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The global cognitive impairment in schizophrenia: Consistent over decades and around the world

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Abstract

Objective—Schizophrenia results in cognitive impairments as well as positive, negative, and disorganized symptomatology. The present study examines the extent to which these cognitive deficits are generalized across domains, potential moderator variables, and whether the pattern of cognitive findings reported in schizophrenia has remained consistent over time and across cultural and geographic variation.

Method—Relevant publications from 2006 to 2011 were identified through keyword searches in Pubmed and an examination of reference lists. Studies were included if they (1) compared the cognitive performance of adult schizophrenia patients and healthy controls, (2) based schizophrenia diagnoses on contemporary diagnostic criteria, (3) reported information sufficient to permit effect size calculation, (4) were reported in English, and (5) reported data for neuropsychological tests falling into at least 3 distinct cognitive domains. A set of 100 non-overlapping studies was identified, and effect sizes (Hedge's *g*) were calculated for each cognitive variable.

Results—Consistent with earlier analyses, patients with schizophrenia scored significantly lower than controls across all cognitive tests and domains (grand mean effect size, g = −1.03). Patients showed somewhat larger impairments in the domains of processing speed (g = −1.25) and episodic memory (g = −1.23). Our results also showed few inconsistencies when grouped by geographic region.

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JS, EG, and DD collected and analyzed the data and prepared the first draft of the manuscript. All authors contributed to manuscript revisions.

Conflict of Interest
The authors declare that they have no conflict of interest.

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Conclusions—The present study extends findings from 1980–2006 of a substantial, generalized cognitive impairment in schizophrenia, demonstrating that this finding has remained robust over time despite changes in assessment instruments and alterations in diagnostic criteria, and that it manifests similarly in different regions of the world despite linguistic and cultural differences.

Keywords

schizophrenia; cognition; neuropsychology; meta-analysis; processing speed; memory

1. Introduction

Schizophrenia is a “global” condition in many respects. It impacts widely-acting neurotransmitter systems (e.g. dopamine, glutatmate, GABA) through subtle changes in brain microstructure, physiology, and connectivity, and these neurobiological differences give rise to a variety of affective, cognitive, and psychotic symptoms. Epidemiologically, the disorder cuts across cultures, regions, and genders, with an estimated lifetime prevalence of about 1% of the world’s population. Functionally, schizophrenia is associated with considerable generalized disability, as affected individuals experience low rates of employment and marriage, decreased somatic health and quality of life, lower levels of educational achievement, and a marked decrease in life expectancy.

The effect that schizophrenia exerts on cognition can fairly be described as “global” as well. Resting on evidence from hundreds of studies and thousands of individuals, the finding that schizophrenia is associated with impairment across a wide range of higher-order cognitive performance domains is now well-established. Although some reviews highlight particularly large cognitive deficits in the domains of verbal episodic memory (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), executive functioning (Reichenberg and Harvey, 2007), or processing speed (Dickinson et al., 2007), the most consistent finding across studies has been an overall, generalized impairment across neuropsychological measures that persists in every clinical state and across patients’ lifespans (Hughes et al., 2003; Albus et al., 2002; Hill et al., 2004; Hyde et al., 1994). The relationship of cognitive impairment in schizophrenia to symptom severity is modest (Hughes et al., 2003; Dominguez et al., 2009; Rund et al., 2004; Ventura et al., 2010). However, cognitive impairment shows consistent association with indexes of everyday functional capacity. Several studies using a variety of cognitive assessment strategies have shown consistent associations between cogition and the UCSD Performance-based Skills Assessment, suggesting a high degree of criterion validity (Leifker et al., 2010). Cognitive variables are also widely used as intermediate phenotypes in genetic studies of schizophrenia, as attenuated cognitive deficits are seen even in the asymptomatic parents and siblings of schizophrenia patients (Dickinson et al., 2007), with some studies showing reduced impairment in more distant relatives (Glahn et al., 2007; Toulopoulou et al., 2007; Tuulio-Henriksson et al., 2003).

In 1998, Heinrichs and Zakzanis published the first large-scale meta-analysis of cognitive deficit findings in schizophrenia, drawing on more than 200 studies conducted between 1980 and 1997 (Heinrichs and Zakzanis, 1998) and documenting an overall mean impairment of 0.92 standard deviations relative to community comparison groups (Heinrichs, 2005). Various smaller reviews followed, generally focused on a particular cognitive domain

(Aleman et al., 1999) or set of measures (Bokat and Goldberg, 2003). Although narrower in focus than the Heinrichs review, our 2007 meta-analysis (Dickinson et al., 2007) offered a general update for studies completed in the decade following Heinrichs & Zakzanis (1998) and reported a similar outcome. Across measures and samples, this later analysis found a grand mean effect size of schizophrenia on cognitive performance of 0.98 standard deviations.

