

Neurocognition in First-Episode Schizophrenia: A Meta-Analytic Review

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Compromised neurocognition is a core feature of schizophrenia. Following Heinrichs and Zakzanis's (1998) seminal meta-analysis of middle-aged and predominantly chronic schizophrenia samples, the aim of this study is to provide a meta-analysis of neurocognitive findings from 47 studies of first-episode (FE) schizophrenia published through October 2007. The meta-analysis uses 43 separate samples of 2,204 FE patients with a mean age of 25.5 and 2,775 largely age- and gender-matched control participants. FE samples demonstrated medium-to-large impairments across 10 neurocognitive domains (mean effect sizes from -0.64 to -1.20). Findings indicate that impairments are reliably and broadly present by the FE, approach or match the degree of deficit shown in well-established illness, and are maximal in immediate verbal memory and processing speed. Larger IQ impairments in the FE compared to the premorbid period, but comparable to later phases of illness suggests deterioration between premorbid and FE phases followed by deficit stability at the group level. Considerable heterogeneity of effect sizes across studies, however, underscores variability in manifestations of the illness and a need for improved reporting of sample characteristics to support moderator variable analyses.

Keywords: schizophrenia, psychosis, first-episode, neurocognition, meta-analysis

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It is well established that individuals with schizophrenia, as a group, reliably demonstrate performance below healthy controls on a broad array of neurocognitive measures (Heinrichs & Zakzanis, 1998). Neurocognitive dysfunction is strongly associated with functional disability (Green, 1996) and, despite noteworthy heterogeneity among individuals with schizophrenia (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2004; Seidman, 1990), is regarded by many as a core feature of the illness (Green, 1997; Nuechterlein & Dawson, 1984; Seidman, 1983; Seidman, Cassens, Kremen, & Pepple, 1992). However, the course of neurocognitive dysfunction in schizophrenia remains uncertain. Until the early 1990s, the majority of studies of neurocognition in schizophrenia

had been conducted with heterogeneous samples of adults largely composed of institutionalized individuals with chronic schizophrenia and long histories of somatic treatments (Bilder et al., 1992). Thus, in these mainly chronic samples, the nature of neurocognitive dysfunction is potentially confounded by the effects of age, clinical symptoms, illness duration and severity, and/or treatment. Over the past 15 to 20 years, however, a growing interest in the clinical and neurocognitive characteristics of early phases of schizophrenia emerged, a focus that has the potential to minimize many of the interpretive difficulties associated with studying chronically ill samples (Keshavan & Schooler, 1992; Lieberman et al., 1992).

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The study of individuals with schizophrenia beginning in the first episode (FE) has accelerated for several reasons. Perhaps most important was the observation that earlier treatment leads to better outcome (Wyatt, 1991), initiating a series of FE treatment studies that included extensive neuropsychological batteries (Keefe et al., 2004; Keefe, Seidman, et al. 2006; Keefe et al., 2007). It was also recognized that to test Kraepelin's (1919) notion of deterioration, neurocognitive assessment would have to be conducted at the "beginning" of full-blown psychosis, or as close as possible to the outset of the FE (Saykin et al., 1991). Moreover, as neurodevelopmental models accrued an evidence base (Lewis & Murray, 1987; Weinberger, 1987), it was increasingly recognized that neurocognitive impairments are often present before the illness begins (Fish, Marcus, Hans, Auerbach, & Perdue, 1992; Seidman, 1990). This raised interest in evaluating the nature and severity of neurocognitive function in the FE, in part to estimate how much impairment occurs in the evolution of the illness from its prepsychotic phases.

We conducted a meta-analysis of neurocognitive studies in FE schizophrenia because they hold the promise of shedding light on the course of cognitive deterioration in schizophrenia. To our knowledge, there are no published meta-analyses to organize this rapidly growing literature, and there is only one published qualitative review (Townsend & Norman, 2004). Meta-analytic procedures are superior to the traditional method of tallying statistically significant and nonsignificant results used in most narrative reviews because the latter disproportionately penalizes highly reliable studies with null findings. Moreover, a meta-analysis of studies with FE samples provides a quantitative benchmark for two critical comparisons. First, a comparison with the 204 studies of older and more chronic samples included in Heinrichs and Zakzanis' (1998) seminal meta-analytic work will enable modest inferences to be drawn about the degree to which neurocognition may change between the relatively early and later phases of the illness. Second, a comparison of FE samples with prodromal or premorbid samples will allow inferences to be drawn about the course of neurocognition as the illness evolves from a period of prepsychosis vulnerability to onset of frank symptoms of psychosis.

In regard to the first issue, the most robust evidence regarding the course of cognitive dysfunction associated with schizophrenia should be based on studies in which "early phase" or FE patients are followed over time (Milev, Ho, Arndt, & Andreasen, 2005). Although there are few methodologically strong longitudinal studies, those that have been published provide little evidence of ongoing deterioration in cognitive functioning after illness onset (Heaton, 2001; Rund, 1998; Stirling et al., 2003; Townsend & Norman, 2004). In contrast, some studies have documented mild improvements in cognition following the early acute phase (Simonsen et al., 2007), and improvements have sometimes been associated with medication effects (Keefe et al., 2004; Keefe, Seidman, et al. 2006). These changes in level of performance are typically modest (Simonsen et al., 2007) and may well be due to practice effects (Goldberg et al., 2007).

Regarding the second issue, Keefe, Perkins, et al. (2006) suggested that available studies indicated that the development of cognitive deficits in individuals with schizophrenia show a progressive pattern over the broad stages of the illness. They noted that numerous "premorbid" studies of children at familial risk for schizophrenia and follow-back studies converge to suggest that

cognitive deficits are often present before the onset of psychosis, at least in some mild form (e.g., Bilder et al., 2006; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Fuller et al., 2002; Seidman et al., 2006). We examine this idea by contrasting the results of the present meta-analysis with one recently completed on studies of premorbid IQ (Woodberry, Giuliano, & Seidman, 2008); over the past 40 years, IQ has probably been the most studied index of cognition in the prepsychosis phase.

Our primary goals then are to (a) identify the level and pattern of cognitive impairment in individuals in the FE of schizophrenia; (b) discern the extent to which individuals in the FE show levels and patterns of cognitive deficits comparable to people beyond the early phase of established illness; (c) examine the degree to which FE samples show greater cognitive impairment than those within their premorbid or possibly prodromal phases; and (d) determine the influence of moderator variables (e.g., sample characteristics and clinical features) on effect size (ES) differences between FE and control group samples' levels of neurocognition. Given the findings to date that bear on these issues, we predicted that (a) FE individuals would show moderate-to-large deficits across the range of neurocognitive domains studied; (b) FE samples would show a nearly comparable level and pattern of neurocognitive impairment to that reported in studies of individuals with established or chronic schizophrenia; (c) FE samples would show greater levels of impairment in cognition than samples drawn from familial or clinical high risk (or prodromal) groups; and (d) ES estimates of differences between FE and control samples would vary to some extent based on sample characteristics and study design features.

Method

Literature Search

Neuropsychological studies of adults in the FE of schizophrenia were identified through computerized searches of the Medline (PubMed) and PsycINFO bibliographic databases during 2005 to 2007. Search terms included combinations of the following: *schizophrenia*, *first episode*, *psychosis*, *cognitive*, and *neuropsychological*. References from studies retrieved were reviewed to identify additional articles. We explicitly excluded studies of affective psychoses, severe personality disorder at the border of psychosis (e.g., schizotypal personality disorder), and clinical high risk syndromes. The search cutoff date for all articles, including in-press articles, was October 2007. To be included in this review, studies needed (a) to be written in English, (b) to have a healthy comparison group, and (c) to include study statistics convertible to ESs (e.g., means, standard deviations, F , t , χ^2 ; see Wolf, 1986). For separately published studies that used the same participant samples but different cognitive tests, we decided to treat these studies as a single study with multiple-independent variables (Hedges & Olkin, 1985). The literature search yielded 47 publications (based on 43 separate samples) that were deemed suitable for meta-analysis. The studies ranged in publication date from 1994 to 2008 (although the search cutoff date was October 2007, some in-press articles had been published online by the time of this manuscript submission), with the bulk of these studies (93%) published in or after 2000. The 47 publications represented 14 different countries, with the majority of the studies conducted in the United States (US; 27.9%), Germany (14%), and Australia and Canada (9.3% each).

Sample and Procedures

Across the field of schizophrenia research and the studies reviewed, there is no firm consensus on criteria or methods for identifying *first-episode* schizophrenia. Of the 23 studies in this meta-analysis reporting these methods, most included participants at their first presentation of psychosis, index psychiatric hospitalization, or with a minimal length of prior treatment. Most investigators (95% of the studies) used *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., revised [*DSM-III-R*]; American Psychiatric Association, 1987) or *DSM-IV* (4th ed., American Psychiatric Association, 1994) criteria. Diagnostic criteria were typically determined through structured or semistructured interviews administered by trained professionals. Approximately 42% of participants were diagnosed only with schizophrenia, 10% only with schizophreniform disorder, and the remaining 48% included mixed samples of schizophrenia, schizoaffective, and schizophreniform disorders; a minority of the sample from one study (Bertrand, Sutton, Achim, Malla, & Lepage, 2007) included individuals diagnosed with psychosis not otherwise specified (16%).

Control participants typically underwent a similar screening process to clinical samples, with comparable exclusion criteria designed to identify the presence of psychiatric, neurologic, or medical illness that might impair cognitive functioning and confound results. Controls with positive family histories for psychosis (i.e., first or second degree relatives) or mental illness were typically excluded because they were expected to manifest some of the neurocognitive deficits in milder form found in people with schizophrenia (Faraone et al., 1995); however, not all studies provided explicit exclusionary criteria in this regard. Moreover, control samples varied on the basis of ascertainment process and exclusion criteria, particularly with regard to the presence or absence of current or past psychiatric disorders.

Statistical Analyses

Descriptive analyses were performed with SPSS, Versions 15 and 16 (SPSS Inc., Chicago). Meta-analytic procedures were computed with STATA, Version SE 9 (Stata Corp., College Station, TX) using the *metan*, *metabias*, and *metareg* programs. ESs for each dependent measure were expressed as the standardized mean difference (*SMD*) between schizophrenia and control group performance. *SMDs* were computed using Cohen's (1988) method as the difference between schizophrenia and control group means divided by the pooled standard deviation. ESs were interpreted according to Cohen's recommendations of cutoffs of 0.80, 0.50, and 0.20 for large, medium, and small ESs, respectively.

We did not use Hedge's correction for small samples because Cohen's *d* is more widely understood and the samples were sufficiently large according to the criteria of Green and Hall (1984; see also Hunter & Schmidt, 2004). We used the *Q* statistic to assess heterogeneity among studies. The meta-analyses used the random-effects model of DerSimonian and Laird (1986). Studies were weighted by the precision of their *SMD* estimate (which is proportional to the study sample size). We assessed publication bias (i.e., whether the available literature was biased toward excluding negative studies) using the method of Egger, Smith, Schneider, and Minder (1997). When enough studies were present to generate reasonable power, meta-analytic regression (using

metareg) was used to test whether ESs were influenced by specific study design features or sample characteristics (e.g., mean age).

