Journal of the International Neuropsychological Society (2011), **17**, 956–969.

doi:10.1017/S1355617711000968

CRITICAL REVIEW

Does Antiretroviral Therapy Improve HIV-Associated Cognitive Impairment? A Quantitative Review of the Literature

Timour Al-Khindi,[1] Konstantine K. Zakzanis,[1] AND Wilfred G. van Gorp[2]

[1]Department of Psychology, University of Toronto Scarborough, Toronto, Ontario
[2]Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, New York

(RECEIVED March 3, 2011; FINAL REVISION June 21, 2011; ACCEPTED June 22, 2011)

Abstract

The development of antiretroviral therapy (ART) has dramatically improved survival for those living with human immunodeficiency virus (HIV), but whether ART improves cognitive functioning remains unclear. The aim of the present review was to examine systematically the extent to which ART improves cognition among individuals with HIV using meta-analytic methods. Twenty-three studies were included in the quantitative review. ART was associated with modest improvements in attention (mean $d = .17$; $p < .001$; 95% confidence interval [CI], .09/.25), executive function (mean $d = .18$; $p < .001$; 95% CI, .10/.26), and motor function (mean $d = .24$; $p < .001$; 95% CI, .16/.32). ART did not improve language, verbal memory, visual memory or visuospatial function. The extent to which cognition improved was correlated with the change in CD4 cell count following ART, suggesting a link between cognitive outcome and immune system integrity. Together, the present findings indicate that the neuropsychological test performance of most HIV patients taking ART is comparable to those not taking ART. Development of pharmaceutical treatments and rehabilitation strategies that target the cognitive effects of HIV infection is needed. (*JINS*, 2011, *17*, 956–969)

Keywords: Acquired immune deficiency syndrome, Antiretroviral therapy, Cognitive outcome, Human immunodeficiency virus, Meta-analysis, Neuropsychological assessment

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a progressive disorder of the immune system characterized by selective destruction of CD4 T cells by the human immunodeficiency virus (HIV). The lack of a functional immune system results in greater risk of opportunistic infection (Orenstein, Fox, & Wahl, 1997). HIV infection is known to have profound effects on both brain and behavior. Neuroimaging studies have observed reduced cortical thickness among patients with HIV, particularly in premotor cortex, primary sensory and motor cortices, and visual cortex (Thompson et al., 2005). HIV-associated brain changes are not restricted to cortical areas, however. Aylward et al. (1993) found that HIV patients show basal ganglia atrophy, whereas Chen et al. (2009), using diffusion tensor imaging, found that HIV infection is associated with global reductions in white matter integrity. These brain changes have profound effects on cognition. Up to 52% of individuals with HIV experience some form of cognitive impairment (Heaton et al., 2010; McArthur, Steiner, Sacktor, & Nath, 2010). Commonly affected domains include motor function, executive function, attention, visual memory, and visuospatial function (Reger, Welsh, Razani, Martin, & Boone, 2002). Given its prevalence, treating cognitive dysfunction has become a central goal for therapies aiming to improve outcome among individuals with HIV.

The development of antiretroviral therapy (ART) was a major landmark in HIV treatment. Antiretroviral medications act by inhibiting HIV proteins such as reverse transcriptase and viral protease (for a detailed review, see Adamson & Freed, 2008). Early studies observed robust increases in CD4

Correspondence and reprint requests to: Konstantine K. Zakzanis, Department of Psychology, University of Toronto Scarborough, 1265 Military Trail, Toronto, Ontario, M1C 1A4, Canada. E-mail: zakzanis@utsc.utoronto.ca

cell count and life expectancy following ART (Fischl et al., 1987). The beneficial effects of antiretroviral medications are amplified when several drugs are given in combination. This approach, known as highly active antiretroviral therapy (HAART), reduces disease progression and mortality substantially more than monotherapy (Hammer et al., 1997). The efficacy of ART in reducing HIV-related cognitive impairment, however, remains unclear. Most studies have observed beneficial effects of ART on cognitive functioning (Baldeweg et al., 1995; Cohen et al., 2001; Robertson et al., 2004; Suarez et al., 2001), but some have documented no effect (Tozzi et al., 2007). The benefits of ART must also be weighed against the costs. A growing body of literature suggests that ART has numerous toxic side-effects, including mitochondrial toxicity, liver dysfunction, cardiovascular dysfunction, and, most pertinent to cognition, central nervous system hyperstimulation (Carr, 2003; Marzolini et al., 2001).

The question of whether ART improves HIV-related cognitive impairment has been explored in several narrative reviews (Cysique & Brew, 2009; Joska, Gouse, Paul, Stein, & Flisher, 2010; Liner, Hall, & Robertson, 2008; Liner, Ro, & Robertson, 2010). These narrative reviews do not, however, reveal the magnitude of efficacy across studies. Moreover, traditional narrative reviews typically champion only statistically significant findings using vote count strategies as evidence of efficacy. By doing so, conclusions drawn using this method of research synthesis fail to give due consideration to the magnitude of effect beyond its statistical significance. Hence, the present quantitative review used meta-analytic methods so as to examine the efficacy of ART in reducing HIV-related cognitive dysfunction. Given that deficits in motor function, executive function, attention, visual memory, and visuospatial function are particularly pronounced among individuals with HIV (Reger et al., 2002), ART is hypothesized to have the most beneficial effects in these cognitive domains. Analyses were guided by three questions: (1) To what extent does ART reduce HIV-associated cognitive dysfunction? (2) Does HAART reduce HIV-associated cognitive dysfunction more than monotherapy? (3) To what extent do changes in immunological markers of HIV infection, such as CD4 cell count, predict changes in cognitive functioning?

METHODS

Meta-analysis

We used standard meta-analytic techniques to perform our review of the literature (Cooper & Hedges, 1994; Hedges & Olken, 1985; Rosenthal, 1991, 1995). In addition to solving problems with traditional narrative reviews, meta-analysis provides tools for the analysis of magnitude. Magnitude can be indexed with the effect size estimate *d* that is meant to reflect the degree to which the dependent variable is present in the sample group or the degree to which the null hypothesis is false (Cohen, 1988). In mathematical terms, *d* is the difference between two group means calibrated in pooled standard deviation units. Individual study results (typically means and standard deviations from each group) and relevant moderator variables can be abstracted, quantified, and assembled into a database that is statistically analyzed (Lipsey & Wilson, 1993). The main statistic presented in a meta-analysis is the mean effect size, which reflects the average individual effect across the sample of studies included in the synthesis. Moderator variables are then correlated with the effect size to tease out relationships that may influence the magnitude of the effect.

Heterogeneity of effect sizes across studies was examined using the *Q* statistic and *T*, an estimate of the standard deviation of effect size across studies. The effect sizes were also transformed into a non-overlap percentage using Cohen's (1988) idealized distributions, which can be further transformed into an overlap percentage (OL%) to articulate the meaningfulness of an effect size (Zakzanis, 1998, 2001). The OL% statistic represents the degree of overlap by subtracting the non-overlap from 100. In the present context, the OL% statistic represents the degree of overlap between participants in the treatment group (i.e., individuals with HIV receiving ART) and participants in the control group (i.e., individuals with HIV patients not receiving ART).