The newest cohort of neuropsychological studies, however, differs from those sampled in previous meta-analyses in several ways. First, while Heinrichs & Zakzanis's (1998) seminal publication included samples of patients diagnosed according to DSM-III and DSM-III-R criteria, studies conducted within the past decade have virtually all defined schizophrenia according to criteria laid out in the DSM-IV and DSM-IV-TR. Second, since Heinrichs & Zakzanis's (1998) meta-analysis, several canonical neuropsychological measures have been revised (e.g. WAIS, WMS, CPT), and expert judgment regarding the most appropriate measures for the study of schizophrenia has evolved, resulting in the emergence of testing arrays like the MATRICS Consensus Cognitive Battery (Kern et al., 2008; Nuechterlein et al., 2008). Finally, driven in part by the power requirements of genetics analyses, the most recent cohort of studies examining cognition in schizophrenia is uniquely international. The degree to which cognitive deficit findings in schizophrenia are similar across regions that differ substantially in both language and culture is unknown, however, and some performance differences have been reported across sites in different areas of the world (Harvey et al., 2003). As cognitive impairment is considered for inclusion as a possible specifier for psychotic disorders in ICD-11, the possibility of regional differences in neuropsychological measurement and/or performance is especially relevant.

A question in the field is whether decreased PubMed references to a "generalized deficit" in schizophrenia literature in recent years accurately reflects the reduced salience of generalized impairment for the field (Green et al., 2013). We believe the phenomenon remains of central relevance, hypothesizing that despite geographic dispersion of research samples as well as evolving assessment and diagnostic practices, evidence from recent years would show (1) broad impairment of cognitive performance in schizophrenia (2) a magnitude and pattern of impairment consistent with what was documented in earlier reviews, and (3) a similar magnitude and pattern of impairment in data from different geographic regions. We also investigated the effects of potential moderator variables on effect size, examining both clinical variables (e.g. medication, symptom ratings, chronicity of illness) and demographic variables (e.g. participants' sex, education).

2. Materials and methods

2.1 Study and variable selection

Articles incorporated into this analysis were identified through a series of PubMed searches using combinations of key words *schizophreni*, cogniti*, neurocogniti*, neuropsychologi*, executive function*, verbal, processing speed, psychomotor speed, perceptual speed,* and *attention*. The searches were conducted for the period from January 2006 through June 2012. The year 2006 was selected as a start date because it represents the end of the period reviewed by the most recent meta-analysis of schizophrenia and cognition (3) in the current

literature. In total, nearly 4000 articles were identified in preliminary searches. We retained a subset of these articles for examination in greater detail based on a review of their titles and abstracts. Additional publications were also found by searching the reference lists of these articles, yielding 376 studies in total.

Studies were included in the present analysis if they (1) compared the cognitive performance of adult schizophrenia patients and healthy controls (and mean ages of both samples were between 18 and 50 yrs), (2) based schizophrenia diagnoses on contemporary diagnostic criteria (e.g. *DSM-IV*, *DSM-IV-TR*, or *ICD-9* or later), (3) reported information sufficient to permit effect size calculation, (4) were reported in English, and (5) reported data for neuropsychological tests falling into at least 3 distinct cognitive domains. Of the 376 studies, we excluded 99 because of insufficient test batteries, 68 because of problems with the presentation of values, 18 because they did not compare schizophrenia patients and healthy controls, 17 because patients did not meet DSM-IV criteria for schizophrenia, 11 because subjects were matched for IQ, 9 because subjects' mean age fell outside of the acceptable range, and 2 because of abnormalities in the data due to study methodology (e.g. extreme flooring or ceiling effects). Where studies appeared to use the same (or overlapping) samples, we used data from only one of the studies. Accordingly, an additional 52 studies were eliminated due to overlap concerns, leaving exactly 100 studies that met all meta-analytic inclusion criteria.

Specific cognitive variables were included in our analysis if they appeared in at least 4 of the included studies. Altogether, we collected data on 46 cognitive variables, and assembled them into 10 familiar cognitive domains for presentation. In general, measures were combined on an individual test by individual test basis, but we also combined very similar measures in some instances. For example, we combined data across different list-learning tasks and across different sets of prompts for letter and category fluency tasks. Similarly, full-battery IQ scores and estimates based on IQ battery short forms were also combined, as were word reading scores from the Wide Range Achievement and National Adult Reading Tests.

Finally, we recorded information about a number of potential moderator variables. The clinical variables included severity/chronicity of illness, the presence and dose of antipsychotic medication, measures of symptom severity, and measures of global functioning. We also examined demographic variables including participants' sex, level of education, and the geographic location of the sample. Because several of these moderator variables were inconsistently reported, many moderator analyses had to be conducted in subsets of studies rather than in the entire group.