Data were culled as available from each study on potential demographic and moderator variables of interest for both FE and control groups. These variables are listed in Table 1 along with information as to how often these variables were reported and whether the variable could be used as a moderator variable.

The most commonly reported demographic and other descriptive data are listed in Table 2. Among the 47 studies considered for the meta-analysis, 7 included overlapping participant samples but different cognitive tests. Of these studies, the 4 with the smallest sample sizes, compared to the studies they overlapped with, were omitted from analyses of demographic characteristics but included in analyses of cognitive test findings. In all, 43 study samples made up the 47 studies included in the meta-analysis yielding a total of 2,204 persons with FE schizophrenia and 2,775 control participants. Forty-one of 43 studies (95%) reported matching their FE and control samples. Although there were numerous combinations of matching variables, the most frequent variables included age (85%) and sex (76%). Other matching variables included education (34%), handedness (24%), estimated IQ (20%), parental education (20%), parental socioeconomic status (15%), race (12%), and country of birth (2%). Of the 40 studies reporting medication treatment, 37.4% of FE samples were medication naïve or medication free at the time of testing. Of the 22 studies reporting on clinical state during testing, 4 noted that the FE samples' symptoms were acute, whereas the other 18 studies indicated that the FE group was stable enough to tolerate testing procedures. Only 14 (33%) studies reported on mean length of illness and several listed approximate durations; with the exception of 2 studies, all others reported an average of 2 years or less for length of illness of FE samples. Few studies reported additional detailed information about potentially relevant demographic or clinical variables (see Table 1).

Dependent Variables

A wide variety of neuropsychological tests were used across the studies reviewed, including 156 cognitive test variables that contributed to our data analyses (see Table 3). Although some of these tests are not widely used, most are either well-recognized or variations of well-recognized instruments in the field of neuropsychology.

We categorized the tests into a set of broadly defined and putatively separable cognitive domains to provide a general framework for this review. Categorizing the test variables into cognitive domains was based predominantly on a review of prior meta-analyses of schizophrenia (e.g., Heinrichs & Zakzanis, 1998) and methods used by other groups who characterized neuropsychological functioning in schizophrenia, particularly FE schizophrenia (e.g., Bilder et al., 1995; 1988; 2000; Bilder, Mukherjee, Rieder, & Pandurangi, 1985; Blanchard & Neale, 1994; Heinrichs & Zakzanis, 1998; Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992; Saykin et al., 1991; 1994). Ten cognitive domains (see Table 3) are presented to organize the findings, though we readily acknowledge that this is but one of a number of classification systems that could have been used to facilitate interpretation, in large part because neuropsychological tests are multifactorial and not easily classified into single domains. These 10 cognitive domains include immediate verbal

Table 1
Potential Moderator Variables

Potential moderator variable	No. of studies reporting variable ^a	Usable for moderator analyses ^b
Publication year	43	Yes
Country where study conducted	43	Yes
Age	41	Yes
Gender (% male)	40	Yes
Education	26	Yes
Handedness (% right-handed)	17	Yes
Race/ethnicity	8 FE, 7 Controls	No
Participant SES	1	No
Parental SES	6	No
Parental education	5	No
Matching between patient and control groups	41	No
Variables specific to FE groups:		
Diagnosis	43	Yes
% treated with antipsychotic medications	40	Yes
Type of antipsychotic medication	40	No
Chlorpromazine-equivalent medication dose	7	No
Medication treatment duration	13	No
Conceptualization/definition of FE psychosis	23	No
Clinical state during testing	22	No
Duration of untreated psychosis	9	No
Length of prodrome	0	No
Age of onset	8	No
Duration of illness	14	No
Premorbid functioning	0	No
Psychosocial trauma exposure	0	No
First degree family history of psychotic illness	4	No
Family functioning	0	No
Comorbid medical disorders	18 reported none	No
Comorbid psychiatric disorders	12 (10 reported none)	No
Comorbid learning/developmental disorders	8 reported none	No
Comorbid neurological disorders	27 reported none	No
Severity of psychosis	36 reported scores from a variety of scales (1 reported a qualitative overall rating)	No
Number of hospitalizations for psychosis	17	No
Mean length of hospitalizations	3	No

Note. For moderator data to be usable in regressions, the data must have been reported in sufficient detail and have shown variability across studies. FE = first episode; SES = social economic status.

^a Includes total number of studies (of the 43 separate study samples) reporting the variable; however, moderator analyses were done separately for each neurocognitive domain, so the number of variables available for each domain-specific analysis varied based on the studies reporting test data for that particular domain. ^b If enough studies and data were present to generate reasonable power, meta-analytic regression was used to test whether neurocognitive domain effect sizes were influenced by the moderator variable of interest.

memory, attention (divided into three subdomains of processing speed, working memory, and vigilance), nonverbal memory, general cognitive ability, language functions, visuospatial abilities, delayed verbal memory and learning strategies, executive functioning, social cognition, and motor skills. We recognize that working memory is probably best conceptualized as a domain of executive functioning (Miyake et al., 2000), but we followed Heinrichs and Zakzanis (1998) to support direct comparative analysis. Similarly, we maintained the test categorizations that Heinrichs and Zakzanis termed *global* and *selective* verbal memory to support our goal of direct quantitative and interpretive comparisons. However, we relabeled these test categories as “immediate verbal memory” and “delayed verbal memory and learning strategies,” respectively, to reflect more meaningful descriptions of the test groupings. Our detailed tables provide ample transparency for identifying test-specific ESs.

Results

To facilitate comparisons with Heinrichs and Zakzanis' (1998) meta-analysis, results of our meta-analysis are organized and presented in a similar fashion by reporting mean *SMDs* and analyses by neurocognitive domain. However, to address questions related to differential impairment on specific tests, we have provided additional ES information (e.g., immediate verbal memory encoding or California Verbal Learning Test [CVLT] Trials 1 to 5 vs. Wechsler Memory Scale [WMS] Logical Memory Immediate Recall). The tables are organized by rank order from the largest to smallest ES within and across tables, such that Table 5 (immediate verbal memory) has the largest mean ES across tests and Table 16 (motor) has the smallest mean ES. Text presentation follows this same order. However, this rank ordering method is used only for organizational purposes, and, for reasons related to a variety of psychometric issues, is not meant to imply equivalent differential

Table 2
Study and Sample Characteristics

Characteristic	First episode schizophrenia			Control		
	<i>M</i> (<i>SD</i>) ^a	Range	<i>N</i>	<i>M</i> (<i>SD</i>) ^a	Range	<i>N</i>
Publication year	2003.9 (2.9)	1994–2008	43		n/a	
Country where study conducted (% in U.S.)	27.9	n/a	43		n/a	
Sample size	51.3 (42.8)	8–213	43	64.5 (94.7)	8–452	43
Age	25.5	15.6–33.0	41	28.5	16.8–49.0	41
% male	65.0	37.0–100	40	54.6	31.7–100	41
Education	11.8	9.2–14.1	26	12.5	10.3–15.4	26
% right-handed	90.3	71.3–100	17	95.4	75–100	17
No. hospitalizations for psychosis	1.0	0–1.65	17		n/a	
% on antipsychotics	62.6	0–100	40		n/a	

^a Standard deviations are only listed for the two characteristics, publication year and sample size, that did not require weighting by sample size.

deficits in specific brain systems or substrates, or specific relationships to developmental processes.

Neurocognitive Domains and Tests

This meta-analysis revealed medium-to-large deficits for FE schizophrenia compared to controls. Negative ES values indicate that FE groups performed worse than controls. Table 4 is organized in descending order by magnitude of ES. It shows that *SMDs* for each neurocognitive domain ranged from -1.20 in the immediate verbal memory domain to -0.64 in the domain of motor skills. These findings can be compared to Heinrich and Zakzanis' (1998) Table 11 (p. 434), which provides mean ESs ordered by magnitude and corrected for sample size. Note, however, that in our meta-analysis, "attention" is divided into three "subdomains": processing speed, working memory, and vigilance, following the approach of Nuechterlein et al. (2004).

As can be seen from a review of Tables 5 to 16, FE participants showed statistically significant impairments in each domain ($Z = 6.48$ to 21.21 , $ps < .001$) compared to controls. Not surprisingly, analyses frequently revealed significant heterogeneity across all neurocognitive domains and studies ($\chi^2s \geq 53.49$, $ps < .001$). Limited information relevant for moderator analyses limited our ability to identify sources of influence on the variability of ESs.

Memory. ESs for the three groups of memory tests are shown in Tables 5 to 7. The results show significant impairments in immediate verbal memory, including both serial list learning and story memory immediate recall ($SMD = -1.20$). Delayed verbal memory and learning strategies showed a smaller ES (-0.85) than immediate verbal memory. Similarly, though less frequently included in studies of cognition in individuals with schizophrenia, the nonverbal memory domain *SMD* was significant and substantial (-0.91).

Across all three memory domains, analyses revealed a significantly high degree of heterogeneity of ESs across studies. In terms of possible moderator variables, gender and diagnosis showed significant relationships with ES estimates for the immediate verbal memory domain, with smaller ESs observed in FE samples with smaller percentages of males, $t(32) = -2.12$, $p = .04$ and in publications with higher proportions of FE patients diagnosed with schizophrenia alone (compared to those that included schizophreniform disorder, or mixed samples of schizophrenia, schizoaffective and schizophreniform disorders), $t(36) = -2.09$, $p = .04$. Across the delayed verbal memory

and learning strategies domain, smaller ESs were found in more recent publications, $t(40) = 2.07$, $p = .05$. For nonverbal memory, smaller ESs were also reported in more recent publications, $t(22) = 2.86$, $p = .009$, in studies with higher percentages of FE participants on antipsychotic medication, $t(19) = 2.86$, $p = .01$, and in those conducted outside of the US, $t(21) = 3.58$, $p = .002$.

Attention: Processing speed, working memory, and vigilance. Attention was divided into three subcategories to include processing speed, working memory, and vigilance (comprised solely of indices from various versions of computerized continuous performance tests). Results for these domains are summarized in Tables 8 to 10.

The attention-processing speed domain is presented in Table 8. Meta-analysis yielded a significant overall domain ES of -0.96 , the second largest across all the domains. Among the specific tests within the processing speed domain and compared to all other individual tests analyzed, Digit Symbol-Coding yielded the largest ES ($SMD = -1.59$). A large ES was also contributed by the Stroop Color Naming task (Stroop, 1935; $SMD = -1.33$). Significantly smaller ESs were shown in more recent publications, $t(87) = 2.06$, $p = .04$ and in studies with higher percentages of right-handed and male FE participants, $t(31) = 2.09$, $p = .05$; $t(78) = 2.10$, $p = .04$, respectively.