To assess publication bias, funnel plot analyses were conducted. In this technique, asymmetry in the funnel plot signifies publication bias (Borenstein, Hedges, Higgins, & Rothstein, 2009). The trim and fill method described by Duval and Tweedie (2000a, 2000b) was used to correct for any publication bias detected by funnel plot analyses. To ascertain how robust our findings were, Orwin's (1983) fail-safe *N* formula was used to provide an index of how many studies would be theoretically needed to overturn the obtained effect size and yield a non-significant effect (i.e., $d = 0.1$).

Finally, it should be noted that statistical analysis of meta-analytic studies is not entirely uncontroversial (see Hunter & Schmidt, 1990). Since studies with large sample sizes have more statistical power than studies with smaller sample sizes, computations of mean effect size must be weighted accordingly. In the present meta-analysis, the weight given to the effect size of an individual study was inversely proportional to the variance of each study and directly proportional to the sample size of each study. This method has previously been validated by Hedges and Olkin (1985).

Literature Search

The literature review was restricted to peer-reviewed research articles and dissertations on the effects of ART on cognitive functioning in individuals with HIV or AIDS. Studies were identified using PubMed, PsycINFO, and Medline with the following search terms: ("human immunodeficiency virus" OR "HIV" OR "acquired immune deficiency syndrome" OR "AIDS") AND ("antiretrov*" OR "ART" OR "HAART") AND ("neuropsychol*" OR "cognit*" OR "neurocog*). A secondary search involved checking the reference sections of relevant review papers for articles that may have been missed

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

in the computerized search. Only articles in English were reviewed. Case studies were excluded.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: studies that compare cognitive functioning between HIV-positive patients receiving ART and those not receiving ART; studies that compare cognitive functioning before and after the initiation of ART; studies that use at least one commercially available neuropsychological test to evaluate cognitive functioning; study statistics must be convertible to effect size (e.g., means, standard deviations, *F*, *t*). Exclusion criteria were as follows: studies using HIV-positive patients who are comorbid with major neurological or psychiatric conditions (e.g., schizophrenia, Parkinson's disease); studies that measure cognitive functioning using self-report or experimental cognitive tasks.

Recorded Variables

Recorded variables included the full study reference and any moderator variables reported (e.g., age, duration of illness, and so on). Effect sizes were calculated for each neuropsychological test that measured some aspect of cognitive functioning. Organizing the myriad of cognitive test variables reported in the literature into a coherent classification was a major challenge. Several strategies exist in the literature for organizing diverse tests into categories of cognitive function, and each of these strategies has advantages and disadvantages. To this end, there exist *a priori* approaches such as Lezak, Howieson, and Loring's (2004) classification, which are influenced by theoretical and practice-related considerations about the test measures and their putative underlying processes. For example, Lezak et al. (2004) include motor and executive ability tasks in the same chapter, presumably on the basis of a common substrate in the frontal brain or some other assumed link. Such classifications have no quantitative statistical underpinning, and even advocates of this approach admit to an element of arbitrariness in test organization (see Lezak et al., 2004). A second approach is based on factor analytic studies of neuropsychological test batteries (see Goldstein, 1984). Factor analysis provides a quantitative description that relates different tests to a smaller number of underlying abilities. The validity of this approach as a general strategy for organizing tests in a meta-analysis, however, depends in part on the availability of factor analyses that include all of the tests in the literature on cognitive function in the treatment of HIV/AIDS. In the present case, we were unable to find factor analytic studies of ART in HIV/AIDS patient samples that included all, or even most, of the cognitive test variables reported in the literature. Finally, it is possible to avoid constructs altogether and simply compile effects for individual tests. This approach incorporates the fewest assumptions about the data, although it is unwieldy in view of the dozens of tests in common use and the inconsistency with which different scores from the same test are reported in the literature (e.g., categories vs. perseverative errors on the Wisconsin Card Sorting Test; see Heaton, Chelune, Talley, Kay, & Curtiss, 1993).

A further consideration is that regardless of classification method, several component processes probably influence many cognitive tests. Thus, scores on the Vocabulary subtest of the Wechsler Adult Intelligence Test (WAIS), for example, may reflect both language abilities and general intelligence while scores on the Trail Making Test may reflect visual scanning and perception but also motor speed, hand eye coordination, and attention (Lezak et al., 2004). Hence, it may be misleading to categorize tests on the basis of a faulty assumption that test performance is determined by only one process. Accordingly, we tried to avoid aggregating different tests and their effect sizes into our own hypothetical categories and adopted those defined by Lezak et al. (2004), and Strauss, Sherman, and Spreen (2006) as follows: attention, executive function, language, motor function, visuospatial function, immediate verbal memory, delayed verbal memory, immediate visual memory, and delayed visual memory. Table A1 (see Appendix) illustrates the specific neuropsychological tests that were aggregated into each generated category. Finally, to meet the assumption of independence, when multiple test variables in a study contributed to any one neuropsychological domain, the effect sizes were pooled together into a mean effect size (Borenstein et al., 2009). For each neuropsychological domain, these mean effect sizes were aggregated and analyzed further.

The following moderator variables were extracted from each study: age, education, HIV status (asymptomatic HIV, symptomatic HIV, or AIDS), length of time since HIV diagnosis, duration of ART treatment, type of ART (monotherapy vs. HAART), magnitude of change in CD4 cell count (measured by Cohen's *d*), magnitude of change in plasma viral RNA concentration (measured by Cohen's *d*), and year of publication.

Statistical Analyses

The Student's *t* test was used to compare the efficacy of HAART and monotherapy. Bonferroni correction was used to correct for multiple comparisons. For the moderator variable analyses, the relationship between individual effect sizes and moderator variables was initially explored using Pearson correlations. Significant univariate predictors of effect size were subsequently entered into a multiple linear regression model weighted by sample size. Significance was defined as $p < .05$. Analyses were performed using Comprehensive Meta Analysis 2.0 (Englewood, NJ) and SPSS 17.0 (Chicago, IL).

RESULTS

Study Characteristics

The literature search yielded 1014 articles. Of these, 23 articles met inclusion criteria. In total, cognitive functioning was assessed in 1598 HIV patients taking ART and in 996 HIV patients not taking ART. Mean age and education of HIV patients was 37.8 years ($SD = 4.0$ years) and 13.6 years

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table 1. Effect size results stratified by cognitive domain

Cognitive domain	*N*	Mean *d*	*SD*	95% CI	p_d	OL%	*Q*	p_Q	*T*
Attention	25	.17	.04	.09/.25	<.001	85.3	48.92	.002	.22
Executive function	27	.18	.04	.10/.26	<.001	85.3	92.81	<.001	.54
Language	9	.08	.10	−.13/.28	.48	92.3	1.36	.99	0
Motor function	20	.24	.04	.16/.32	<.001	85.3	64.99	<.001	.29
Visuospatial function	7	−.06	.07	−.20/.08	.37	92.3	24.72	<.001	.41
Immediate verbal memory	12	.04	.05	−.07/.15	.48	100.0	86.89	<.001	.55
Delayed verbal memory	15	.11	.05	.00/.21	.04	92.3	74.92	<.001	.44
Immediate visual memory	3	−.17	.07	−.31/−.02	.03	85.3	2.92	.23	.11
Delayed visual memory	5	.09	.10	−.12/.29	.42	92.3	25.22	<.001	.57

Note. *N* = number of studies; *SD* = standard deviation; CI = confidence interval; OL% = overlap percentage.