2.2. Data analysis

All analyses were performed using the Comprehensive Meta-analysis software package (Borenstein et al., 2000). Effect sizes for each cognitive variable were calculated as the mean difference between schizophrenia and healthy control performance divided by the pooled standard deviation and adjusted for small sample size bias (Hedges and Olkin, 1985). With few exceptions, the directions of these effect sizes were negative on a study-by-study level, indicating that schizophrenia patients performed worse than comparison subjects.

These values were then weighted and combined using a conservative random effects model. We also calculated 95% confidence intervals as well as a χ^2 statistic, Q, an indicator of variability across studies for a given effect size estimate. In our analysis of quantitative moderator variables, we also calculated the homogeneity statistics Q_{within} and $Q_{between}$. The Q_{within} statistic denotes the homogeneity or heterogeneity of studies within moderator variable subgroups, whereas the $Q_{between}$ statistic tests the significance of differences in effect size magnitude between moderator variable subgroups, similar to an F statistic.

To compare the current findings to past meta-analytic work, we compiled findings from two other non-overlapping meta-analyses that have addressed the same or comparable cognitive variables in this population (Heinrichs and Zakzanis, 1998; Dickinson et al., 2007), allowing us to examine the extent to which cognitive impairment in schizophrenia has remained stable across time and across changes in testing materials and diagnostic criteria. Additionally, as the vast majority of samples used in this analysis (N = 92) were from one of three distinct geographic clusters (closely approximating North America, Europe, and Asia), we divided these studies into three separate geographic regions to examine the consistency of generalized cognitive impairment across different cultures and areas of the world, again calculating Q_{within} and $Q_{between}$ statistics as measures of within-region and between-region variability, respectively.

3. Results

3.1 Main meta-analysis

The results of the main meta-analysis are presented in Table 1. Across these studies, data were analyzed from 9048 patients with schizophrenia and 8814 healthy comparison subjects. Of our 100 studies, 96 reported the mean ages of both patients and controls. The sample weighted mean age for the schizophrenia group was 35.1 years (range of study means: 20.1 to 48.5) years, compared with 35.6 years for controls (range: 19.0 to 48.7 years). In the set of 91 studies reporting participant sex, 49.9% of control participants and 66.8% of probands were male. The sample-weighted average of years of education across the 70 studies that provided this information was 12.1 years for patients (range: 9.0 to 14.3) and 13.9 for controls (range: 10.3 to 16.9). Finally, the average duration of illness for patients according to the 55 studies reporting this information was 13.2 years (range: 0.8 to 25.0), indicating considerable chronicity across the study sample as a whole.

Negative effect sizes in Table 1 indicate impairment in the schizophrenia group relative to healthy controls. As shown in this table, neuropsychological performance was significantly impaired in the schizophrenia group across all measures tested and all domains, with a grand mean weighted effect size of $g = -1.03$. The range of effect sizes for individual variables grouped by domain is illustrated in Figure 1. In line with our earlier meta-analysis (3), the largest effect size observed was for the Digit-Symbol Coding test ($g = -1.55$). The smallest effect size observed was for the WAIS Information subtest ($g = -0.43$).

Table 1 also provides weighted average effect sizes for each cognitive domain. Although different investigators may group cognitive variables differently, such summaries provide an approximate index of domain specificity. Across domains, impairment among schizophrenia

patients was substantial and fairly consistent, with most measure-by-measure and domain-level effect sizes falling in the medium to large range (−0.63 to −1.11). Inconsistency from study to study in terms of which variables and domains were available prevented a formal test of differences in degree of impairment across domains (e.g., group-by-domain interaction analyses). Although some effect sizes vary widely within a given domain (e.g. episodic memory; −0.68 to −1.41), these ranges largely reflect grouping decisions; some previous studies, for example, have elected to list tests of recognition memory separately from the rest of the episodic memory domain. Nevertheless, with the magnitude of the grand mean effect size (−1.03) nearly twice the range of the domain-level effect sizes (−0.68 to −1.25), it does not appear that the broad cognitive impairment across domains hinges on variable grouping decisions.

3.2 Moderator variable analyses

As displayed in Table 2, the results from this and two previous meta-analyses indicate that the profile of cognitive impairment in schizophrenia has remained remarkably stable over the past several decades. Although the earlier reviews did not provide enough information to analyze effect size differences statistically, most of the differences from review to review are small relative to the overall impairment.

