative to studies of other memory processes; this is presented in Figure 7. There was no significant difference in ESs for intervention studies (experimental groups) that contained a control group versus intervention studies that did not contain a control group.

Figure 5. 95% Confidence Interval for Treatment Type (Patient Category) ESs

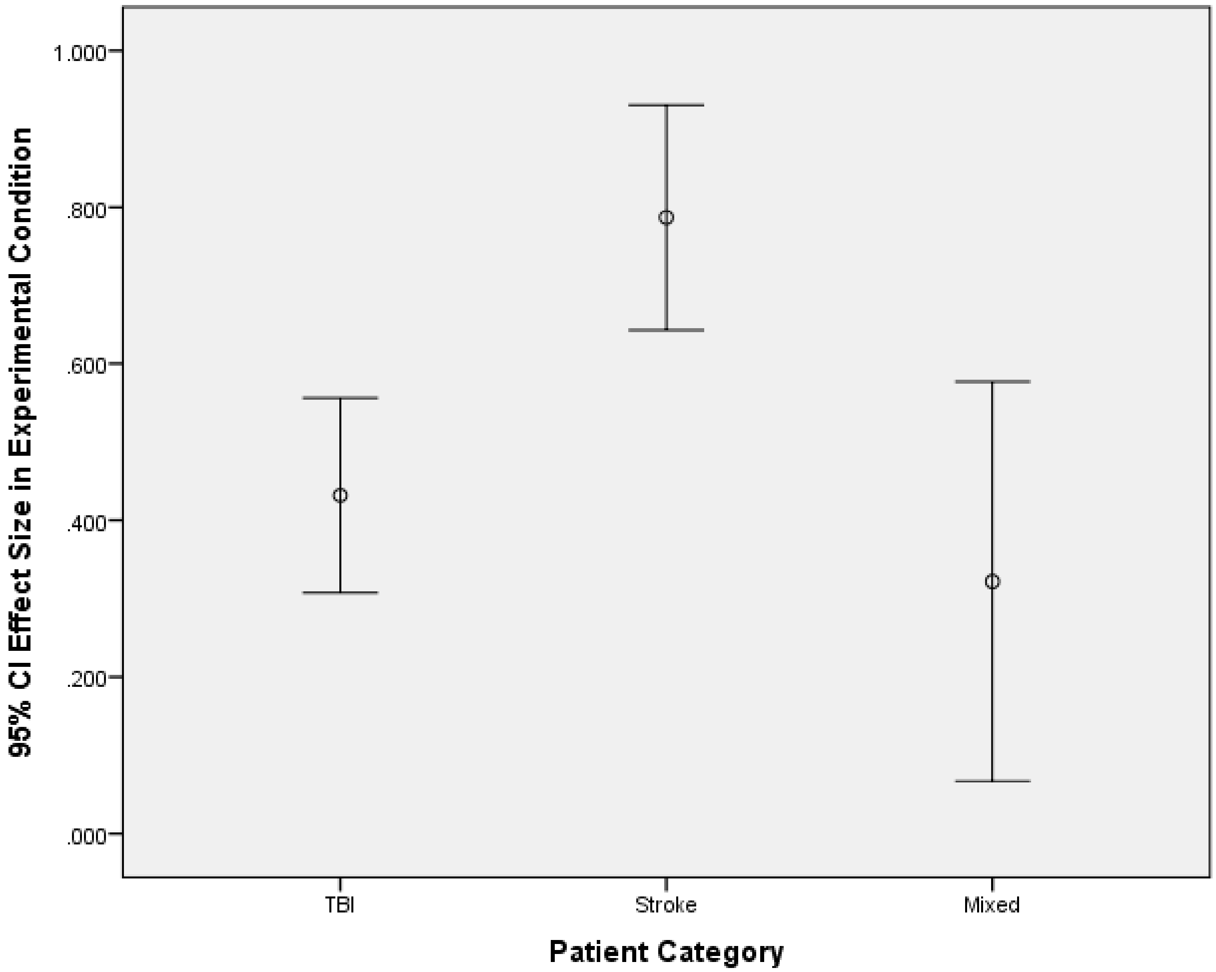