(*SD* = 4.9 years), respectively. Mean duration of ART was 16.7 months (*SD* = 15.7 months). Five studies examined the effects of monotherapy on cognitive outcome, 16 studies examined the effects of HAART on cognitive outcome, and 2 studies did not specify the type of ART regimen used. Nine studies used a between-subjects design, 11 studies used a within-subjects design, and 3 studies used a mixed design. Eight studies used patients who were naive to ART, 11 studies used patients who had prior exposure to ART, and 4 did not state whether their patients were treatment naïve. Only 1 study used a blind design. Three studies reported the mean time since AIDS diagnosis, whereas only three studies stratified their results according to stage of HIV illness (i.e., asymptomatic HIV, symptomatic HIV, or AIDS).

Mean Effect Sizes

Table 1 displays the mean effect sizes stratified by cognitive domain. Tables A2 and A3 (see Appendix) display the mean effect sizes stratified by neuropsychological test and study, respectively. The number of effect sizes in several domains exceeds the number of studies because some studies contributed more than one effect size (e.g., a study may have examined the effects of ART in several independent patient samples). The data indicate that, following ART, improvements in cognitive functioning were only observed in attention (mean $d = .17$; $p < .001$; 95% CI, .09/.25), executive function (mean $d = .18$; $p < .001$, 95% CI, .10/.26), motor function (mean $d = .24$; $p < .001$; 95% CI, .16/.32), and delayed verbal memory (mean $d = .11$; $p = .04$; 95% CI, .00/.21). Improvements in these domains were modest at best; examination of overlap percentages reveals that, with respect to attention, executive function, motor function, and delayed verbal memory, 85% to 92% of HIV patients taking ART performed at levels comparable to HIV patients not taking ART.

Examination of the *Q* statistic and *T* values (Table 1) indicates significant variation of effect size estimates for attention, executive function, motor function, and delayed verbal memory across studies. Funnel plot analyses for attention, executive function, motor function, and delayed verbal memory revealed asymmetry toward positive effect sizes, suggesting moderate publication bias (Figure 1). The high fail-safe *N* values for attention, executive function, and motor function (values ranging from 17 to 29; see Table 2), however, indicate that the improvements in these domains are robust and are unlikely to be artifacts of publication bias. Nevertheless, when effect sizes were corrected for publication bias using Duval and Tweedie's (2000a, 2000b) trim and fill method (Table 2), estimates of effect size for attention, executive function, and motor function were reduced from .17, .18, and .24 to .07, .12, and .15, respectively. Unlike attention, executive function, and motor function, the slight improvement in delayed verbal memory may be an artifact of publication bias, for it was driven by a small number of studies showing large effect sizes rather than a moderate number of studies showing moderate effect sizes. Indeed, examination of fail-safe *N* reveals that only one published study is needed to overturn the observed improvement in delayed verbal memory. The enhancement in delayed verbal memory performance must thus be interpreted with caution.

ART had no observable benefits for other domains such as immediate verbal memory, delayed visual memory, language, or visuospatial function. Patients taking ART showed slightly poorer performance on immediate visual memory tasks compared with patients not taking ART. This finding, however, must be interpreted with caution, for it is only based on three studies. The low fail-safe *N* value further suggests that the result is not robust and may be an artifact of publication bias.

Influence of Moderator Variables

Although the mean effect size was greater for HAART than for monotherapy in all domains, no significant differences were observed after correcting for multiple comparisons (Figure 2). None of the studies using monotherapy examined visual memory, so comparing HAART and monotherapy in this domain was not possible.

Table 3 displays univariate correlations between effect sizes in particular cognitive domains and moderator variables. Across cognitive domains, the degree of improvement in cognitive functioning strongly correlated with changes in CD4 cell count. In particular, greater improvements in attention, executive function, motor function, and visuospatial function were strongly associated with greater increases in

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

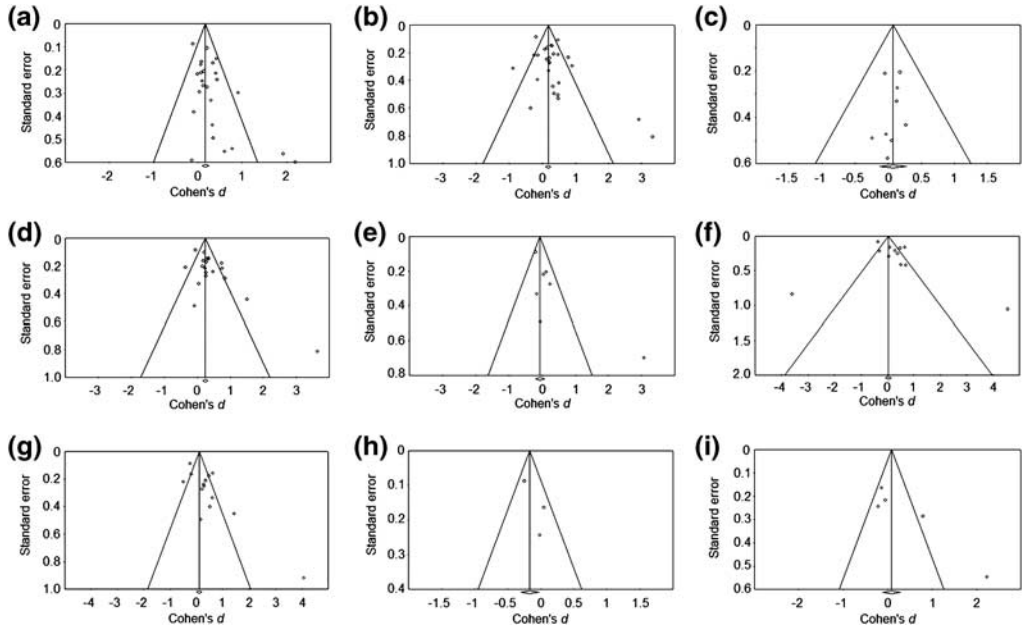

Fig. 1. Funnel plots for the domains of (a) attention, (b) executive function, (c) language, (d) motor function, (e) visuospatial function, (f) immediate verbal memory, (g) delayed verbal memory, (h) immediate visual memory, and (i) delayed visual memory. Asymmetry in the funnel plot indicates publication bias. Moderate publication bias favoring positive effect sizes was present in all cognitive domains except language, immediate verbal memory, and immediate visual memory.

CD4 cell count. Improvements in attention, executive function, visuospatial function, immediate verbal memory, and delayed verbal memory were negatively correlated with participant age. No correlations were observed between changes in cognitive performance and changes in viral load, as measured by plasma HIV RNA concentration, duration of ART, education, or year of publication. The negative correlation between delayed visual memory and year of publication can be attributed to a single study that reported an unusually large effect size rather than to several studies that reported moderate effect sizes; as a result, this correlation must be interpreted with caution.