The attention-working memory domain is presented in Table 9. We found a moderately large ES of -0.79 . Although only two studies contributed data, the largest ES within this domain came from tests of mental arithmetic ($SMD = -1.10$). Notably, the ES for the combined Digit Span test ($SMD = -0.86$) was greater than either the Digit Span Forward ($SMD = -0.50$) or Backward ($SMD = -0.79$) subtests alone, and the ES produced by Digit Span Backward was greater than that elicited by the Forward task. The computerized working memory tests ($SMD = -0.80$) showed a comparable ES with the combined and backward Digit Span tasks. Analysis of patterns of relationships among demographic and clinical variables showed significantly smaller ESs in studies with a higher percentage of right-handed controls, $t(11) = 2.31$, $p = .04$ and a lower percentage of right-handed FE patients, $t(11) = -2.29$, $p = .04$.

The attention-vigilance ES of -0.71 was significant (see Table 10). Moderator variable analyses revealed significantly smaller ESs in studies with a higher percentage of right-handed FE participants, $t(18) = 2.97$, $p = .008$ and a lower proportion of

Table 3

Neurocognitive Tests Used in Meta-Analyses Ordered by Neurocognitive Domain and Magnitude of Effect Sizes

Domain	Test
Immediate verbal memory	<ul style="list-style-type: none"> • WMS Logical Memory (LM) Immediate Recall from WMS, WMS-R and WMS-III (one study also included immediate recall scores from the Children's Memory Scale when age appropriate) • CVLT: List A, Trial 1; List A, Trial 5; Sum of Trials 1-5 Recall • RAVLT Trial 1; Trial 5; Sum of Trials 1-5 Recall • HVLT-R Sum of Trials 1-3 Recall • WMS Verbal Paired Associates (VPA) Immediate Recall from WMS and WMS-R
Attention: Processing speed	<ul style="list-style-type: none"> • Digit Symbol from WAIS-R and WAIS-III • Stroop: Word Task; Color Task; Color-Word Task; Color-Word Interference Score • Trail Making Test: Part A; Part B • Reaction time scores from computerized tasks: 27 scores from 8 studies
Nonverbal memory	<ul style="list-style-type: none"> • Benton Visual Retention Test • WMS Visual Reproduction (VR) Delayed Recall from WMS, WMS-R and WMS-III (one study also included delayed recall scores from the Children's Memory Scale when age appropriate) • WMS VR Immediate Recall from WMS, WMS-R and WMS-III (one study also included immediate recall scores from the Children's Memory Scale when age appropriate) • ROCFT Immediate Recall; Delayed Recall
General cognitive ability	<ul style="list-style-type: none"> • WAIS Full Scale IQ (FSIQ): FSIQ from WAIS, WAIS-R, WAIS-III, and WISC-III, prorated FSIQ from WAIS, Kaufman 4 test Short Form FSIQ from WAIS-R • WAIS Verbal IQ (VIQ): Prorated VIQ from WAIS, VIQ from WAIS-R and WAIS-III • Non-WAIS FSIQ: Ammons Quick Test IQ
Language functions	<ul style="list-style-type: none"> • Comprehension from WAIS-R and WAIS-III • Category Fluency: Animal Naming (COWAT); Animals, Occupations and Fruits; Stanford-Binet Word Fluency (Animals); Supermarket Test • Sentence Repetition from MAE • Boston Naming Test • Vocabulary from WAIS, WAIS-R (English versions and 1 Korean version), and WAIS-III • Similarities from WAIS, WAIS-R and WAIS-III • Other fluency tasks: Creative verbal fluency (write uses for can and string); FAS + animals combined; Verbal fluency (unspecified type; Chan, Chen, & Law, 2006) • Word Reading: NART; WRAT-R; WRAT-3 • Information from WAIS, WAIS-R and WAIS-III • Letter Fluency: FAS (COWAT); CFL (COWAT); CFL-PRW; LPS Subtask 6-Verbal Fluency; Verbal fluency (consonants, words per epoch; Boksman et al., 2005) • MWT-B Multiple-Choice Vocabulary Test
Visuospatial abilities	<ul style="list-style-type: none"> • Picture Arrangement from WAIS-R • Block Design from WAIS-R and WAIS-III (one study included scores from WISC-III when age appropriate) • Object Assembly from WAIS-R • Picture Completion from WAIS-R • Benton Judgment of Line Orientation Test • ROCFT Copy condition
Delayed verbal memory and learning strategies	<ul style="list-style-type: none"> • WMS Delayed Recall from WMS, WMS-R, and WMS-III (one study also included delayed recall scores from the Children's Memory Scale when age appropriate) • RAVLT Long Delay Free Recall; Recognition Hits/Discriminability • CVLT: Storage (Long Delay Free Recall-Trial 5); Semantic Clustering; Short Delay Free Recall; Short Delay Cued Recall; Long Delay Free Recall; Long Delay Cued Recall; Recognition Hits/Discriminability • WMS-R LM Savings
Executive functioning	<ul style="list-style-type: none"> • WCST: Perseverative Responses; Categories; Perseverative Errors; Total Errors
Attention: Working memory	<ul style="list-style-type: none"> • Arithmetic: WAIS-R and Israeli Draft Board Test • Digit Span from WAIS, WAIS-R and WAIS-III • Computerized Working Memory tasks: 13 variables from six studies; variables included % correct, omission errors, commission errors, and distance to target on delayed response for spatial working memory task • Digit Span Backwards from WAIS-R and WAIS-III • Digit Span Forward from WAIS-R and WAIS-III (one study included scores from WISC-III when age appropriate)

(table continues)

Table 3 (continued)

Domain	Test
Social cognition	· Computerized and noncomputerized Social Cognition tasks: 19 scores from five studies; tasks measured emotional acuity, labeling, differentiation/discrimination and matching, affective and linguistic prosody recognition, pragmatic language intention, and understanding thoughts, feelings and intentions of others.
Attention: Vigilance	· Computerized CPT Tasks: 37 variables from 15 studies; variables included CPT Hits, D-prime, omission errors, and commission errors
Motor skills	· Grooved Pegboard: Preferred (faster) and nonpreferred (slower) hands · Finger Tapping: Preferred (faster) and nonpreferred (slower) hands

Note. WMS = Wechsler Memory Scale (Wechsler, 1945); WMS-R = Wechsler Memory Scale-Revised (Wechsler, 1987); WMS-III = Wechsler Memory Scale-3rd edition (Wechsler, 1997b); Children's Memory Scale (Cohen, 1997); CVLT = California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987); RAVLT = Rey Auditory Verbal Learning Test (Lezak, 1995, pp. 438-442); HVLTL-R = Hopkins Verbal Learning Test-Revised (Brandt & Benedict, 2001); Benton Visual Retention Test (Benton, 1974); ROCFT = Rey-Osterrieth Complex Figure Test (Lezak, 1995, pp. 475-480); WAIS = Wechsler Adult Intelligence Scale (Wechsler, 1955); WAIS-R = Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981); WAIS-III = Wechsler Adult Intelligence Scale-3rd edition (Wechsler, 1997a); Stroop Test (Golden, 1978; Stroop, 1935); Trail Making Test (Reitan, 1958); Israeli Draft Board Test (Gal, 1986, pp. 77-96); WISC-III = Wechsler Intelligence Scale for Children-3rd edition (Wechsler, 1991); Ammons Quick Test (Ammons & Ammons, 1962); Kaufman Short Form (Kaufman, 1990); COWAT = Controlled Oral Word Association Test (Benton & Hamsher, 1989), Stanford-Binet Word Fluency (Terman & Merrill, 1973); Supermarket Test from Dementia Rating Scale (Mattis, 1988); Sentence Repetition from MAE (Multilingual Aphasia Examination; Benton & Hamsher, 1989); Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983); Creative Verbal Fluency (Schoppe, 1975); NART = National Adult Reading Test (Nelson, 1982); WRAT-R = Wide Range Achievement Test-Revised (Jastak & Wilkinson, 1984); WRAT-3 = Wide Range Achievement Test-3rd Edition (Wilkinson, 1993); LPS = Das Leistungsprüfungssystem (Horn, 1962); MWT-B Multiple Choice Vocabulary Test (Lehrl, 1991); Benton Judgment of Line Orientation Test (Lezak, 1995, pp. 400-401); WCST = Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Key, & Curtiss, 1993); Grooved Pegboard (Trites, 1977); Finger Tapping Test (Reitan & Wolfson, 1993).

right-handed control participants, $t(18) = -3.35, p = .004$, as well as in publications with fewer FE patients diagnosed with schizophrenia alone (compared to those that included schizophreniform disorder or mixed samples of schizophrenia, schizoaffective, and schizophreniform disorders), $t(35) = 2.06, p = .05$.

General cognitive ability. ESs for general cognitive ability is presented in Table 11. Meta-analysis of the 15 studies that included measures relevant to this domain yielded a large *SMD* of -0.91 . No available demographic or clinical variable was reliably associated with the magnitude of the ES across studies in this domain.

Language. ESs for language processing tests is shown in Table 12. Meta-analysis yielded a moderately large ES for this domain (*SMD* = -0.88). This domain is particularly heterogeneous in the measures included, ranging from a multiple-choice vocabulary test to measures such as Wechsler Adult Intelligence Scale (WAIS - all versions; see Table 3) Similarities and Comprehension, which require higher level abstraction and more complex verbal formulation and expression. As shown in Table 12, individual test ESs ranged from greater than -1.2 for WAIS Comprehension and category fluency tests to -0.67 for the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) Multiple-Choice Vocabulary test. Analysis of possible moderator variables on ES estimates suggested that more recent publications, studies conducted outside of the United States and those with a higher percentage of FE participants taking antipsychotic medication showed smaller ESs, $t(70) = 2.30, p = .024$, $t(69) = 2.99, p = .004$, $t(63) = 2.52, p = .01$, respectively, although studies that included controls with higher educational levels displayed larger ESs, $t(53) = -2.0, p = .05$.

Visuospatial abilities. A large ES was shown for the visuospatial ability domain (*SMD* = -0.88 ; see Table 13). Within this domain, ESs ranged between -1.36 for Picture Arrangement to -0.61 for the copy condition of the ROCFT. Moderator variable

analyses revealed significantly smaller ESs in studies with a higher percentage of males in the patient group, $t(18) = 2.13, p = .05$.