Regarding the current analysis, significant Q-values in Table 1 signify greater variation in cognitive performance from study to study than would be expected by chance for 38 of the 46 individual effect sizes. We performed a series of analyses to examine the influence of moderator variables on effect size variability within the schizophrenia sample. Our first analysis examined the effect of geographic region on neuropsychological functioning (Table 3). Results indicated that the grand mean effect size, reflecting overall impairment, was strikingly consistent across the three regions examined ($Q_{between} = 0.21$, $p = 0.98$), a finding that also extended to the measure-by-measure analyses, with the exception of Vocabulary ($Q_{between} = 8.94$, $p = 0.01$) and Trails B ($Q_{between} = 21.54$, $p = 8.13 \times 10^{-5}$) tests.

Meta-regressions for age and education effects on impairment effect size were confounded in these data. Across studies, as the schizophrenia sample mean age increased, so did the degree to which the schizophrenia sample was relatively older than the control sample ($K = 96$, $r = .376$, $p = 8.02 \times 10^{-5}$), making it difficult to separate within group age effects from between groups age-disparity effects. Similarly, across studies, the mean years of education achieved by controls was highly correlated with the magnitude of the difference in years of education between controls and patients ($K = 70$, $r = .686$, $p < 1 \times 10^{-5}$). In regard to sex, the effect sizes derived from a given study tended to be larger in studies reporting a greater percentage of male patients ($K = 92$; $z = 2.45$, $p = 0.01$).

Among clinical variables, we found that neither schizophrenia age of onset ($K = 39$; $z = -0.36$, $p = 0.72$), duration of illness ($K = 55$; $z = 0.42$, $p = 0.68$), nor CPZE ($K = 28$; $z = -0.11$, $p = 0.91$) were significantly related to the magnitude of impairment observed. Consistent with the literature (e.g. 8), after excluding an outlying, medication-naïve, first episode sample from the analysis (115), we found no significant relationship between patient's scores on the PANSS positive symptom scale and cognition ($K = 40$, $z = -0.01$, $p = 0.99$). Somewhat surprisingly, we also observed no significant relationship between

impairment effect size and patient's scores on both the PANSS negative symptom scale (K = 41; z = 0.44, p = 0.66) and measures of total symptomatology, such as patient's PANSS Total Scores (K = 24; z = −1.04, p = 0.30), or scores on the BPRS (K = 15; z = −0.02, p = 0.98). In a small selection of studies reporting the data, cognitive impairment was not significantly associated with patients' global functioning (GAF) scores (K = 11; z = −0.72, p = 0.47).

4. Discussion

The current analysis updates the evidence of broad cognitive impairment in schizophrenia, again revealing moderate to severe impairment in people with schizophrenia relative to controls across all neuropsychological measures studied, and somewhat larger cognitive differences in the domains of processing speed and episodic memory (see Figure 1). These findings are quite consistent with earlier reviews. Remarkably, despite significant changes in diagnostic criteria, assessment materials and practice, and sample ascertainment, the observed variation in the overall, grand mean effect size of cognitive impairment in schizophrenia over three decades of research is about 0.1 standard deviations, less than 10% of the total impairment observed.

Geographic variation in the pattern of cognitive impairment in schizophrenia has not been examined in previous reviews. Our analyses indicate that the region of the world in which a cognition study is conducted has little impact on the effect sizes reported. The average grand means across groups of studies from Asia, Europe, and the United States are strikingly consistent (ranging from 1.02 to 1.08), despite substantial geographic, cultural, and linguistic differences across groups. Similar consistency can also be observed at the level of individual measures, with the exception of Vocabulary and Trails B tests. The reason for the differences by region in Vocabulary and Trails B performance is unclear, but variation in Vocabulary performance might relate in part to varying levels of multilingualism among the samples studied (Paez et al., 2006; Windsor and Kohnert, 2006). Variation in Trails B, on the other hand, may be partially attributable to differences in testing stimuli used in different countries (e.g. some Chinese versions of the test replace the letters with corresponding Chinese characters).

In an attempt to explain the substantial effect size heterogeneity observed in our main meta-analysis (see Table 1), we also examined several other moderator variables. Consistent with studies that report poorer cognitive functioning in male schizophrenia patients relative to females (Vaskinn et al., 2011), we found that studies with larger percentages of male patients tended to report larger effect sizes. In addition, we found that cognitive impairment was relatively unrelated to most measures of symptomatology, somewhat in contrast to studies highlighting modest but statistically reliable associations between cognition and negative or disorganized symptoms, including a recent meta-analysis on the topic (Dominguez et al., 2009).