Figure 6. ES Difference for Intervention (Experimental) Versus Control Studies

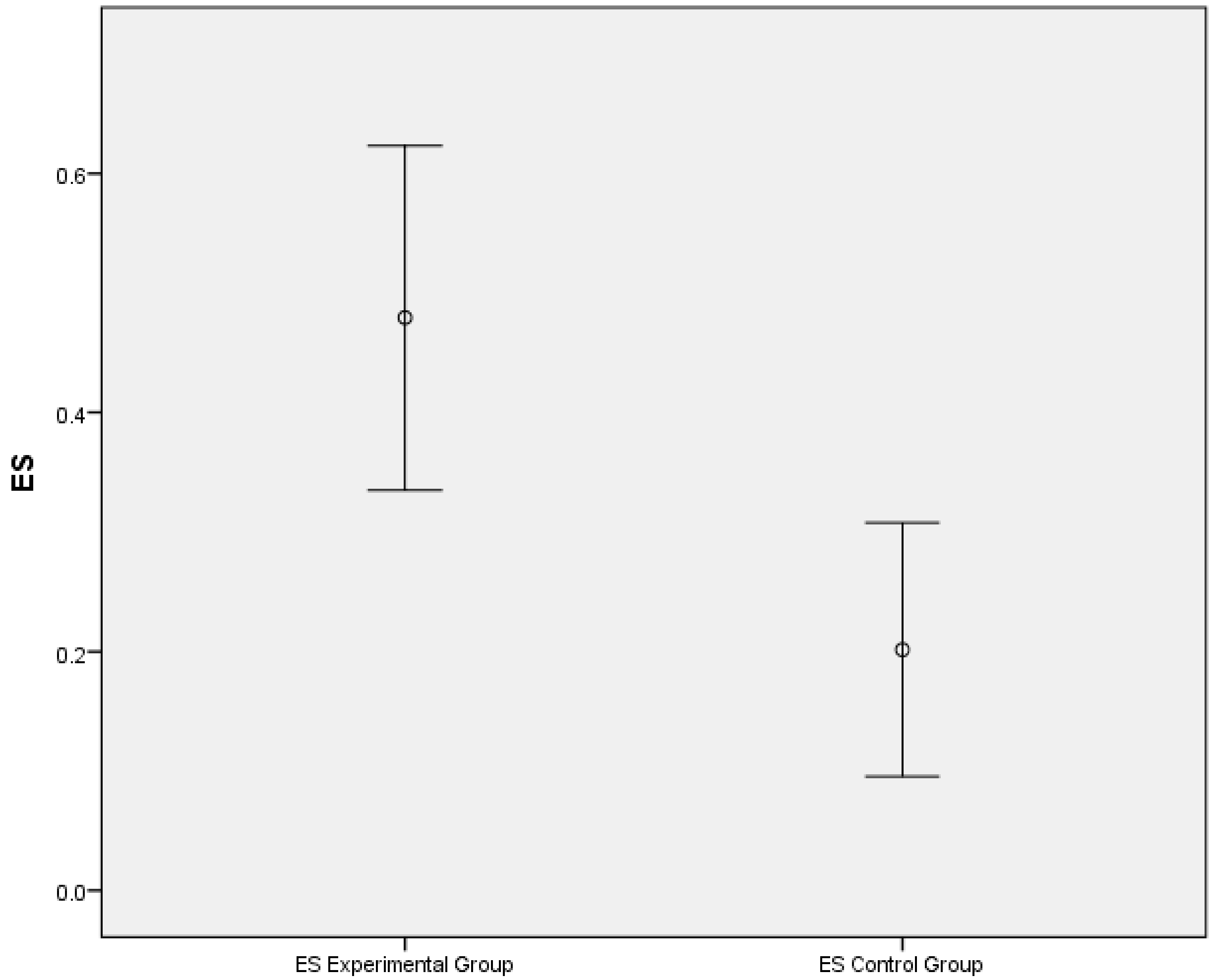
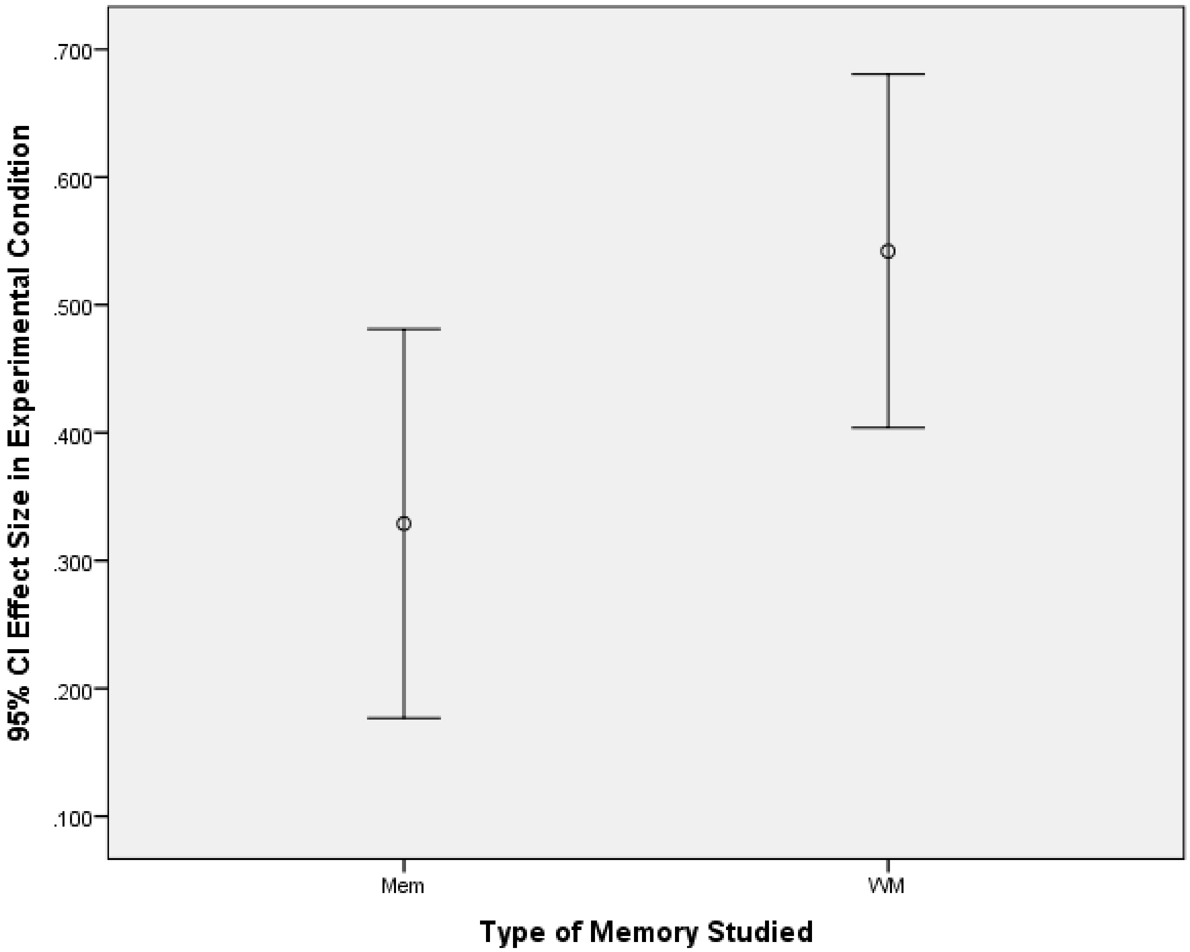


Figure 7. ES Differences in Types of Memory



Post-hoc correlation analyses investigating the relationship between dependent variables in the control and intervention conditions and ESs did not reveal any significant relationship ($p > .05$) between the ESs and the number of dependent variables in either the control or the experimental conditions. Additional post-hoc correlation analyses show that there was no significant correlation ($p > .05$) between sample sizes and ESs for intervention (experiment) group studies, but that there was a significant correlation ($p < .05$) between sample sizes and ESs for control group studies. There were no other significant covariate/ES correlations.