Executive functioning (EF). The EF domain is comprised only of variables derived from the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Key, & Curtiss, 1993): perseverative responses, total categories achieved, perseverative errors, and total errors. We recognize that EF is a large and complex domain comprised of many subcomponents including working memory, shifting, and inhibition (Miyake et al., 2000; Pennington & Ozonoff, 1996), constructs that Heinrichs and Zakzanis (1998) considered attention. Nevertheless, to compare our results with Heinrichs and Zakzanis, we used their categorization scheme. The WCST results document a large ES (*SMD* = -0.83 ; see Table 14). Across individual WCST variables, *SMDs* ranged from -0.57 for total errors to -0.99 for perseverative responses. We found a significant degree of heterogeneity across studies for the overall EF domain and for the WCST categories achieved and perseverative errors indices. Moderator variable analysis revealed significantly smaller ESs for studies published more recently, $t(28) = 3.18, p = .004$, studies conducted outside of the US, $t(27) = 2.38, p = .03$, and for those with a higher percentage of the FE sample on antipsychotic medication, $t(26) = 2.06, p = .05$.

Social cognition. Heinrichs and Zakzanis' (1998) meta-analysis examined only measures of nonsocial cognition. As shown in Table 15, meta-analysis of the five studies that included measures of social cognition yielded a moderately large ES (*SMD* = -0.77), highlighting the potential significance of this area of inquiry alongside traditional studies of nonsocial cognition. Moderator variable analyses revealed that ESs increased with the mean age of the control group, $t(13) = -5.56, p < .001$, recency of publication, $t(17) = -2.75, p = .01$ and the percentage of males in the FE group, $t(13) = -2.33, p = .04$. Smaller ESs were observed in studies conducted outside of the US, $t(16) = 3.88, p = .001$, with higher proportions of males in

Table 4
Mean Neurocognitive Effect Sizes Ordered by Magnitude

Domain or test	SMD	95% CI	nES	k
WAIS Digit Symbol	-1.59	-1.73 to -1.45	9	9
WMS Logical Memory I	-1.47	-1.76 to -1.17	10	10
WMS/CMS Logical Memory/Stories II	-1.37	-1.68 to -1.05	8	8
WAIS-R Picture Arrangement	-1.36	-1.57 to -1.14	2	2
CVLT Sum Trials 1-5	-1.34	-1.69 to -1.00	8	8
Stroop Color Task	-1.33	-1.53 to -1.13	5	5
RAVLT Sum Trials 1-5	-1.30	-1.87 to -0.73	5	5
WAIS Comprehension	-1.29	-1.62 to -0.96	3	3
Category Fluency	-1.24	-1.42 to -1.05	8	8
Immediate verbal memory domain	-1.20	-1.35 to -1.05	38	21
Benton Visual Retention Test	-1.20	-1.68 to -0.73	2	2
HVLT-R Sum Trials 1-3	-1.15	-1.57 to -0.73	2	2
Stroop Color-Word Task	-1.13	-1.27 to -0.99	8	8
RAVLT Trial 5	-1.11	-1.33 to -0.89	2	2
Arithmetic (WAIS-R & Israeli Draft Board)	-1.10	-1.40 to -0.80	2	2
Sentence Repetition	-1.08	-1.36 to -0.80	2	2
Stroop Word Task	-1.07	-1.25 to -0.89	6	6
RAVLT Long Delay Free Recall	-1.04	-1.38 to -0.71	7	7
WAIS Full Scale IQ	-1.01	-1.40 to -0.62	11	11
WMS Visual Reproduction I	-1.01	-1.24 to -0.78	7	7
Boston Naming Test	-1.01	-1.22 to -0.80	4	4
WCST Perseverative Responses	-0.99	-1.18 to -0.81	6	6
WMS Verbal Paired Associates I	-0.99	-1.37 to -0.62	3	3
WMS Visual Reproduction II	-0.98	-1.22 to -0.75	6	6
Attention-processing speed subdomain	-0.96	-1.05 to -0.86	89	25
WAIS Verbal IQ	-0.95	-1.57 to -0.32	3	3
WAIS Vocabulary	-0.94	-1.17 to -0.71	8	8
CVLT Long Delay Free Recall	-0.92	-1.25 to -0.60	4	4
Nonverbal memory domain	-0.91	-1.03 to -0.79	24	12
General cognitive ability domain	-0.91	-1.21 to -0.61	16	15
Trails B	-0.91	-1.07 to -0.74	15	15
WAIS Block Design	-0.90	-1.14 to -0.66	7	7
WAIS-R Object Assembly	-0.90	-1.17 to -0.63	3	3
Language functions domain	-0.88	-0.96 to -0.80	72	31
Visuospatial abilities domain	-0.88	-1.01 to -0.75	23	12
WAIS Similarities	0.88	-1.12 to -0.64	7	7
Grooved Pegboard, non-preferred hand	-0.88	-1.07 to -0.68	4	4
WAIS Digit Span	-0.86	-1.16 to -0.55	8	8
WAIS-R Picture Completion	-0.86	-1.04 to -0.69	3	3
Other Verbal Fluency	-0.86	-1.11 to -0.62	3	3
CVLT List A, Trial 5	-0.86	-1.62 to -0.10	2	2
Delayed verbal memory and learning strategies domain	-0.85	-0.99 to -0.71	42	16
WCST Categories	-0.84	-1.04 to -0.64	12	12
Executive functioning domain	-0.83	-0.95 to -0.72	30	17
Benton Judgment of Line Orientation	-0.83	-1.08 to -0.59	3	3
ROCFT Delayed Recall	-0.82	-1.07 to -0.57	5	5
WCST Perseverative Errors	-0.81	-1.01 to -0.60	10	10
RAVLT Trial 1	-0.81	-1.09 to -0.53	4	4
Trails A	-0.80	-0.93 to -0.67	15	15
Computerized Working Memory Tasks	-0.80	-1.05 to -0.54	13	6
Attention-working memory subdomain	-0.79	-0.93 to -0.65	32	21
WAIS Digit Span backward	-0.79	-1.01 to -0.57	5	5
Social cognition domain	-0.77	-1.01 to -0.54	19	5
CVLT Long Delay Cued Recall	-0.75	-1.01 to -0.48	3	3
Word Reading	-0.74	-0.92 to -0.56	14	14
WAIS Information	-0.73	-0.91 to -0.55	6	6
Attention-vigilance subdomain	-0.71	-0.87 to -0.55	37	15
Grooved Pegboard, preferred hand	-0.70	-0.89 to -0.50	4	4
Computerized Reaction Time Tasks	-0.69	-0.88 to -0.50	27	8
Letter Fluency	-0.69	-0.83 to -0.55	14	14
RAVLT Recognition Hits/Discriminability	-0.69	-1.14 to -0.23	4	4
CVLT Short Delay Cued Recall	-0.68	-0.96 to -0.40	3	3
MWT-B Vocabulary	-0.67	-1.19 to -0.15	3	3
CVLT Short Delay Free Recall	-0.66	-0.90 to -0.43	3	3

(table continues)

Table 4 (continued)

Domain or test	<i>SMD</i>	95% CI	<i>nES</i>	<i>k</i>
ROCFT Immediate Recall	-0.65	-0.80 to -0.49	4	4
CVLT List A, Trial 1	-0.65	-1.02 to -0.27	2	2
Motor skills domain	-0.64	-0.77 to -0.52	24	9
Stroop Color-Word Interference Score	-0.63	-1.01 to -0.26	4	4
Finger Tapping, preferred hand	-0.62	-0.90 to -0.34	8	8
ROCFT Copy	-0.61	-0.91 to -0.31	5	5
WMS-R Logical Memory Savings	-0.58	-1.07 to -0.09	2	2
WCST Total Errors	-0.57	-0.81 to -0.33	2	2
CVLT Semantic Clustering	-0.52	-0.83 to -0.21	3	3
Finger Tapping, non-preferred hand	-0.50	-0.74 to -0.27	8	8
WAIS Digit Span forward	-0.50	-0.91 to -0.10	4	4
CVLT Recognition Hits/Discriminability	-0.44	-0.67 to -0.22	3	3
CVLT Storage	-0.34	-0.62 to -0.06	2	2
Non-WAIS Full Scale IQ	-0.28	-0.60 to 0.05	2	2

Note. All effect sizes have already been corrected for sample size. Domains are bolded, and tests are in plain text. Further information about tests and domains are included in Tables 5-16. *SMD* = standardized mean difference; CI = confidence interval; *nES* = number of effect sizes; *k* = number of studies; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale; CMS = Children's Memory Scale; CVLT = California Verbal Learning Test; HVLTR = Hopkins Verbal Learning Test-Revised; RAVLT = Rey Auditory Verbal Learning Test; WCST = Wisconsin Card Sorting Test; MWT-B = Mehrfachwahl-Wortschatz Test (Form B); ROCFT = Rey-Osterrieth Complex Figure Test.

the control group, $t(13) = 5.29, p < .001$, and for those with a higher percentage of the FE sample on antipsychotic medication, $t(16) = 2.63, p = .02$.

Motor skills. FE schizophrenia individuals showed medium-sized deficits in fine motor speed and dexterity (*SMD* = -0.64; see Table 16). Analysis of moderator variables showed that larger ESs were observed in studies with younger patient samples, $t(21) = 2.34, p = .03$ and older control samples, $t(21) = -2.35, p = .03$, more males in the control group, $t(15) = -2.61, p = .02$, more FE participants on antipsychotic medication, $t(20) = -3.04, p = .006$ and more FE and control participants with higher educational levels, $t(16) = -2.09, p = .05$ and $t(16) = -3.34, p = .004$, respectively. Smaller ESs were reported in publications with higher percentages of right-handed individuals in the control group, $t(5) = 3.78, p = .01$.

Discussion

Overview

Our meta-analysis documents that FE or early phase schizophrenia shows statistically significant and clinically meaningful deficits across all neuropsychological domains. The weighted mean ESs across the 10 domains was medium to large, ranging from -.64 to -1.20. In short, neuropsychological deficits are broadly and reliably established by the FE, regardless of the variety of ways in which this early phase of the illness is operationalized for FE sample ascertainment.