Interestingly, our moderator analyses found no significant relationship between duration of illness and cognitive impairment. This finding is in line with data from longitudinal studies. A recent meta-analysis examining cognition in first-episode psychosis concluded that the

degree of cognitive change over time tends to be similar in cases and controls (Bozikas and Andreou, 2011). Although other studies have shown an association between cognition and indexes of everyday functioning (Green et al., 2000, 2004, 2006), including the Global Assessment of Functioning (GAF; Karilampi et al., 2011), we found no significant association between patient GAF scores and cognitive ability. This null finding may reflect the relatively small number of studies reporting GAF data in our sample (K = 11) or the mixture of symptom severity with everyday functioning in GAF ratings.

As with all meta-analyses, the findings reported in this paper are shaped by study selection methods, analytical methods, and the information made available to researchers in the studies selected for review. One difference between this review and some previous analyses is that we elected to include only studies that included at least one cognitive measure across at least three distinct domains. This resulted in a high representation in our study sample of "full neuropsychological battery" studies. We imposed this limitation because we judged such studies most likely to yield consistent, unbiased information about cognitive performance across measures. Despite this limitation, the present analysis is, as measured by combined sample size, the largest of its kind and results show a remarkable degree of consistency with past reviews.

In summary, this analysis of studies using contemporary neuropsychological tests and measures adds to the ample evidence of generalized cognitive impairment in schizophrenia. This impairment is probably the end-product of years of compromised neurodevelopment (Weinberger and Levitt, 2011) – and may be etiologically variable from person to person. Newer investigative methods from the cognitive and affective neuroscience literature will test whether this broad impairment can be divided into separable component processes (Carter and Barch, 2007). In its enthusiasm for these methods, the field has sometimes shown an inclination to question whether the cognitive impairment in this disorder is truly as generalized as it appears (Green et al., 2013). We would argue that the evidence for generalized cognitive impairment in schizophrenia – spanning decades and many thousands of research participants from around the globe – has reached the point of being overwhelming. Generalized cognitive impairment may present an unwieldy target for study, but it remains the clearest cognitive signal in schizophrenia research and a fundamental challenge for investigators trying to understand and treat this illness.

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(studies indicated with an asterisk were included in the main meta-analysis)

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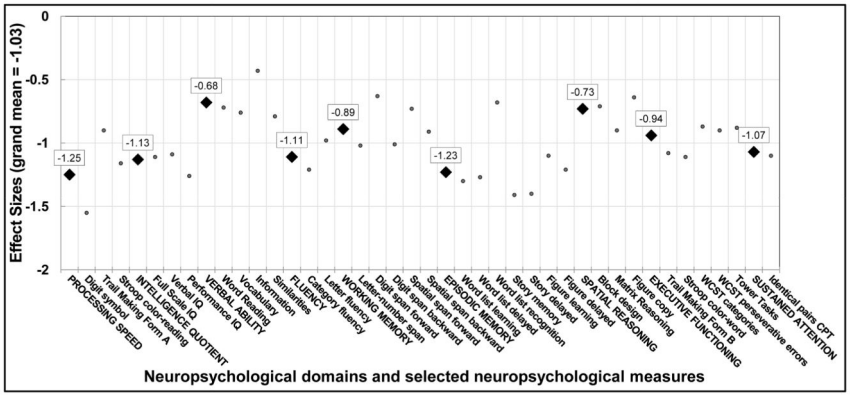

Figure 1.

Selected effect sizes for impairment in schizophrenia relative to control performance. Neuropsychological domain names are labeled in capital letters with black diamonds as effect size markers. Selected individual variables in each domain are marked with small black circles.

Table 1

Summary of meta-analytic results based on selected neuropsychological measures from 100 studies and 9048 people with schizophrenia.