Age and change in CD4 cell count were subsequently entered as predictor variables into a multiple linear regression model weighted by sample size. Effect size for attention, executive function, motor function, visuospatial function, immediate verbal memory, and delayed verbal memory were the dependent variables. Table 4 presents the results from the multiple regression analyses. The regression models were significant for attention, visuospatial function, and delayed verbal memory ($ps < .05$), but not executive function ($p = .20$), motor function ($p = .11$), and immediate verbal memory ($p = .32$). Greater change in CD4 cell count was a marginal predictor of improved attention ($\beta = .36$; $p = .13$), motor function ($\beta = .42$; $p = .11$), and visuospatial function ($\beta = .63$; $p = .05$). Older age was a significant predictor of smaller improvements in attention ($\beta = -.55$; $p = .03$) and delayed verbal memory ($\beta = -.63$; $p = .02$) and a marginal predictor of improved visuospatial function ($\beta = -.52$; $p = .08$). Together, age and change in CD4 cell count explained a substantial proportion of the variance in attention, visuospatial function, and delayed verbal memory, with adjusted R^2 ranging from .34 to .71.

Table 2. Analysis of publication bias

	Duval and Tweedie (2000a; 2000b)'s trim and fill				
Cognitive domain	Trimmed studies	Adjusted mean *d*	Adjusted 95% CI	Adjusted OL%	N_{fs}
Attention	9	.07	.00/.15	92.3	17
Executive function	6	.12	.04/.20	92.3	22
Language	0	.07	−.13/.28	92.3	<1
Motor function	6	.15	.08/.23	85.3	29
Visuospatial function	4	−.18	−.30/−.06	85.3	<1
Immediate verbal memory	4	−.09	−.19/.01	92.3	<1
Delayed verbal memory	7	−.11	−.19/−.02	92.3	1
Immediate visual memory	2	−.25	−.37/−.12	78.7	2
Delayed visual memory	1	.00	−.20/.21	100	<1

Note. CI = confidence interval; N_{fs} = fail-safe *N*; OL% = overlap percentage.

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

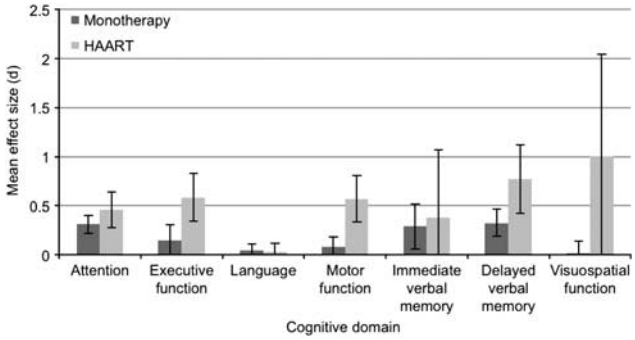

Fig. 2. Comparing the efficacy of highly active antiretroviral therapy (HAART) and monotherapy in different cognitive domains. After correcting for multiple comparisons, there were no statistical differences in effect size between monotherapy and HAART for any cognitive domain. Qualitatively, however, HAART showed a greater mean effect size than monotherapy across all cognitive domains. Values are mean ± *SEM*.

DISCUSSION

The present findings indicate that the efficacy of ART in alleviating HIV-associated cognitive dysfunction is modest. Results from our quantitative review indicate that 85% to 92% of HIV patients taking ART performed at levels comparable to HIV patients not taking ART. The modest benefits of ART may explain why the prevalence of HIV-associated cognitive impairment has remained high despite the advent of HAART (Robertson et al., 2007; Sacktor, 2002). Individual patients may exhibit dramatic improvement in cognitive functioning after taking ART, but the present data suggest that these patients are the exception rather than the rule.

Additionally, the benefits of ART are restricted to particular cognitive domains. Robust improvements were observed only in attention, motor function, and executive function. Enhanced performance in these domains was expected; a meta-analysis by Reger and colleagues (2002) found that attention, motor function, and executive function were particularly compromised among individuals with HIV. The observed improvement in motor function is consistent with recent data from the national CHARTER study showing a reduction in the prevalence of motor impairments since the advent of HAART (Heaton et al., 2011). Of interest, patients taking ART showed poorer immediate visual memory than patients not taking ART, suggesting that ART may have detrimental effects on certain aspects of cognition. This finding is consistent with prior studies showing persistent inflammation in the hippocampus, a brain region involved in memory (Squire, Stark, & Clark, 2004), among HIV patients taking HAART (Anthony, Ramage, Carnie, Simmonds, & Bell, 2005). Mechanistically, ART may exert its detrimental effects by facilitating central nervous system hyperstimulation (Marzolini et al., 2001). The finding that HIV patients show poorer immediate visual memory after ART, however, must be interpreted with caution. The result was only based on three studies and the low fail-safe *N* value suggests that the finding is not robust and may be an artifact of publication bias.

There were no observed benefits of ART on delayed visual memory or visuospatial function, two other domains commonly impaired in HIV patients (Reger et al., 2002). Despite the importance of these two domains, only four and seven studies examined the effects of ART on delayed visual memory and visuospatial function, respectively. The paucity of research on visual memory and visuospatial function after ART is surprising given that atrophy of the visual cortex is commonly observed among patients with HIV (Thompson et al., 2005). Additional studies are needed to further explore the integrity of visual memory and visuospatial function after ART.

Despite no statistical differences in effect size between studies using HAART and those using monotherapy, a qualitative examination of the data indicates that, across cognitive domains, the mean effect size for HAART is greater than the mean effect size for monotherapy (Figure 2). The failure to find statistical differences between monotherapy and HAART may be attributed to the small number of studies using monotherapy. The superior benefits of HAART may be partially attributed to its ability to normalize CD4 cell count

Table 3. Univariate Predictors of Improved Cognitive Functioning After ART

	Moderator variable					
Cognitive domain	Change in CD4 cell count (*d*)	Change in plasma RNA level (*d*)	Duration of ART (months)	Age (years)	Education (years)	Year of publication
Attention	.63**	.00	−.17	−.55**	−.30	−.10
Executive function	.62*	.02	−.03	−.49*	−.39	.01
Language	−.46	N/A	−.18	−.08	−.03	−.07
Motor function	.63**	−.04	−.17	−.49	−.42	−.14
Visuospatial function	.85*	.64	−.26	−.76*	−.62	−.05
Immediate verbal memory	−.14	−.06	−.15	−.61*	−.56	.18
Delayed verbal memory	.51	.09	−.40	−.69**	−.49	.14
Immediate visual memory	.10	N/A	N/A	−.58	.46	.30
Delayed visual memory	.87	N/A	−.63	−.73	−.56	−.82*

Note. *$p < .05$; **$p < .01$. N/A = not applicable (sample size was too small to conduct meaningful analysis).

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table 4. Multivariate analysis of moderator variables associated with improved cognitive functioning after ART

	Moderator variable				
	Change in CD4 cell count (*d*)		Age (years)		
Cognitive domain	β	*p*	β	*p*	Adjusted R^2 for entire model
Attention	.36	.13	−.55	.03	.38
Executive function	.35	.24	−.25	.39	.12
Motor function	.42	.11	N/A	N/A	.12
Visuospatial function	.63	.05	−.52	.08	.71
Immediate verbal memory	N/A	N/A	−.33	.32	.01
Delayed verbal memory	N/A	N/A	−.63	.02	.34

Note. N/A = not applicable (variable was not entered in regression analysis).