DISCUSSION

This meta-analytic review investigated differences in studies with and without a memory rehabilitation intervention, for individuals with TBI or stroke. One goal of this meta-analysis was to supplement the work published by Cicerone et al. (2000; 2005) and Rohling et al. (2009). The former article did not quantitatively evaluate ESs and the later study had a relatively low sample size for memory studies. The results obtained in this investigation for the intervention group show a significant moderate effect (r = 0.51) of the interventions which could not be attributed to the passage of time. However, the control analyses show a smaller, but also significant and moderate effect (r = 0.31) for recovery without a treatment intervention. This pattern of results replicated the ES relationship found in Rohling et al. (2009). In both studies there was a small ES that could not be the result of spontaneous recovery. Unlike Rohling et al. (2005), the present analysis found that this difference in ESs was significant. Additionally, both the intervention and control ESs were significant in the present analysis. This shows that overall; the memory rehabilitation strategies produced the desired effect. The fact that the confidence intervals computed around the ESs in the control groups show the average ES is significantly greater than zero, indicates that significant spontaneous improvement in memory occurs after brain injury and stroke. The fact that some amount of the ES in the experimental treatment condition cannot be attributed to the passage of time indicates that therapeutic intervention may accelerate this improvement.

The heterogeneity of ESs in these studies could be accounted for partially by a few moderating variables. Analyses show that studies of stroke recovery produced significantly larger ESs than were apparent in studies of TBI recovery or mixed injury recovery. This ES difference occurred across intervention and control group studies, indicating that stroke patients had the best recovery prognosis in these studies. Studies of Working Memory produced significantly larger effect sizes relative to studies of other types of memory. These results suggest that cognitive rehabilitation therapy may be most effective when applied to stroke rehabilitation and when the goal of the therapy is to improve working memory functions. The fact that significant improvement in memory occurred in the control condition suggests the need for baseline evaluations immediately following the stroke or TBI so that the rate of spontaneous improvement can be measured and documented once a therapeutic intervention begins.

The results are also interesting regarding which covariates did not predict the ESs. The Beggs's test was not significant which indicates that the ESs in most published studies is accurately estimated even with small sample sizes. Other characteristics of the experimental designs, for example, the number of dependent variables that were measured during the experiment did not seem to affect the ESs. Finally, there were no significant differences between the average ES for the treatment and control conditions in this study relative to those reported by Rohling et al. (2009) which suggests that the findings reported in both of these meta-analyses are stable.

The present study investigated solely the domain of memory. It is therefore possible that additional meta-analyses of attention, visual spatial, and language could reveal efficacy in those domains as well. Although the ES in studies of stroke survivors are larger than those obtained in studies of TBI, it is unclear why. Future studies should therefore investigate why cognitive rehabilitation of memory produces a larger effect in stroke patients. It will also be necessary to evaluate the types of treatments that are provided to either patient group with the eventual goal of amalgamating a group of treatments that can be developed into a standardized treatment model with proven efficacy.

Head injury, stroke, and cognitive decline are extremely common. Age-related vascular disorders, NFL football tackling, US army combat injury, car crashes, and many other forms of head trauma occur every day. Fortunately, modern medical advancements are now able to keep many more people alive after a brain injury or stroke. The major problem is that there are few-to-no effective medical treatments for cognitive deficits post- brain injury (BIAA, 2012; Kim et al, 2005). This makes the need for evidence-based cognitive rehabilitation exceptionally relevant. Identifying and improving successful treatments will become increasingly valuable as brain injury incidence continues to rise.

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