Cognitive domain/measure	Number of Studies	Total Sample Size	Effect Size	Standard Error	95% Confidence Interval	Z-value	P-value	Heterogeneity Test	
								Q Statistic	P-value
Grand mean	100	17146	−1.03	0.03	−1.09 to −0.96	30.26	$<1 \times 10^{-8}$	329.98	$<1 \times 10^{-8}$
Processing speed (ES = −1.25)									
Digit symbol coding	22	7861	−1.55	0.11	−1.75 to −1.34	14.67	$<1 \times 10^{-8}$	271.79	$<1 \times 10^{-8}$
Trail Making Test part A	31	6388	−0.90	0.06	−1.02 to −0.78	15.05	$<1 \times 10^{-8}$	137.73	$<1 \times 10^{-8}$
Stroop color-reading condition	9	1117	−1.16	0.13	−1.42 to −0.90	8.75	$<1 \times 10^{-8}$	25.21	0.0014
IQ (ES = −1.13)									
General IQ	31	6661	−1.11	0.08	− 1.26 to −0.96	14.54	$<1 \times 10^{-8}$	183.65	$<1 \times 10^{-8}$
Verbal IQ	8	2091	−1.09	0.20	−1.48 to −0.70	5.49	4.0×10^{-8}	92.71	$<1 \times 10^{-8}$
Performance IQ	8	2096	−1.26	0.14	−1.54 to −0.99	8.87	$<1 \times 10^{-8}$	44.43	1.7×10^{-7}
Verbal ability (ES = −0.68)									
Word Reading	23	4579	−0.72	0.07	−0.86 to −0.58	10.30	$<1 \times 10^{-8}$	85.30	$<1 \times 10^{-8}$
Vocabulary	21	4008	−0.76	0.08	−0.90 to −0.61	10.01	$<1 \times 10^{-8}$	81.72	$<1 \times 10^{-8}$
Information	10	3524	−0.43	0.07	−0.56 to −0.29	6.02	$<1 \times 10^{-8}$	20.72	0.0140
Similarities	11	3811	−0.79	0.09	−0.97 to −0.62	8.80	$<1 \times 10^{-8}$	46.54	$<1 \times 10^{-8}$
Comprehension	6	684	−1.08	0.18	−1.43 to −0.74	6.11	$<1 \times 10^{-8}$	18.84	0.0021
Fluency (ES = −1.11)									
Category fluency	41	6853	−1.21	0.07	−1.35 to −1.07	17.012	$<1 \times 10^{-8}$	229.66	$<1 \times 10^{-8}$
Letter fluency	36	4845	−0.98	0.06	−1.09 to −0.86	16.87	$<1 \times 10^{-8}$	95.25	1.7×10^{-7}
Design fluency	4	464	−1.06	0.13	−1.31 to −0.80	8.12	$<1 \times 10^{-8}$	4.36	0.2252
Working memory (ES = −0.89)									
Letter-number sequencing	25	4871	−1.02	0.05	−1.12 to −0.93	20.52	$<1 \times 10^{-8}$	47.69	0.0031
N back (2 back)	4	1939	−0.94	0.19	−1.32 to −0.56	4.87	1.1×10^{-6}	30.58	1.0×10^{-6}
Digit span forward	18	4589	−0.63	0.09	−0.81 to −0.45	6.77	$<1 \times 10^{-8}$	111.37	$<1 \times 10^{-8}$
Digit span backward	20	4466	−1.01	0.10	−1.21 to −0.81	9.84	$<1 \times 10^{-8}$	145.80	$<1 \times 10^{-8}$
Spatial span forward	7	705	−0.73	0.15	−1.03 to −0.44	4.87	1.1×10^{-6}	20.53	0.0022
Spatial span backward	9	804	−0.91	0.10	−1.11 to −0.70	8.70	$<1 \times 10^{-8}$	14.31	0.0739