The degree of impairment we showed for FE schizophrenia across domains approximates or matches that documented by

Table 5
Tests and Effect Sizes for Immediate Verbal Memory Domain

Test	<i>nES</i>	<i>k</i>	Participants		<i>M ES</i>				Heterogeneity		Publication bias (Egger's) ^a	
			<i>nFE</i>	<i>nC</i>	<i>SMD</i>	95% CI	<i>z</i>	<i>p</i>	χ^2	<i>p</i>	Coefficient	<i>p</i>
WMS Logical Memory I ^b	10	10	832	905	-1.47	-1.76 to -1.17	9.73	<.001	57.64	<.001	-3.38	.40
CVLT Sum Trials 1-5	8	8	451	504	-1.34	-1.69 to -1.00	7.69	<.001	34.53	<.001	-4.92	.28
RAVLT Sum Trials 1-5	5	5	420	184	-1.30	-1.87 to -0.73	4.48	<.001	31.55	<.001	0.53	.94
HVLTR Sum Trials 1-3	2	2	50	61	-1.15	-1.57 to -0.73	5.34	<.001	0.03	.87	—	—
RAVLT Trial 5	2	2	124	335	-1.11	-1.33 to -0.89	9.78	<.001	0.00	.97	—	—
WMS Verbal Paired Associates I ^c	3	3	202	238	-0.99	-1.37 to -0.62	5.18	<.001	5.97	.05	-15.09	.35
CVLT List A, Trial 5	2	2	120	141	-0.86	-1.62 to -0.10	2.23	.03	8.66	.003	—	—
RAVLT Trial 1	4	4	233	259	-0.81	-1.09 to -0.53	5.66	<.001	5.17	.16	-0.08	.98
CVLT List A, Trial 1	2	2	120	141	-0.65	-1.02 to -0.27	3.37	.001	2.25	.13	—	—
Global domain ES	38	21	1,396	1,441	-1.20	-1.35 to -1.05	15.42	<.001	207.21	<.001	-1.66	.30

Note. ES = effect size; *nES* = number of effect sizes; *k* = number of studies; *nFE* = number of First Episode participants; *nC* = number of Control participants; *SMD* = standardized mean difference; CI = confidence interval; WMS = Wechsler Memory Scale; HVLTR = Hopkins Verbal Learning Test-Revised; RAVLT = Rey Auditory Verbal Learning Test; CVLT = California Verbal Learning Test.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WMS (see Table 3). ^c Includes the WMS and WMS-R (see Table 3).

Table 6
Tests and Effect Sizes for Delayed Verbal Memory and Learning Strategies Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
WMS/CMS Logical Memory/Stories II ^b	8	8	698	774	-1.37	-1.68 to -1.05	8.52	<.001	43.05	<.001	-3.36	.46
RAVLT Long Delay Free Recall	7	7	544	519	-1.04	-1.38 to -0.71	6.09	<.001	28.59	<.001	1.87	.54
CVLT Long Delay Free Recall	4	4	235	201	-0.92	-1.25 to -0.60	5.58	<.001	7.10	.07	-0.56	.92
CVLT Long Delay Cued Recall	3	3	141	165	-0.75	-1.01 to -0.48	5.59	<.001	2.41	.30	0.96	.85
RAVLT Recognition												
Hits/Discriminability	4	4	248	392	-0.69	-1.14 to -0.23	2.97	.003	14.94	.002	3.08	.48
CVLT Short Delay Cued Recall	3	3	141	165	-0.68	-0.96 to -0.40	4.73	<.001	2.79	.25	1.09	.84
CVLT Short Delay Free Recall	3	3	141	165	-0.66	-0.90 to -0.43	5.62	<.001	1.05	.59	1.42	.65
WMS-R Logical Memory Savings	2	2	165	376	-0.58	-1.07 to -0.09	2.32	.02	5.64	.02	—	—
CVLT Semantic Clustering	3	3	223	155	-0.52	-0.83 to -0.21	3.32	.001	4.01	.14	-8.49	.44
CVLT Recognition Hits/ Discriminability	3	3	141	165	-0.44	-0.67 to -0.22	3.81	<.001	1.10	.58	0.99	.77
CVLT Storage	2	2	161	88	-0.34	-0.62 to -0.06	2.40	.02	1.08	.30	—	—
Global domain ES	42	16	1,126	1,070	-0.85	-0.99 to -0.71	11.91	<.001	232.95	<.001	0.47	.75

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WMS = Wechsler Memory Scale; CMS = Children's Memory Scale; RAVLT = Rey Auditory Verbal Learning Test; CVLT = California Verbal Learning Test.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WMS (see Table 3).

Heinrichs and Zakzanis (1998; *ds* = -.46 to -1.41) in their meta-analysis of adults (see Figure 1) who were, on average, 9 years older, had greater chronicity, and had substantially longer durations of medication exposure. Similarly, the ESs of our meta-analysis are largely comparable to those with other recent domain- or test-specific meta-analytic studies of mixed and mostly chronic samples of people with schizophrenia (e.g., memory: Aleman, Hijman, de Haan, & Kahn, 1999; executive functioning: Johnson-Selfridge & Zalewski, 2001; Laws, 1999; working memory: Lee & Park, 2005). Thus, illness chronicity and/or treatment exposure probably does not account for the most meaningful share of cognitive impairment in schizophrenia.

Although there is evidence of neurocognitive impairment in the premorbid and prodromal stages of schizophrenia (e.g., premorbid: Niemi, Suvisaari, Tuulio-Henriksson, & Lonnqvist, 2003; Seidman et al., 2006; prodrome: Brewer et al., 2006), the

magnitude of deficit appears to be significantly smaller than that observed at the onset of psychosis, and in some areas such as IQ, premorbid and prodromal deficits are clearly smaller. For example, in our meta-analysis of 18 studies of IQ among individuals who later develop schizophrenia, we documented a moderate ES of -0.54 (Woodberry et al., 2008). As shown in Figure 2, comparisons among ESs reported in the meta-analysis of premorbid IQ, this meta-analytic review, and those of Heinrichs and Zakzanis (1998) suggest that there is a moderate decline in IQ as the illness progresses into the FE. However, given that this trajectory is inferred from cross-sectional studies, we cannot be certain when this occurs.

Although the literature on pre-post psychosis neuropsychological assessment is surprisingly sparse, a number of studies also indicate a decline in IQ (Caspi et al., 2003; Lubin, Gieseking, & Williams, 1962; Seidman, Buka, Goldstein, & Tsuang,

Table 7
Tests and Effect Sizes for Nonverbal Memory Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
Benton Visual Retention Test	2	2	152	379	-1.20	-1.68 to -0.73	4.94	<.001	4.42	.04	—	—
WMS Visual Reproduction I ^b	7	7	422	442	-1.01	-1.24 to -0.78	8.56	<.001	13.51	.04	0.38	.90
WMS Visual Reproduction II ^b	6	6	321	358	-0.98	-1.22 to -0.75	8.19	<.001	9.10	.11	0.37	.91
ROCFT Delayed Recall	5	5	436	445	-0.82	-1.07 to -0.57	6.37	<.001	9.40	.05	-0.71	.83
ROCFT Immediate Recall	4	4	502	444	-0.65	-0.80 to -0.49	8.37	<.001	2.92	.40	0.99	.74
Global domain ES	24	12	977	917	-0.91	-1.03 to -0.79	14.74	<.001	58.90	<.001	-1.13	.38

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WMS = Wechsler Memory Scale; ROCFT = Rey-Osterreith Complex Figure Test.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WMS (see Table 3).

Table 8
Tests and Effect Sizes for Attention: Processing Speed Subdomain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ^2	p	Coefficient	p
WAIS Digit Symbol ^a	9	9	565	731	-1.59	-1.73 to -1.45	22.27	<.001	8.40	.40	0.30	.82
Stroop Color Task	5	5	263	310	-1.33	-1.53 to -1.13	13.24	<.001	2.30	.68	-0.91	.62
Stroop Color-Word Task	8	8	375	665	-1.13	-1.27 to -0.99	15.57	<.001	4.91	.67	0.58	.56
Stroop Word Task	6	6	310	317	-1.07	-1.25 to -0.89	11.59	<.001	3.82	.58	2.33	.20
Trails B	15	15	965	680	-0.91	-1.07 to -0.74	10.73	<.001	29.96	.008	-2.58	.08
Trails A	15	15	988	914	-0.80	-0.93 to -0.67	12.05	<.001	20.58	.11	-1.24	.25
Computerized Reaction Time Tasks	27	8	268	576	-0.69	-0.88 to -0.50	7.11	<.001	62.18	<.001	-0.42	.58
Stroop Color-Word Interference Score	4	4	256	415	-0.63	-1.01 to -0.26	3.29	.001	10.33	.02	-3.95	.07
Global domain ES	89	25	1365	1,652	-0.96	-1.05 to -0.86	19.97	<.001	313.72	<.001	-0.38	.51

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WAIS = Wechsler Adult Intelligence Scale.

^a Includes all versions of the WAIS (see Table 3).

2006). Again, however, it is difficult to determine from these studies when and in what proportion of subjects IQ declined. The emerging longitudinal prodromal studies may help to identify if there is a generalized or specific decline in cognitive functions within the interval from just before diagnosable illness to shortly thereafter (Caspi et al., 2003; Cornblatt et al., 2003; Niendam et al., 2006; Simon et al., 2007); these studies also hold the promise of elucidating the effects of developmental stage on levels and patterns of cognitive performance (e.g., age of onset, age at testing, change over time). Given the existing data, several models of neurocognitive functioning over the course of illness progression are plausible. Although there may be a gradual deterioration from the premorbid period to illness onset, a sharp decline immediately before or as the FE begins is also possible. At the same time, given evidence that there is a significant minority of people with schizophrenia who

demonstrate relatively normal neuropsychological functioning (e.g., Heinrichs & Awad, 1993; Heinrichs, Ruttan, Zakzanis, & Case, 1997; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997), some individuals may show little or no decline as the illness progresses, and still others may show some improvement in neurocognition following their initial acute episode. Studies of the period from the prodrome through the duration of untreated psychosis and into the treated early phase of schizophrenia may lead to a better understanding of the pattern and trajectory of neurocognitive functioning. Further research is needed to test the accuracy of these models, research that requires well-designed longitudinal studies that control for practice effects (see Goldberg et al., 2007) and examine factors that may contribute to heterogeneity (e.g., sex, age of onset, premorbid status) in patterns of cognitive change across illness phases and among individuals.

Table 9
Tests and Effect Sizes for Attention: Working Memory Subdomain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ^2	p	Coefficient	p
Arithmetic (WAIS-R & Israeli Draft Board)	2	2	138	80	-1.10	-1.40 to -0.80	7.16	<.001	0.09	.77	—	—
WAIS Digit Span ^b	8	8	493	636	-0.86	-1.16 to -0.55	5.53	<.001	32.92	<.001	-3.05	.19
Computerized Working Memory Tasks	13	6	290	332	-0.80	-1.05 to -0.54	6.19	<.001	25.72	.007	-0.03	.98
WAIS Digit Span backward ^b	5	5	318	510	-0.79	-1.01 to -0.57	7.04	<.001	5.88	.21	-2.46	.10
WAIS Digit Span forward ^b	4	4	258	472	-0.50	-0.91 to -0.10	2.44	.01	12.42	.006	-0.80	.84
Global domain ES	32	21	1198	1553	-0.79	-0.93 to -0.65	11.14	<.001	92.96	<.001	-1.14	.13

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WAIS = Wechsler Adult Intelligence Scale.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WAIS (see Table 1).

Table 10
Tests and Effect Sizes for Attention: Vigilance Subdomain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's)	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
Global domain ES	37	15	982	1,435	-0.71	-0.87 to -0.55	8.78	<.001	164.57	<.001	-0.48	.60

Note. Each test in this domain was a computerized test and was represented once across all studies, so all tests were combined to produce a global vigilance subdomain effect size (see Table 3 for further test information). ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval.