(Hammer et al., 1997; Mocroft et al., 2007). Indeed, univariate and multivariate analyses revealed that, in the case of attention, executive function, motor function, and visuospatial function, the extent to which ART improved cognitive outcome was correlated with its ability to enhance CD4 cell count. The integrity of the immune system thus appears to be linked to cognitive outcome among individuals with HIV. This finding supplements recent data from the national CHARTER study in which nadir CD4 cell count was found to correlate with neurocognitive functioning (Heaton et al., 2011). Since only 3 of the 23 included studies reported nadir CD4 cell count, the predictive strength of this variable could not be assessed in the current meta-analysis.

The observed relationship between CD4 cell count and cognitive functioning stands in stark contrast to several studies observing no correlation between CD4 cell count and neuropsychological test performance (Ferrando et al., 1998; Sun et al., 2010). By virtue of their small sample size, these individual studies may have had insufficient statistical power to detect correlations between CD4 cell count and cognitive functioning. By contrast, meta-analytic techniques, by synthesizing data across multiple studies, may possess sufficient power to detect such correlations (Borenstein et al., 2009).

As well as CD4 cell count, patient characteristics also mediate the ability of ART to improve cognitive functioning. Older patients showed smaller improvements in attention, visuospatial function, immediate verbal memory, and delayed verbal memory after taking ART. Why older individuals experienced smaller improvements in cognitive functioning after ART is unknown. Older individuals may have been infected with HIV for a longer time period. As a result, brain injury in older patients may have progressed to a stage where ART could no longer improve cognitive functioning. Prior studies suggest that time since AIDS diagnosis and stage of HIV illness are important determinants of the extent of cognitive impairment (Cysique & Brew, 2009; Heaton et al., 2011; Reger et al., 2002). Unfortunately, only 3 studies reported the time since AIDS diagnosis and the stage of HIV illness, so analyzing the contributions of these variables was not possible. Future studies should investigate how the efficacy of ART changes depending on the duration and stage of HIV illness.

The development of antiretroviral medications has transformed HIV infection from an inevitably fatal disease into a treatable condition. Despite the positive effects of ART on survival and immunological functioning (Fischl et al., 1987), the present results indicate that ART has only modest benefits in reducing HIV-associated cognitive impairment. Our findings may, therefore, be of interest to the practicing clinical neuropsychologist when interpreting change scores in the context of serial neuropsychological examinations of patients with HIV/AIDS before and after ART. Development of novel pharmaceutical treatments and rehabilitation strategies is needed to address the pressing issue of HIV-associated cognitive dysfunction.

ACKNOWLEDGMENTS

No financial support was provided for the present research. The authors note that they have no financial or other relationships that could be interpreted as a conflict of interest affecting this manuscript.

REFERENCES

References preceded by an asterisk were included in the meta-analysis.

Adamson, C.S., & Freed, E.O. (2008). Recent progress in antiretrovirals – Lessons from resistance. *Drug Discovery Today*, *13*, 424–432.

Anthony, I.C., Ramage, S.N., Carnie, F.W., Simmonds, P., & Bell, J.E. (2005). Influence of HAART on HIV-related CNS disease and neuroinflammation. *Journal of Neuropathology and Experimental Neurology*, *64*, 529–536.

Aylward, E.H., Henderer, J.D., McArthur, J.C., Brettschneider, P.D., Harris, G.J., Barta, P.E., & Pearlson, G.D. (1993). Reduced basal ganglia volume in HIV-1-associated dementia: Results from quantitative neuroimaging. *Neurology*, *43*, 2099–2104.

*Baldeweg, T., Catalan, J., Lovett, E., Gruzelier, J., Riccio, M., & Hawkins, D. (1995). Long-term zidovudine reduces neurocognitive deficits in HIV-1 infection. *AIDS*, *9*, 589–596.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., & Rothstein, H.R. (2009). *Introduction to meta-analysis*. West Sussex, UK: John Wiley & Sons, Ltd.

*Brouwers, P., Hendricks, M., Lietzau, J.A., Pluda, J.M., Mitsuya, H., Broder, S., & Yarchoan, R. (1997). Effect of combination

therapy with zidovudine and didanosine on neuropsychological functioning in patients with symptomatic HIV disease: A comparison of simultaneous and alternating regimens. *AIDS*, *11*, 59–66.

Carr, A. (2003). Toxicity of antiretroviral therapy and implications for drug development. *Nature Reviews Drug Discovery*, *2*, 624–634.

*Carvalhal, A.S., Rourke, S.B., Belmonte-Abreu, P., Correa, J., & Goldani, L.Z. (2006). Evaluation of neuropsychological performance of HIV-infected patients with minor motor cognitive dysfunction treated with highly active antiretroviral therapy. *Infection*, *24*, 357–360.

*Chang, L., Ernst, T., Witt, M.D., Ames, N., Walot, I., Jovicich, J., … Miller, E.N. (2003). Persistent brain abnormalities in antiretroviral-naïve HIV patients 3 months after HAART. *Antiviral Therapy*, *8*, 17–26.

Chen, Y., An, H., Zhu, H., Stone, T., Smith, J.K., Hall, C., … Lin, W. (2009). White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. *Neuroimage*, *47*, 1154–1162.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates.

*Cohen, R.A., Boland, R., Paul, R., Tashima, K.T., Schoenbaum, E.E., Celentano, D.D., … Carpenter, C.C. (2001). Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. *AIDS*, *15*, 341–345.

Cooper, H., & Hedges, L.V. (1994). *The handbook of research synthesis*. New York: Russell Sage Foundation.

Cysique, L.A., & Brew, B.J. (2009). Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: A review. *Neuropsychology Review*, *19*, 169–185.

Duval, S., & Tweedie, R. (2000a). A nonparametric 'trim and fill' method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association*, *95*, 89–98.

Duval, S., & Tweedie, R. (2000b). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta analysis. *Biometrics*, *56*, 455–463.

*Ferrando, S., van Gorp, W., McElhiney, M., Goggin, K., Sewell, M., & Rabkin, J. (1998). Highly active antiretroviral treatment in HIV infection: Benefits for neuropsychological function. *AIDS*, *12*, F65–F70.

Fischl, M.A., Richman, D.D., Grieco, M.H., Gottlieb, M.S., Volberding, P.A., Laskin, O.L., … King, D. (1987). The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. *New England Journal of Medicine*, *317*, 185–191.

Goldstein, G. (1984). Comprehensive neuropsychological assessment batteries. In G. Goldstein & M. Herson (Eds.), *Handbook of psychological assessment* (pp. 181–210). New York, NY: Pergamon Press.

Hammer, S.M., Squires, K.E., Hughes, M.D., Grimes, J.M., Demeter, L.M., Currier, J.S., … Fischl, M.A. (1997). A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS clinical trials group 320 study team. *New England Journal of Medicine*, *337*, 725–733.

*Hayman-Abello, S.E. (2006). The effects of highly active antiretroviral therapy (HAART) on neuropsychological status in HIV-infection: A prospective study. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, *67*, 4106.

Heaton, R.K., Chelune, G.J., Talley, J., Kay, G.G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test manual-revised and expanded*. Odessa, FL: Psychological Assessment Resources.

Heaton, R.K., Clifford, D.B., Franklin, D.R., Jr., Woods, S.P., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*, 2087–2096.