Cognitive domain/measure	Number of Studies	Total Sample Size	Effect Size	Standard Error	95% Confidence Interval	Z-value	P-value	Heterogeneity Test	
								Q Statistic	P-value
Spatial span total	5	657	−0.81	0.22	−1.24 to −0.39	3.77	1.6×10^{-4}	26.32	2.7×10^{5}
Motor speed (ES = −1.00)									
Grooved pegboard dominant	5	530	−0.86	0.17	−1.19 to −0.53	5.11	3.1×10^{-7}	10.71	0.0300
Grooved pegboard nondominant	4	478	−0.94	0.22	−1.37 to −0.50	4.24	2.2×10^{-5}	12.01	0.0073
Token Motor Task (BACS)	4	459	−1.23	0.17	−1.55 to −0.90	7.37	$<1 \times 10^{-8}$	6.89	0.0756
Episodic memory (ES = −1.23)									
Word list learning	42	8906	−1.30	0.06	−1.42 to −1.19	21.83	$<1 \times 10^{-8}$	202.18	$<1 \times 10^{-8}$
Word list learning delayed	32	4601	−1.27	0.06	−1.38 to −1.15	21.24	$<1 \times 10^{-8}$	85.26	5.8×10^{-7}
Word list recognition	10	2858	−0.68	0.06	−0.80 to −0.56	11.07	$<1 \times 10^{-8}$	13.25	0.1517
Story memory	16	5053	−1.41	0.09	−1.59 to −1.24	15.74	$<1 \times 10^{-8}$	92.90	$<1 \times 10^{-8}$
Story memory delayed	14	4681	−1.40	0.11	−1.60 to −1.19	13.09	$<1 \times 10^{-8}$	104.16	$<1 \times 10^{-8}$
Figure learning	14	4345	−1.10	0.14	−1.37 to −0.84	8.18	$<1 \times 10^{-8}$	171.98	$<1 \times 10^{-8}$
Figure learning delayed	16	4528	−1.21	0.14	−1.48 to −0.94	8.78	$<1 \times 10^{-8}$	209.49	$<1 \times 10^{-8}$
Visuospatial/problem solving (ES = −0.73)									
Block design	11	4930	−0.71	0.09	−0.89 to −0.52	7.60	$<1 \times 10^{-8}$	69.21	$<1 \times 10^{-8}$
Matrix Reasoning	12	1813	−0.90	0.07	−1.03 to −0.78	14.00	$<1 \times 10^{-8}$	14.65	0.1989
Figure copy	7	943	−0.64	0.17	−0.97 to −0.31	3.84	1.2×10^{-4}	31.49	2.0×10^{-5}
Picture completion	5	505	−0.64	0.12	−0.87 to −0.41	5.41	6×10^{-8}	6.14	0.1891
Executive functioning (ES = −0.94)									
Trail Making Test part B	37	7267	−1.08	0.06	−1.18 to −0.97	19.72	$<1 \times 10^{-8}$	128.24	$<1 \times 10^{-8}$
Stroop color-word condition	11	2764	−1.11	0.13	−1.36 to −0.85	8.55	$<1 \times 10^{-8}$	76.24	$<1 \times 10^{-8}$
Stroop interference	11	1222	−0.62	0.11	−0.83 to −0.41	5.80	$<1 \times 10^{-8}$	25.56	0.0044
WCST categories	33	6264	−0.87	0.07	−1.00 to −0.74	12.97	$<1 \times 10^{-8}$	157.86	$<1 \times 10^{-8}$
WCST perseverative errors	31	5232	−0.90	0.08	−1.05 to −0.75	11.78	$<1 \times 10^{-8}$	163.09	$<1 \times 10^{-8}$
WCST % perseverative errors	5	547	−0.68	0.10	−0.86 to −0.49	7.18	$<1 \times 10^{-8}$	3.31	$<1 \times 10^{-8}$
WCST total errors	7	695	−0.85	0.08	−1.01 to −0.69	10.58	$<1 \times 10^{-8}$	1.01	0.9854
Zoo Map	4	415	−1.09	0.11	−1.31 to −0.88	10.08	$<1 \times 10^{-8}$	2.33	0.5072
Tower Tasks total correct score	9	1358	−0.88	0.13	−1.13 to −0.64	6.97	$<1 \times 10^{-8}$	31.71	1.0×10^{-4}
Sustained attention (ES = −1.07)									

Cognitive domain/measure	Number of Studies	Total Sample Size	Effect Size	Standard Error	95% Confidence Interval	Z-value	P-value	Heterogeneity Test	
								Q Statistic	P-value
Identical pairs CPT (d′)	9	1257	−1.10	0.09	−1.28 to −0.91	11.72	$<1 \times 10^{-8}$	15.67	0.0474
Degraded stimulus CPT (rt)	5	750	−1.04	0.15	−1.33 to −0.75	6.97	$<1 \times 10^{-8}$	10.88	0.0279

Table 2

Side by side comparison of results from three meta-analysis samples comparing schizophrenia cognitive performance to controls, covering the years 1980 to 2012.

	Heinrichs & Zakzanis (1998); Zakzanis et al. (1999)		Dickinson et al. (2007)		Current analysis	
Time period covered	1980–1997		1995–2006		2006–2012	
Schizophrenia % male	82.4		…		66.8	
Overall number of studies included	204		37		100	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Schizophrenia sample age	34.4	10.0	31.5	7.3	35.1	9.5
Schizophrenia sample education	12.0	1.1	12.3	1.1	12.1	2.6
Duration of illness	12.7	7.6	9.1	5.9	13.2	9.3
Sample size per study	36.1	30.2	53	33.9	90.5	128.4
	Effect Size	**Schizophrenia Sample Size**	**Effect Size**	**Schizophrenia Sample Size**	**Effect Size**	**Schizophrenia Sample Size**
Meta-analysis Grand Mean	0.92	7420	0.98	1961	1.02	8617
Full Scale or Estimated IQ	1.1	1018	1.19	863	1.11	3273
Word Reading (“Premorbid IQ”)	0.42	1069	0.59	450	0.72	2087
WAIS Vocabulary	0.53	2046	0.9	586	0.76	1791
WAIS Block Design	0.46	1166	0.84	607	0.71	2179
Combined Verbal Learning	1.41	1088	…	…	…	…
Story Learning	…	…	1.19	863	1.41	2358
List Learning	…	…	1.25	1254	1.30	4730
Nonverbal/Figure Learning	0.74	379	0.82	544	1.10	1949
WCST Categories	1.01	1387	0.81	1018	0.87	2999
WCST Perseverative Errors	1.06	1387	0.79	1295	0.90	2393
Coding/Digit Symbol	1.11	1204	1.57	1961	1.55	3680
Trail Making Test, Form A	0.7	1204	0.88	1081	0.90	3114
Trail Making Test, Form B	0.8	1387	0.92	1190	1.08	3362