Generalized Versus Selective Cognitive Impairment

We must be cautious when discussing selective deficits because, as shown by Chapman and Chapman (1973, 1978), differences in the reliability between tests can mimic selective deficits. Our findings are consistent with research over the past decade that has repeatedly shown that schizophrenia is characterized by moderate to severe cognitive deficits that can be viewed as a generalized impairment (Blanchard & Neale, 1994; Dickinson & Harvey, 2009) or as multiple specific selective deficits of differential magnitude (Saykin et al., 1994). Among the most striking aspects of the cognitive profile of individuals with schizophrenia is that, at the group level, no cognitive function operates comparably to age- and gender-matched healthy control participants. We found that cognitive impairments were greatest for the domain of immediate verbal memory (SMD = -1.20) in the early phase of the illness, or, more specifically, new verbal learning and memory or encoding. This is consistent with Heinrichs and Zakzanis (1998; *d* = -1.41), as well as others (Aleman et al., 1999; Cirillo & Seidman, 2003; Saykin et al., 1991) who have shown or argued that if a selective or disproportionate cognitive deficit does exist at the “domain level” in schizophrenia, it would be in the domain of verbal declarative memory.

In contrast, unilateral motor skills showed the least but still significant (SMD = -.64) degree of impairment. The magnitude of this standardized difference between FE and control participants is lower than that reported by Heinrichs and Zakzanis (1998; *M_d* = -0.86). Although this finding indicates that some neuropsychological tasks (such as Finger Tapping) are less sensitive and reflect relatively milder deficits in motor speed/dexterity in the early

phase of schizophrenia, the reliably medium ES simultaneously contributes to the notion of broad-based neuropsychological impairments in schizophrenia.

In addition, like the difference between our immediate verbal memory domain ES and that reported by Heinrichs and Zakzanis (1998), our unilateral motor skills domain weighted mean ES is approximately one-fifth of a standard deviation lower. Although one or more variables may be contributing to these FE-control sample differences, one obvious possibility is that age and medication exposure or anticholinergic load (Minzenberg, Poole, Benton, & Vinogradov, 2004) may have a differential impact on performance in these domains, with younger and more treatment-naïve FE individuals likely to perform better than older, chronically medicated individuals with more established or multi-episode illness trajectories. Younger patients are also more likely to be taking atypical medications than those in the Heinrichs and Zakzanis meta-analysis, and the atypicals have fewer motor side effects than the typicals (Tandon & Fleischhacker, 2005).

Profile and Magnitude of Impairment Associated With FE Schizophrenia

This meta-analysis documents significant memory impairment in FE schizophrenia maximized in immediate episodic or verbal declarative memory. On measures of immediate verbal learning and memory, our large ES of -1.20 is comparable to the work of Aleman and colleagues (1999; *d* = -1.22) and Dickinson, Ramsey, and Gold (2007; *ds* = -1.12 to -1.25); both of these meta-analytic studies, like Heinrichs and Zakzanis (1998), were

Table 11
Tests and Effect Sizes for General Cognitive Ability Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
WAIS Full Scale IQ ^b	11	11	406	306	-1.01	-1.40 to -0.62	5.05	<.001	75.65	<.001	-6.91	.03
WAIS Verbal IQ ^b	3	3	232	132	-0.95	-1.57 to -0.32	2.95	.003	13.46	.001	8.99	.70
Non-WAIS Full Scale IQ	2	2	70	75	-0.28	-0.60 to 0.05	1.65	.10	0.01	.92	—	—
Global domain ES	16	15	614	477	-0.91	-1.21 to -0.61	5.94	<.001	101.43	<.001	-4.08	.10

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WAIS = Wechsler Adult Intelligence Scale.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WAIS (see Table 3).

Table 12
Tests and Effect Sizes for Language Functions Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ^2	p	Coefficient	p
WAIS												
Comprehension ^b	3	3	208	464	-1.29	-1.62 to -0.96	7.64	<.001	5.06	.08	3.84	.46
Category Fluency	8	8	727	486	-1.24	-1.42 to -1.05	13.20	<.001	12.73	.08	-3.06	.22
Sentence Repetition	2	2	131	167	-1.08	-1.36 to -0.80	7.59	<.001	0.85	.36	—	—
Boston Naming Test	4	4	207	258	-1.01	-1.22 to -0.80	9.38	<.001	2.37	.50	2.44	.33
WAIS Vocabulary ^b	8	8	405	653	-0.94	-1.17 to -0.71	7.98	<.001	15.58	.03	-0.47	.78
WAIS Similarities ^b	7	7	475	689	-0.88	-1.12 to -0.64	7.14	<.001	18.59	.005	-0.99	.78
Other Fluency	3	3	185	118	-0.86	-1.11 to -0.62	6.88	<.001	1.76	.42	-2.89	.53
Word Reading	14	14	667	654	-0.74	-0.92 to -0.56	8.10	<.001	33.44	.001	-2.95	.07
WAIS Information ^b	6	6	431	645	-0.73	-0.91 to -0.55	7.79	<.001	8.36	.14	0.36	.91
Letter Fluency	14	14	917	1,222	-0.69	-0.83 to -0.55	9.62	<.001	22.35	.05	-2.48	.004
MWT-B												
Vocabulary	3	3	153	246	-0.67	-1.19 to -0.15	2.52	.01	9.63	.008	5.49	.33
Global domain ES	72	31	1,934	2,135	-0.88	-0.96 to -0.80	21.21	<.001	221.14	<.001	-1.28	.08

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WAIS = Wechsler Adult Intelligence Scale.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WAIS (see Table 3).

mostly comprised of older, medicated and chronically ill schizophrenia samples. For reasons perhaps most related to the dominant perspective in the field that verbal memory impairment is a selective cognitive deficit and is associated with models of schizophrenia that emphasize left temporal and left prefrontal brain dysfunction (e.g., Cirillo & Seidman, 2003; Seidman et al., 2003), nonverbal memory has received markedly less attention in research and theory. However, as shown in this and other meta-analyses (Aleman et al., 1999; Heinrichs & Zakzanis, 1998), the memory impairment in schizophrenia is not modality specific. Our findings support the presence of a smaller, but still large, impairment in nonverbal memory ($SMD = -0.91$). Our nonverbal memory ES estimate is intermediate between that reported by Heinrichs and

Zakzanis ($d = -0.74$) and Aleman and colleagues ($ds = -1.0$ to -1.09) for similar measures, and is comparable to our delayed verbal memory and learning strategies domain ($d = -0.85$), which included a variety of delayed verbal recall measures.

It is also notable that a meta-analysis of memory impairment in adults with major depression (Burt, Zembler, & Niederehe, 1995) showed a more modest ES ($d = -0.56$) across 54 studies. Such a comparison further underscores that memory impairment in schizophrenia is substantially more severe. At the same time, it is important to recognize that of those individuals with schizophrenia who demonstrate memory impairments, nearly 50% show a clinically significant abnormality in only one modality (Nayak, Palmer, Jeste, & Heaton, 2004).

Table 13
Tests and Effect Sizes for Visuospatial Abilities Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ^2	p	Coefficient	p
WAIS-R Picture												
Arrangement	2	2	188	341	-1.36	-1.57 to -1.14	12.40	<.001	0.05	.83	—	—
WAIS Block Design ^b	7	7	382	627	-0.90	-1.14 to -0.66	7.30	<.001	14.12	.03	-1.23	.52
WAIS-R Object												
Assembly	3	3	225	472	-0.90	-1.17 to -0.63	6.52	<.001	3.91	.14	-2.42	.65
WAIS-R Picture												
Completion	3	3	202	507	-0.86	-1.04 to -0.69	9.72	<.001	1.62	.45	-3.07	.32
Benton Judgment of Line												
Orientation	3	3	162	130	-0.83	-1.08 to -0.59	6.75	<.001	0.39	.82	-0.94	.37
ROCFT Copy	5	5	455	447	-0.61	-0.91 to -0.31	4.00	<.001	12.44	.01	-0.74	.79
Global domain ES	23	12	834	851	-0.88	-1.01 to -0.75	13.15	<.001	64.79	<.001	-0.81	.48

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WAIS = Wechsler Adult Intelligence Scale; ROCFT = Rey-Osterreith Complex Figure Test.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses. ^b Includes all versions of the WAIS (see Table 3).

Table 14
Tests and Effect Sizes for Executive Functioning Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's) ^a	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
WCST perseverative responses	6	6	249	321	-0.99	-1.18 to -0.81	10.33	<.001	0.78	.98	-0.33	.67
WCST categories	12	12	749	853	-0.84	-1.04 to -0.64	8.29	<.001	31.00	.001	-3.10	.03
WCST perseverative errors	10	10	703	708	-0.81	-1.01 to -0.60	7.69	<.001	24.43	.004	0.05	.98
WCST total errors	2	2	116	198	-0.57	-0.81 to -0.33	4.68	<.001	0.22	.64	—	—
Global domain ES	30	17	1038	1208	-0.83	-0.95 to -0.72	14.59	<.001	64.58	<.001	-1.77	.04

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval; WCST = Wisconsin Card Sorting Test.

^a Publication bias data is unavailable when fewer than three effect sizes are included in analyses.

Across the memory measures studied, those demonstrating the largest ESs in FE schizophrenia included immediate and delayed story memory (e.g., WMS Logical Memory, I *SMD* = -1.47; II *SMD* = -1.37), serial list learning (*SMDs* = -1.34 to -1.15), Benton Visual Retention Test (Benton, 1974; *SMD* = -1.2), the immediate and delayed recall versions of WMS Visual Reproduction (*SMDs* = -1.01 and -0.98, respectively), and WMS Verbal Paired Associates learning (*SMD* = -0.99). This pattern of findings contrasts slightly with those reported by Dickinson et al. (2007) in which word list learning measures showed the largest ES (*d* = -1.25) followed by story memory learning (-1.19) and paired-associates learning (-1.12).

Another prominent cognitive deficit is in the domain of processing speed that in this meta-analysis demonstrated the second most robust ES (*SMD* = -.96), and to which the most sensitive single measure, Digit Symbol-Coding (*SMD* = -1.59), contributed the largest ES of any neurocognitive test from any domain. Digit Symbol-Coding was not included in Heinrichs' and Zakzanis' (1998) meta-analysis, but is precisely of the same magnitude reported by Dickinson et al. (2007) in their meta-analysis of 37 studies (i.e., *d* = -1.57). It has often been argued that the Digit Symbol-Coding test is multifactorial, requiring the integrity of several component cognitive processes (e.g., visual scanning, matching, switching, graphomotor control/speed, and memory) to complete optimally. It thus appears most sensitive because it shares considerable overlapping variance with many neuropsychological tests and dimensions in schizophrenia. Impairments in processing speed also have been regarded as a central feature of the illness (Dickinson et al., 2007) and shown to be strong predic-

tors of performance in other cognitive domains in schizophrenia, including verbal and working memory (Brebion, Amador, Smith, & Gorman, 1998; Brebion, David, Bressan, & Pilowsky, 2006, 2007; Hartman, Steketee, Silva, Lanning, & McCann, 2003).