Heaton, R.K., Franklin, D.R., Ellis, R.J., McCutchan, J.A., Letendre, S.L., Leblanc, S., … Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *Journal of Neurovirology*, *17*, 3–16.

Hedges, L.V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. Orlando, FL: Academic Press.

Hunter, J.E., & Schmidt, F.L. (1990). *Methods of meta-analysis*. Newbury Park, CA: Sage Publications.

Joska, J.A., Gouse, H., Paul, R.H., Stein, D.J., & Flisher, A.J. (2010). Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. *Journal of Neurovirology*, *16*, 101–114.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological assessment* (4th ed.). New York, NY: Oxford University Press.

*Lindsey, J.C., Malee, K.M., Brouwers, P., & Hughes, M.D. (2007). Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy. *Pediatrics*, *119*, e681–e693.

Liner, K.J., Jr., Hall, C.D., & Robertson, K.R. (2008). Effects of antiretroviral therapy on cognitive impairment. *Current HIV/AIDS Reports*, *5*, 64–71.

Liner, K.J., Jr., Ro, M.J., & Robertson, K.R. (2010). HIV, antiretroviral therapies, and the brain. *Current HIV/AIDS Reports*, *7*, 85–91.

Lipsey, M.W., & Wilson, D.B. (1993). The efficacy of psychological, educational, and behavioral treatment. *American Psychologist*, *12*, 1181–1209.

*Llorente, A.M., van Gorp, W.G., Stern, M.J., George, L., Satz, P., Marcotte, T.D., & Hinkin, C.H. (2001). Long-term effects of high-dose zidovudine on neuropsychological performance in mildly symptomatic HIV-positive patients: Results of a randomized, double-blind, placebo-controlled investigation. *Journal of the International Neuropsychological Society*, *7*, 27–32.

*Martin, E.M., Pitrak, D.L., Novak, R.M., Pursell, K.J., & Mullane, K.M. (1999). Reaction times are faster in HIV-seropositive patients on antiretroviral therapy: A preliminary report. *Journal of Clinical and Experimental Neuropsychology*, *21*, 730–735.

Marzolini, C., Telenti, A., Decosterd, L.A., Greub, G., Biollaz, J., & Buclin, T. (2001). Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*, *15*, 71–75.

McArthur, J.C., Steiner, J., Sacktor, N., & Nath, A. (2010). Human immunodeficiency virus-associated neurocognitive disorders: Mind the gap. *Annals of Neurology*, *67*, 699–714.

*Millikin, C.P., Trépanier, L.L., & Rourke, S.B. (2005). Verbal fluency component analysis in adults with HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology*, *26*, 933–942.

Mocroft, A., Phillips, A.N., Gatell, J., Ledergerber, B., Fisher, M., Clumeck, N., … Lundgren, J.D. (2007). Normalization of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: An observational cohort study. *Lancet*, *370*, 407–413.

Orenstein, J.M., Fox, C., & Wahl, S.M. (1997). Macrophages as a source of HIV during opportunistic infections. *Science*, *276*, 1857–1861.

Orwin, R.G. (1983). A fail-safe N for effect size in meta-analysis. *Journal of Educational Statistics*, *8*, 157–159.

Reger, M., Welsh, R., Razani, J., Martin, D.J., & Boone, K.B. (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society*, *8*, 410–424.

*Richardson, J.L., Martin, E.M., Jiminez, N., Danley, K., Cohen, M., Carson, V.L., … Levine, A.M. (2002). Neuropsychological functioning in a cohort of HIV infected women: Importance of antiretroviral therapy. *Journal of the International Neuropsychological Society*, *8*, 781–793.

*Robertson, K.R., Robertson, W.T., Ford, S., Watson, D., Fiscus, S., Harp, A.G., & Hall, C.D. (2004). Highly active antiretroviral therapy improves neurocognitive functioning. *Journal of Acquired Immune Deficiency Syndromes*, *36*, 562–566.

Robertson, K.R., Smurzynski, M., Parsons, T.D., Wu, K., Bosch, R.J., Wu, J., … Ellis, R.J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, *21*, 1915–1921.

Rosenthal, R. (1991). *Meta-analytic procedures for social research*. Beverly Hills, CA: Sage Publications.

Rosenthal, R. (1995). Writing meta-analytic reviews. *Psychological Bulletin*, *118*, 183–192.

Sacktor, N. (2002). The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *Journal of Neurovirology*, *8*, 115–121.

*Sacktor, N.C., Lyles, R.H., Skolasky, R.L., Anderson, D.E., McArthur, J.C., McFarlane, G., … Miller, E.N. (1999). Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. *Multicenter AIDS cohort study (MACS). Neurology*, *52*, 1640–1647.

*Sacktor, N., McDermott, M.P., Marder, K., Schitto, G., Selnes, O.A., McArthur, J.C., … Epstein, L. (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *Journal of Neurovirology*, *8*, 136–142.

*Sacktor, N., Nakasujja, N., Skolasky, R., Robertson, K., Wong, M., Musisi, S., … Clifford, D.B. (2009). Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. *Neurology*, *72*, 165–170.

*Sacktor, N., Nakasujja, N., Skolasky, R., Robertson, K., Wong, M., Musisi, S., … Katabira, E. (2006). Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. *Neurology*, *67*, 311–314.

Squire, L.R., Stark, C.E., & Clark, R.E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279–306.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms and commentary* (3rd ed.). New York, NY: Oxford University Press.

Suarez, S., Baril, L., Stankoff, B., Khellaf, M., Dubois, B., Lubetzki, C., … Hauw, J. (2001). Outcome of patients with HIV-1-related cognitive impairment on highly active antiretroviral therapy. *AIDS*, *15*, 195–200.

Sun, B., Abadjian, L., Rempel, H., Calosing, C., Rothlind, J., & Pulliam, L. (2010). Peripheral biomarkers do not correlate with cognitive impairment in highly active antiretroviral therapy-treated subjects with human immunodeficiency virus type 1 infection. *Journal of Neurovirology*, *16*, 115–124.

Thompson, P.M., Dutton, R.A., Hayashi, K.M., Toga, A.W., Lopez, O.L., Aizenstein, H.J., & Becker, J.T. (2005). Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 15647–15652.

*Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M.F., Visco-Comandini, U., … Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: Prevalence and risk factors. *Journal of Acquired Immune Deficiency Syndromes*, *45*, 174–182.

*Tozzi, V., Balestra, P., Galgani, S., Narciso, P., Ferri, F., Sebastiani, G., … Benedetto, A. (1999). Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. *AIDS*, *13*, 1889–1897.

*Tozzi, V., Balestra, P., Galgani, S., Pasquale, N., Sampaolesi, A., Antinori, A., … Ippolito, G. (2001). Changes in neurocognitive performance in a cohort of patients treated with HAART for 3 years. *Journal of Acquired Immune Deficiency Syndromes*, *28*, 19–27.

*Tozzi, V., Balestra, P., Salvatori, M.F., Vlassi, C., Liuzzi, G., Giancola, M.L., … Antinori, A. (2009). Changes in cognition during antiretroviral therapy: Comparison of 2 different ranking systems to measure antiretroviral drug efficacy on HIV-associated neurocognitive disorders. *Journal of Acquired Immune Deficiency Syndromes*, *52*, 56–63.