	Heinrichs & Zakzanis (1998); Zakzanis et al. (1999)		Dickinson et al. (2007)		Current analysis	
WAIS Digit Span Forward	0.69	440	0.73	175	0.63	1970
WAIS Digit Span Backward	0.82	440	0.86	155	1.01	2026
Combined Verbal Fluency	1.15	1020	…	…	…	…
Letter Fluency	…	…	0.83	1213	0.98	2300
Category Fluency	…	…	1.41	462	1.21	3166

Table 3

Results of a test-by-test comparative analysis investigating the extent to which effect sizes obtained from the main meta-analysis are robust to differences in geographic location. Measures used in fewer than 3 studies from a given region were excluded from this analysis.

Cognitive domain/measure		North America	Europe	Asia	$Q_{between}$	P-value
Grand mean	**No. of studies**	28	47	17	0.210	0.976
	N Schizophrenics	2114	4435	1498		
	Effect Size	1.04	1.02	1.08		
Processing speed						
Digit symbol coding	**N Schizophrenics**	772	2250	548	0.150	0.928
	Effect Size	1.45	1.58	1.56		
	Q_{within}	86.86**	69.50**	104.63**		
Trail Making Test part A	**N Schizophrenics**	963	1576	365	2.043	0.564
	Effect Size	1.04	0.89	0.87		
	Q_{within}	25.28*	38.99*	30.76**		
Intellectual/verbal ability						
General IQ	**N Schizophrenics**	275	2446	552	1.844	0.605
	Effect Size	1.26	1.09	1.01		
	Q_{within}	8.24	115.95**	55.15**		
Word Reading	**N Schizophrenics**	1247	309	330	3.172	0.205
	Effect Size	0.78	0.51	1.05		
	Q_{within}	32.85**	20.03*	22.42**		
Vocabulary	**N Schizophrenics**	347	1090	354	8.936	0.011
	Effect Size	0.99	0.56	0.95		
	Q_{within}	21.32*	30.01**	7.19*		
Fluency						
Category fluency	**N Schizophrenics**	712	1482	673	1.802	0.615
	Effect Size	1.02	1.29	1.22		
	Q_{within}	43.25**	62.17**	79.75**		
Letter fluency	**N Schizophrenics**	691	1120	285	6.546	0.088

Cognitive domain/measure		North America	Europe	Asia	$Q_{between}$	P-value
	Effect Size	0.90	1.14	0.87		
	Q_{within}	4.45	67.45**	1.33		
Episodic memory						
Word list learning	**N Schizophrenics**	1394	2626	407	1.272	0.736
	Effect Size	1.34	1.27	1.49		
	Q_{within}	48.70**	73.82**	15.84**		
Word list learning delayed	**N Schizophrenics**	577	1260	355	3.711	0.294
	Effect Size	1.32	1.22	1.40		
	Q_{within}	6.75	59.76**	2.06		
Story memory	**N Schizophrenics**	746	786	749	0.948	0.814
	Effect Size	1.52	1.34	1.43		
	Q_{within}	8.55*	30.50**	45.65**		
Story memory delayed	**N Schizophrenics**	667	785	626	1.874	0.599
	Effect Size	1.09	1.43	1.60		
	Q_{within}	35.52**	18.47*	40.82**		
Perceptual/problem solving						
Block design	**N Schizophrenics**	166	1445	568	4.119	0.128
	Effect Size	0.83	0.53	0.85		
	Q_{within}	0.94	20.62**	20.69**		
Executive functioning						
Trail Making Test part B	**N Schizophrenics**	1186	1529	523	21.541	8.13×10^{-5}
	Effect Size	1.26	1.05	0.85		
	Q_{within}	9.73	35.19*	18.82**		
Stroop color-word condition	**N Schizophrenics**	330	433	328	3.219	0.200
	Effect Size	1.17	1.28	0.77		
	Q_{within}	4.35	7.19	14.97**		
WCST categories	**N Schizophrenics**	1086	1009	709	0.455	0.929
	Effect Size	−0.86	−0.86	−0.82		

Cognitive domain/measure		North America	Europe	Asia	$Q_{between}$	P-value
WCST perseverative errors	Q_{within}	77.21**	35.08**	13.56	2.690	0.442
	N Schizophrenics	827	811	701		
	Effect Size	−0.80	−0.82	−1.07		
	Q_{within}	15.68*	18.12	116.75**		

* $p < .05$,

** $p \leq 0.01$