Noteworthy contributions to the processing speed domain ES were also made by FE-control sample performance differences on the Stroop Color Naming task (*SMD* = -1.33) and Trail Making Test (TMT; e.g., Part B *SMD* = -0.91). The smallest ES from this domain was the Stroop Color-Word Interference score (*SMD* = -0.63). This latter finding is in contrast to Heinrichs and Zakzanis' (1998) report in which this index was the sixth largest in their analysis (*M_d* = -1.11). Relatively more comparable between this study and Heinrichs and Zakzanis are the ES estimates for the TMT (Parts A and B), *SMD* = -0.80 and -0.91, respectively. Consistent with Heinrichs and Zakzanis who documented *M_{ds}* of -0.70 and -0.80 for TMT A and B, respectively, our meta-analysis found no difference between the more basic TMT-A and the more complex TMT-B tasks. Assuming that processing demand differences between these tasks are meaningful, it appears that task difficulty and complexity are less important than the more basic visual attention/scanning and/or global processing speed demands of these tasks.

Following Heinrichs and Zakzanis's (1998) categorization of neuropsychological tests, we did not include fluency tasks in the processing speed domain; they contributed to the language domain in our meta-analysis. Our analyses yielded an ES range of -.69 for letter fluency to -1.24 for category fluency, and each further underscores prominent deficits in processing speed

Table 15
Tests and Effect Sizes for Social Cognition Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's)	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
Global domain ES	19	5	151	138	-0.77	-1.01 to -0.54	6.48	<.001	56.59	<.001	-6.24	.001

Note. Each test in this domain was represented once across all studies, so all tests were combined to produce a global social cognition domain effect size (see Table 3 for further test information). ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval.

Table 16
Tests and Effect Sizes for Motor Skills Domain

Test	nES	k	nFE	nC	M ES				Heterogeneity		Publication bias (Egger's)	
					SMD	95% CI	z	p	χ ²	p	Coefficient	p
Grooved Pegboard, nonpreferred hand	4	4	405	154	-0.88	-1.07 to -0.68	8.77	<.001	0.91	.82	-0.61	.66
Grooved Pegboard, preferred hand	4	4	405	154	-0.70	-0.89 to -0.50	7.08	<.001	1.73	.63	1.38	.46
Finger Tapping, preferred hand	8	8	439	637	-0.62	-0.90 to -0.34	4.37	<.001	24.96	.001	1.64	.48
Finger Tapping, nonpreferred hand	8	8	439	637	-0.50	-0.74 to -0.27	4.19	<.001	17.92	.01	1.48	.45
Global domain ES	24	9	652	703	-0.64	-0.77 to -0.52	9.90	<.001	53.49	<.001	1.19	.26

Note. ES = effect size; nES = number of effect sizes; k = number of studies; nFE = number of First Episode participants; nC = number of Control participants; SMD = standardized mean difference; CI = confidence interval.

in FE samples. Other meta-analyses have reported category or word fluency ESs of -1.12 to -1.41 across studies of individuals with schizophrenia (Bokat & Goldberg, 2003; Dickinson et al., 2007; Henry & Crawford, 2005; Heinrichs & Zakzanis, 1998). However, it is noteworthy that word fluency measures varied in their degree of sensitivity to rapid word retrieval deficits in FE samples in this meta-analysis, with category

fluency tasks showing a greater ES than either letter (*SMD* = -0.69) or other (*SMD* = -0.86) fluency tasks.

Heinrichs and Zakzanis (1998) reported a more moderate ES for vocabulary tests (*M_d* = -0.53) than that yielded by our meta-analysis (*SMD* = -0.94), likely due to the wider variety of vocabulary measures employed in their sample of studies. Notably, a related ES for Verbal IQ is more comparable between our

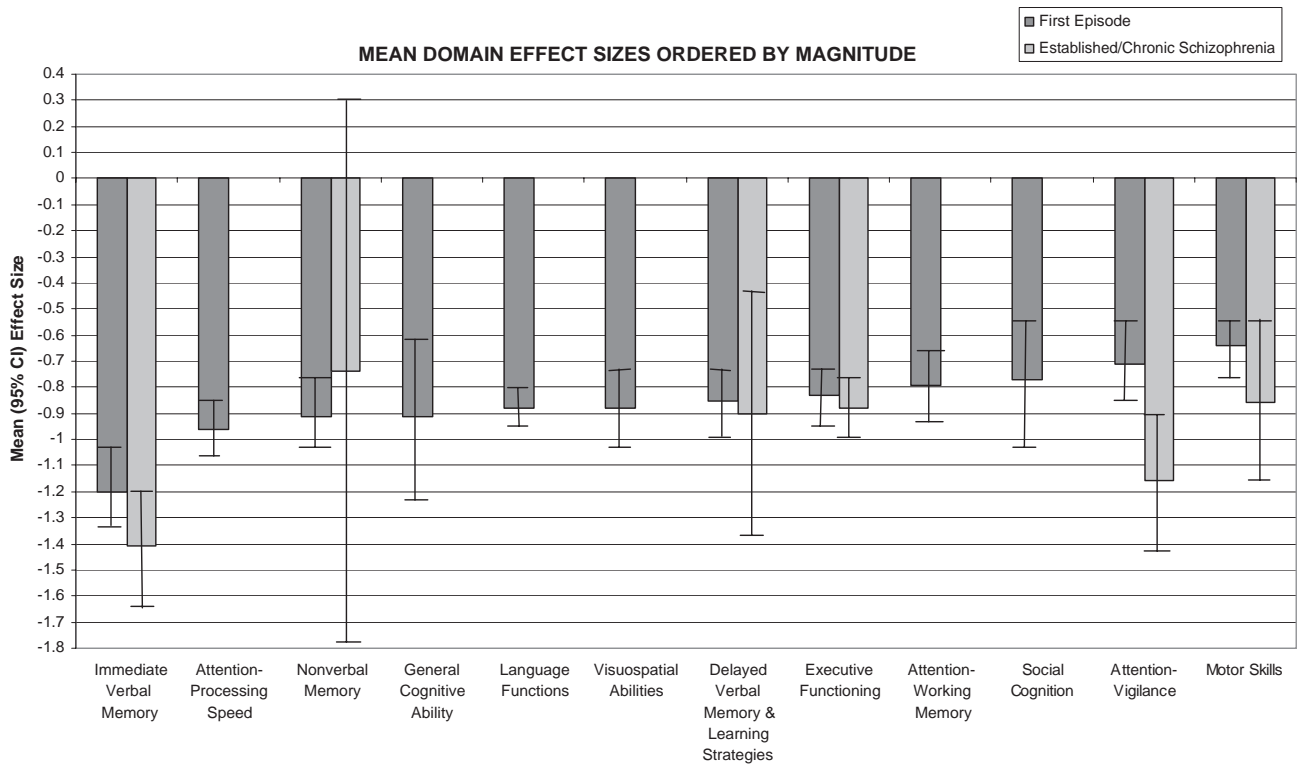


Figure 1. Mean domain effect sizes (ES) ordered by magnitude in the FE samples. Comparisons to ES values for established/chronic schizophrenia are displayed based on available ES data from Heinrichs and Zakzanis (1998); ES values were not reported for all domains reviewed in this meta-analysis (e.g., only one bar with mean First Episode ES data from this meta-analysis is shown for Attention-Processing Speed, as Heinrichs and Zakzanis did not report comparable ES data for this domain). Exact values for the confidence intervals reported in Heinrichs and Zakzanis for the above six domains are as follows: Immediate Verbal Memory [-1.62 to -1.20], Delayed Verbal Memory and Learning Strategies (-1.36 to -0.44), Nonverbal Memory (-1.78 to + 0.30), Executive Functioning/Wisconsin Card Sorting Test (WCST; -1.00 to -0.76), Attention-Vigilance/Continuous Performance Tests (-1.42 to -0.90), Motor Skills/Unilateral Motor Skills (-1.17 to -0.55).

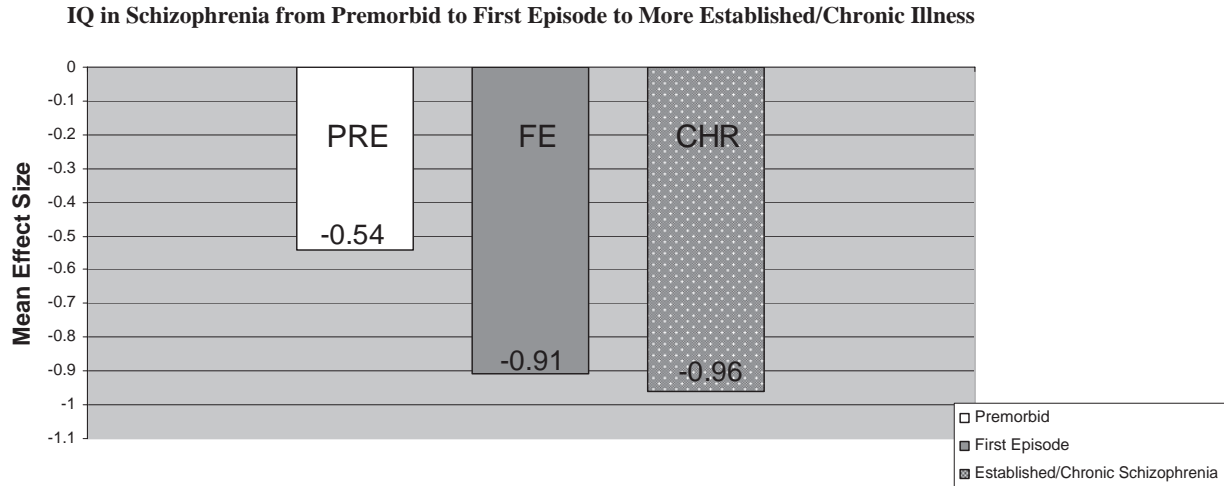


Figure 2. IQ in schizophrenia from premorbid (PRE) to first episode (FE) to more established/chronic (CHR) illness. Premorbid effect size (ES) value is from a meta-analytic review of premorbid IQ in schizophrenia (Woodberry, Giuliano & Seidman, 2008) with IQ data from a wide range of psychometric measures. First-episode ES value is from this meta-analytic review and includes Wechsler (WAIS) Full Scale IQ and Verbal IQ data, as well as non-Wechsler IQ estimates. Both premorbid and first episode ES values are weighted to correct for sample size. Established/chronic schizophrenia ES value is an unweighted estimate based on data from Heinrichs and Zakzanis' meta-analysis (1998); as no global IQ ES value was reported, these authors calculated an approximate IQ ES value from the average of the weighted mean ESs listed for WAIS-R IQ, non-WAIS-R IQ, Verbal IQ, and Performance IQ.

meta-analysis ($SMD = -0.95$) and Heinrichs and Zakzanis' ($M_d = -0.88$), indicating that many core language functions are as impaired in FE samples as they are in samples of individuals with established illness.