*Tozzi, V., Narciso, P., Galgani, S., Sette, P., Balestra, P., Gerace, C., … Visco, G. (1993). Effects of zidovudine in 30 patients with mild to end-stage AIDS dementia complex. *AIDS*, *7*, 683–692.

*Winston, A., Duncombe, C., Li, P.C., Gill, J.M., Kerr, S.J., Puls, R., … Cooper, D.A. (2010). Does choice of combination antiretroviral therapy (cART) alter changes in cerebral function testing after 48 weeks in treatment-naive, HIV-1-infected individuals commencing cART? A randomized controlled study. *Clinical Infectious Diseases*, *50*, 920–929.

Zakzanis, K.K. (1998). Brain is related to behavior ($p < .05$). *Journal of Clinical and Experimental Neuropsychology*, *20*, 419–427.

Zakzanis, K.K. (2001). Statistics to tell the truth, the whole truth, and nothing but the truth: Formulae, illustrative numerical examples, and heuristic interpretation of effect size analyses for neuropsychological researchers. *Archives of Clinical Neuropsychology*, *16*, 653–667.

APPENDIX

Table A1. Neuropsychological tests categorized by cognitive domain

Cognitive domain					
Attention		Executive function		Language	
Test	*N*	Test	*N*	Test	*N*
2 and 7 Test	1	CogState (executive function)	1	Boston Naming Test	1
Choice Reaction Time	3	Colour Trails 2	4	Peabody Picture Vocabulary Test – Revised	1
CogState (Speed Composite)	1	Mental Alternations	1	Semantic Processing Test	1
Color Trails 1	4	Odd Man Out	1	Vocabulary (WAIS-R)	1
Corsi Blocks	3	Raven's Progressive Matrices	2	Wide Ranging Achievement Test – Revised	1
Digit Span	6	Stroop Test (Interference)	10		
Digit Symbol	9	Trail Making Test B	13		
Paced Auditory Serial Addition Test	1	Verbal Fluency	10		
Simple Reaction Time	3	Wisconsin Card Sorting Test	3		
Stroop Test (Color, Word)	7				
Symbol Digit Modalities Test	6				
Trail Making Test A	10				

Notes. *N* = number of studies that included the test; WAIS-R = Wechsler Adult Intelligence Scale – Revised.

Cognitive domain					
Motor function		Visuospatial function		Immediate verbal memory	
Test	*N*	Test	*N*	Test	*N*
Bayley Scale of Infant Development – II	1	Block Design (WAIS-R)	1	California Verbal Learning Test – Trials 1-5	2
Finger Tapping	2	Rey-Osterrieth Complex Figure – Copy	5	Logical memory (WMS-R) – Immediate Recall	1
Grooved Pegboard	14			Rey Auditory Verbal Learning Test – Trials 1–5	10
Timed Gait	4				

Note. *N* = number of studies that included the test; WAIS-R = Wechsler Adult Intelligence Scale – Revised; WMS-R = Wechsler Memory Scale – Revised.

Cognitive domain					
Delayed verbal memory		Immediate visual memory		Delayed visual memory	
Test	*N*	Test	*N*	Test	*N*
4-Word Recall Test	1	Figure Memory Test – Learning	1	Figure Memory Test – Recall	1
Babcock Story Recall Test	1	Rey-Osterrieth Complex Figure – Immediate Recall	1	Rey-Osterrieth Complex Figure – Delayed Recall	4
California Verbal Learning Test – Delayed Free Recall	2	Visual Reproduction (WMS-R) – Immediate Recall	1	Visual Reproduction (WMS-R) – Delayed Recall	1
Logical memory (WMS-R) – Delayed Recall	1				
Rey Auditory Verbal Learning Test – Delayed Free Recall	8				

Note. *N* = number of studies that included the test; WMS-R = Wechsler Memory Scale – Revised.

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table A2. Effect size results stratified by test measure

Cognitive domain	Test and variable		Mean *d*	*SD*	OL%
Attention					
	Choice Reaction Time		.22	.14	85.3
	Color Trails 1		.31	.09	78.7
	Corsi Blocks		.48	.20	66.6
	Digit Span				
		Forward	.41	.18	72.6
		Backward	.56	.19	61.8
	Digit Symbol		.37	.09	72.6
	Symbol Digit Modalities Test		.11	.06	92.3
	Simple Reaction Time		.27	.25	78.7
	Stroop Test (Colour, Word)		−.11	.11	92.3
	Trail Making Test A		.16	.09	85.3
Executive function					
	Color Trails 2		.34	.09	78.7
	Mental Alternations		.21	.16	85.3
	Odd Man Out		−.17	.09	85.3
	Raven's Progressive Matrices		.28	.21	78.7
	Stroop Test (Interference)		.19	.09	85.3
	Trail Making Test B		.13	.08	92.3
	Verbal Fluency		.05	.05	92.3
	Wisconsin Card Sorting Test (perseverative responses)		−.33	.19	78.7
Motor function					
	Finger Tapping		.51	.15	66.6
	Grooved Pegboard				
		Dominant hand	.22	.05	85.3
		Non-dominant hand	.24	.04	85.3
	Timed Gait		.28	.12	78.7
Language					
	Boston Naming Test		−.05	.21	92.3
	Peabody Picture Vocabulary Test – Revised		.14	.24	92.3
	Wide Ranging Achievement Test – Revised		.04	.24	100.0
Visuospatial function					
	Block Design (WAIS-R)		.06	.19	92.3
	Rey-Osterrieth Complex Figure – Copy		−.08	.08	92.3
Verbal memory					
	4-Word Recall Test		.31	.16	78.7
	Babcock Story Recall Test		2.17	.53	15.7
	California Verbal Learning Test				
		Trial 1	.28	.21	78.7
		Trial 5	.30	.21	78.7
		Trials 1-5	.48	.18	66.6
		Delayed free recall	.42	.14	72.6
	Logical Memory (WMS-R)				
		Immediate recall	.70	.42	57.0
		Delayed recall	.52	.40	66.6
	Rey Auditory Verbal Learning Test				
		Trial 1	.40	.26	72.6
		Trial 5	−.28	.08	78.7
		Trials 1-5	−.05	.06	92.3
		Delayed free recall	−.04	.06	100
Visual memory					
	Figure Memory Test				
		Learning	−.01	.24	100.0
		Recall	−.21	.24	85.3
	Rey-Osterrieth Complex Figure				
		Immediate recall	−.25	.09	78.7
		Delayed recall	.44	.16	72.6
	Visual Reproduction (WMS-R)				
		Immediate recall	.05	.16	92.3
		Delayed recall	−.14	.16	92.3

Note. SD = standard deviation; OL% = overlap percentage; WAIS-R = Wechsler Adult Intelligence Scale – Revised; WMS-R = Wechsler Memory Scale – Revised.

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table A3. Effect size results stratified by study

Study	Cognitive domain	Sample size (treatment)	Sample size (control)	Mean *d*	*SD*	OL%
Baldeweg et al. (1995)	Attention	22	35	.21	.27	85.3
		18	24	.30	.33	78.7
		12	9	.34	.49	78.7
	Executive function	22	35	.23	.27	85.3
		18	24	.19	.33	85.3
		12	9	.36	.49	72.6
	Language	22	35	.14	.27	92.3
		18	24	.13	.33	92.3
		12	9	−.24	.49	85.3
	Motor function	22	35	.27	.27	78.7
		18	24	.05	.33	92.3
		12	9	−.08	.49	92.3
	Visuospatial function	22	35	.25	.27	78.7
		18	24	−.15	.33	85.3
		12	9	−.05	.49	92.3
	Delayed verbal memory	22	35	.21	.27	85.3
		18	24	.60	.34	61.8
		12	9	.16	.50	85.3
Brouwers et al. (1997)	Attention	8	N/A	.60	.55	61.8
		6	N/A	−.14	.59	92.3
		9	N/A	.77	.54	52.6
		11	N/A	.33	.44	78.7
	Executive function	8	N/A	.48	.53	66.6
		6	N/A	−.35	.60	72.6
		9	N/A	.48	.51	66.6
		11	N/A	.33	.44	78.7
	Language	8	N/A	.05	.50	92.3
		6	N/A	−.01	.58	100
		9	N/A	−.03	.47	100
		11	N/A	.27	.43	78.7
Carvalhal et al. (2006)	Attention	14	N/A	−.09	.38	92.3
	Executive function	14	N/A	−.14	.39	92.3
	Immediate verbal memory	14	N/A	.70	.42	57.0
	Delayed verbal memory	14	N/A	.52	.40	66.6
Chang et al. (2003)	Attention	33	N/A	.10	.25	92.3
	Executive function	33	N/A	.14	.25	92.3
	Motor function	33	N/A	.27	.25	78.7
	Immediate verbal memory	33	N/A	.40	.26	72.6
	Delayed verbal memory	33	N/A	.30	.25	78.7
Cohen et al. (2001)	Attention	32	70	.40	.22	72.6
		23	70	.43	.24	72.6
	Executive function	32	70	.48	.22	66.6
		23	70	.22	.24	85.3
	Motor function	32	70	.75	.22	52.6
		23	70	.48	.24	66.6
	Delayed verbal memory	32	70	.35	.21	72.6
		23	70	.27	.24	78.7
Ferrando et al. (1998)	Attention	69	61	.06	.18	92.3
	Executive function	69	61	.08	.18	92.3
	Motor function	69	61	.75	.18	52.6
	Immediate verbal memory	69	61	.48	.18	66.6
	Delayed verbal memory	69	61	.47	.18	66.6
Hayman-Abello (2006)	Attention	79	33	.07	.21	92.3
	Executive function	76	31	−.13	.22	92.3
	Language	78	34	−.05	.21	92.3
	Motor function	79	34	−.35	.21	72.6

(Continued)

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table A3. Continued

Study	Cognitive domain	Sample size (treatment)	Sample size (control)	Mean *d*	*SD*	OL%
	Immediate verbal memory	78	34	.29	.21	78.7
	Delayed verbal memory	78	34	.35	.21	72.6
	Immediate visual memory	62	27	−.01	.24	100
	Delayed visual memory	62	27	−.21	.24	85.3
Lindsey et al. (2007)	Motor function	91	54	.28	.17	78.7
Llorente et al. (2001)	Attention	23	23	.04	.30	100
	Executive function	23	23	−.88	.31	48.4
	Immediate verbal memory	23	23	.06	.30	92.3
Martin et al. (1999)	Attention	79	63	.34	.17	78.7
Millikin et al. (2005)	Executive function	92	24	.79	.24	52.6
Richardson et al. (2002)	Attention	82	67	.08	.17	92.3
	Executive function	82	67	.15	.16	85.3
	Motor function	82	67	.18	.17	85.3
	Immediate verbal memory	82	67	.10	.16	92.3
	Delayed verbal memory	82	67	−.19	.17	85.3
	Immediate visual memory	82	67	.05	.16	92.3
	Delayed visual memory	82	67	−.14	.16	92.3
Robertson et al. (2004)	Attention	48	N/A	.14	.21	92.3
	Executive function	48	N/A	.35	.21	72.6
	Language	48	N/A	.18	.21	85.3
	Motor function	48	N/A	.16	.21	85.3
	Visuospatial function	48	N/A	.13	.20	92.3
Sacktor et al. (1999)	Executive function	78	97	.30	.15	78.7
	Motor function	97	97	.34	.14	78.7
		78	97	.29	.15	78.7
Sacktor et al. (2002)	Attention	251	272	−.11	.09	92.3
	Executive function	251	272	−.18	.09	85.3
	Motor function	251	272	−.05	.09	92.3
	Visuospatial function	251	272	−.19	.09	85.3
	Immediate verbal memory	251	272	−.35	.09	72.6
	Delayed verbal memory	251	272	−.24	.09	85.3
	Immediate visual memory	251	272	−.25	.09	78.7
Sacktor et al. (2006)	Attention	23	N/A	1.92	.56	20.6
	Executive function	23	N/A	3.33	.81	4.7
	Motor function	23	N/A	1.51	.44	29.3
	Immediate verbal memory	23	N/A	4.55	1.06	<2
	Delayed verbal memory	23	N/A	4.07	.92	2.3
Sacktor et al. (2009)	Attention	94	N/A	.42	.15	72.6
	Executive function	94	N/A	.28	.15	78.7
	Motor function	94	N/A	.35	.15	72.6
	Immediate verbal memory	94	N/A	.67	.16	57.0
	Delayed verbal memory	94	N/A	.62	.16	61.8
Tozzi et al. (1993)	Executive function	13	N/A	.51	.42	66.6
	Immediate verbal memory	13	N/A	.52	.42	66.6
Tozzi et al. (1999)	Attention	23	N/A	2.20	.60	15.7
	Executive function	23	N/A	2.92	.68	7.2
	Motor function	23	N/A	3.65	.81	3.7
	Visuospatial function	23	N/A	3.07	.70	7.2
	Immediate verbal memory	23	N/A	−3.60	.84	3.7
	Delayed verbal memory	23	N/A	1.43	.45	31.9
	Delayed visual memory	23	N/A	2.23	.55	15.7
Tozzi et al. (2001)	Attention	16	N/A	.91	.30	48.4
	Executive function	16	N/A	.90	.30	48.4
	Motor function	16	N/A	.84	.29	52.6
	Delayed visual memory	16	N/A	.80	.29	52.6

(Continued)

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press

Table A3. Continued

Study	Cognitive domain	Sample size (treatment)	Sample size (control)	Mean *d*	*SD*	OL%
Tozzi et al. (2007)	Attention	32	62	−.01	.22	100
	Executive function	32	62	−.25	.22	78.7
	Motor function	32	62	.24	.22	85.3
	Visuospatial function	32	62	.04	.22	100
	Immediate verbal memory	32	62	−.30	.22	78.7
	Delayed verbal memory	32	62	−.50	.22	66.6
	Delayed visual memory	32	62	−.05	.22	92.3
Tozzi et al. (2009)	Attention	185	N/A	.20	.11	85.3
	Executive function	185	N/A	.48	.11	66.6
	Motor function	185	N/A	.21	.11	85.3
Winston et al. (2010)	Attention	28	N/A	.12	.27	92.3
	Executive function	28	N/A	.21	.27	85.3

Note. SD = standard deviation; OL% = overlap percentage.

https://doi.org/10.1017/S1355617711000968 Published online by Cambridge University Press