To an important extent, the domains of general cognitive ability, language and visuospatial functions share some overlap, given that the former is derived from neurocognitive tests included in each of the latter domains. Similar to that reported by Heinrichs and Zakzanis (1998; WAIS-R IQ $M_d = -1.1$), our meta-analysis documented a large deficit in full scale IQ estimates ($SMD = -1.01$). Moreover, our general cognition domain, as indexed by various tests that produced full scale and domain-specific IQ scores ($SMD = -0.91$), also showed a large FE-control sample difference ES. Although we were unable to calculate a specific ES for Performance IQ like Heinrichs and Zakzanis, the ESs for verbal IQ were similar between meta-analytic studies (i.e., -0.88 in Heinrichs and Zakzanis, 1998, and -0.95 in our meta-analysis).

More generally, our findings indicate that language and visuospatial functions appear equivalently impaired when studied within a meta-analytic framework (both $SMDs = -0.88$), with FE performance on tests of expressive vocabulary ($SMD = -0.94$) and block design (-0.90) similarly deficient when compared to healthy controls. Surprisingly, comparisons with Heinrichs and Zakzanis' (1998) meta-analysis reveal that the magnitude of effects for the Block Design and Judgment of Line Orientation tests are greater in FE samples than in older samples of individuals with established illness. This difference may be related to the small sample sizes of studies included in the Heinrichs and Zakzanis review; in fact, the authors reported considerable shrinkage in ESs when corrections for sample size were employed (e.g., from large to moderate ESs).

The ES estimates in our meta-analysis, though variable, are based on larger samples of FE and control groups. Just as noted in the discussion of verbal and nonverbal memory tests above, it is possible that individuals in their FE may show differential impairments within these broad domains and on these specific tests; however, as a group and across studies, the level of impairment is largely equivalent. This again supports the notion of a large generalized impairment in cognition in schizophrenia.

Both our and Heinrichs and Zakzanis' (1998) meta-analysis documented that non-WAIS measures produce estimates of general intellectual ability that yield smaller between group ESs (Heinrichs & Zakzanis, 1998, $M_d = -0.59$; our $SMD = -0.28$) than the WAIS. Clearly, WAIS and non-WAIS measures of general intellectual function demonstrate differential degrees of sensitivity to these aspects of cognitive functioning in adult FE and control samples. This finding is also consistent with meta-analytic studies of intellectual test performance in other clinical populations (such as attention-deficit/hyperactivity disorder, Frazier, Demaree, & Youngstrom, 2004), and is likely the result of a variety of psychometric factors that contribute to differential test sensitivity.

Similar to Heinrichs and Zakzanis (1998), our attention-vigilance domain combined a number of indices derived from various computerized CPTs. However, our sample of studies of individuals in FE schizophrenia yielded a smaller ES ($SMD = -0.71$) based on 15 studies compared to that reported by Heinrichs and Zakzanis ($M_d = -1.16$) based on 14 studies. At the same time, our moderately large ES estimate falls within the range of ESs reported by Dickinson et al.'s (2007) meta-analysis of various CPTs (-0.66 for the degraded stimulus CPT to -1.13 for the AX-CPT; Table 4, p. 539).

A large ES was also shown for FE-control sample differences on working memory tasks ($SMD = -0.79$), though this estimate is based on the smallest sample of studies contributing to any of the cognitive domains included in this meta-analysis. At the same time, the domain ES estimate and those of specific tests included within the working memory domain are within the range of ES reported by other studies of working memory (e.g., -0.61 to -1.18 , see Table 4 of Dickinson et al., 2007). More interesting, both this meta-analysis and that conducted by Dickinson et al. documented that mental arithmetic was the most sensitive measure (-1.1 in our study, and -1.18 in Dickinson et al., 2007). It is likely that the multifactorial nature of the WAIS Arithmetic subtest contributes to its differential sensitivity (e.g., language processing, math fact retrieval, and maintenance and interference control components of working memory are tapped by higher level items). Similarly, the pattern of findings reported for Digit Span Forward, Backward, and Total are reasonably comparable to that reported by others (i.e., backward span yields larger between-group ESs than forward span), and are consistent with the results of studies within the broader field of neuropsychology (Bogner et al., 2007; Hester & Garavan, 2005).

Our EF domain, like those included in other meta-analytic studies, is comprised only of indices derived from the WCST. Although our analysis yielded a large ES ($SMD = -0.83$) that is nearly the same magnitude as that reported by Heinrichs and Zakzanis (1998), the contributing ESs of its constituent WCST indices varied considerably ($SMDs = -0.57$ for total errors to -0.99 for total perseverative responses). Given that the nature of cognitive processes underlying WCST performance success is complex and requires numerous skills, it is not surprising that different WCST indices would yield different ESs. These findings indicate that some indices, such as perseverative responses, are most sensitive to FE-control sample performance differences. For some indices, such as WCST categories, our ES estimates are at or below those reported by other meta-analyses (e.g., $ds = -0.81$ to -1.06 ; Dickinson et al., 2007; Henry & Crawford, 2005; Laws, 1999). In contrast, our perseverative errors ES estimate falls within the range of those reported by these same investigators ($ds = -0.53$ to -0.98).

Given that we followed the categorization of tests into domains employed by Heinrichs and Zakzanis (1998) to maximize between study comparisons, several tests included in other cognitive domains in our meta-analysis are often regarded as EF measures (Nuechterlein et al., 2004). These include the TMT-B and the Stroop Color-Word condition. The TMT-B produced a large ES of -0.91 , higher than that reported by Heinrichs and Zakzanis ($d = -.80$) but comparable to others (Dickinson et al., 2007; $d = -0.92$). The Stroop Color-Word condition also showed a large ES of -1.13 , though the interference score SMD of -0.63 was considerably lower than the Stroop Interference score d of -1.11 reported by Heinrichs and Zakzanis. Taken together, these findings provide additional support for the presence of moderately severe deficits in aspects of EF studied in FE samples to date.

In contrast to Heinrichs and Zakzanis (1998), our meta-analytic review also included measures of social cognition, and yielded a moderately large ES ($SMD = -0.77$); this ES falls close to the overall mean level of impairment averaged across all 10 cognitive domains studied. The range of ES within and across studies was highly variable (small to large effects: -0.23 to -1.94), thus raising the question as to whether individuals with FE schizophrenia perform differently on the various social cognition tasks

included. More specifically, at least in the early stage of the illness, it remains unclear as to whether individuals with schizophrenia more commonly show impairment in one component of social cognition compared to another. Few studies to date have simultaneously assessed multiple domains of social cognition to address this possibility (Penn, Addington, & Pinkham, 2006). Given that emerging evidence supports the relative independence of social cognition from other aspects of nonsocial cognition (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Fine, Lumsden, & Blair, 2001; Klin, 2000) and that deficits in social cognition are reliably related to behavior, this is a promising area of future study (Couture, Penn, & Roberts, 2006; Green, Olivier, Crawley, Penn, & Silverstein, 2005; Penn et al., 2000; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997).

Moderator Variable Analyses: Influence of Methodological Factors

We found significant within-domain and within-measure heterogeneity of ESs for all domains and most tests. Indeed, all domain heterogeneity chi-squared values were statistically significant at $ps \leq .001$ (see Tables 5 to 16). Heinrichs and Zakzanis (1998) also reported significant heterogeneity in the ESs for the tests and domains examined in their meta-analysis. This heterogeneity is evident from review of confidence intervals displayed in our Figure 1. Although it has been amply documented that neurocognitive deficits are a core feature of schizophrenia at the group level, there is also a large degree of variability in neuropsychological test results across studies, including evidence that a significant minority of individuals are neuropsychologically within normal limits (e.g., Heinrichs & Awad, 1993; Heinrichs et al., 1997; Palmer et al., 1997). There are also indications that many, though not all, individuals with schizophrenia who are neuropsychologically normal show compromised cognition relative to their estimated pre-morbid level of general intellectual functioning (Allen, Goldstein, & Warnick, 2003; Goldstein & Shemansky, 1995; Ilonen et al., 2004; Kremen et al., 2000; Weickert et al., 2000; Wilk et al., 2005). Here again attention to heterogeneity in developmental-cognitive trajectories associated with disease phase and progression remains important.

ES variability within the 10 domains was most frequently associated with publication year (6 domains), gender proportions of FE and/or control samples (5 domains), percentage of patients on antipsychotic medications (5 domains), handedness of FE and/or control samples (4 domains), study country (4 domains), and education of FE and/or control groups, age of FE and/or control groups, and diagnostic composition of FE samples (2 domains each).

Publication year, which is the most common finding of moderator analyses, raises an interesting question, and may be a proxy for cohort effects related to FE and/or control sample characteristics, treatment effects or methodological differences. Five of the six domains showing a relationship between publication year and ES (i.e., delayed verbal memory and learning strategies, nonverbal memory, attention-processing speed, language, executive functioning) displayed smaller ESs in more recent publications; social cognition did not.

Perhaps the most interesting finding is the potential impact on neurocognitive performance of the relative proportion of males and females in patient and control samples. As has been amply documented, males and females demonstrate different levels of performance on neuropsychological measures generally (Mitrushina,

Boone, Razani, & D'Elia, 2005), and those with schizophrenia also show differential degrees of impairment (Goldstein et al., 1998). More specifically, Goldstein and colleagues found that males with schizophrenia perform worse than females with schizophrenia across all neuropsychological functions and the test scores of males were significantly reduced compared to females on measures of attention, verbal memory, and EF. Female patients also showed fewer cognitive deficits than their male counterparts when both groups were compared to their respective control groups. However, interpretation of the influence of proportional sex differences in this meta-analysis is complicated by the inconsistent direction of this relationship across domains. Of the five domains with a significant association between sex and ES, smaller ESs were observed with lower percentages of males in the FE groups for immediate verbal memory, but with higher proportions of males in the FE samples for the attention-processing speed and visuospatial domains. In contrast, larger ESs were associated with higher proportions of males in the FE group for the social cognition domain, but with higher percentages of males in the control group for the motor domain. Moreover, most studies were not adequately designed or powered to examine sex effects, an arguably essential source of heterogeneity in cognitive performance, and group matching is probably inadequate to control for these effects (e.g., "matching fallacy"; Kremen et al., 1996; Meehl, 1970). Nevertheless, these results emphasize the importance of possible sex effects in the neuropsychology of schizophrenia and of effectively matching within sex to better assess these effects.

It is more difficult to speculate about the nature of the effect for handedness, study country, education, age, and diagnostic composition of FE samples. All four domains showing a relationship between handedness and ES variability documented smaller ESs in studies with a higher proportion of right-handed individuals, but two were specific to FE samples (attention-vigilance and attention-processing speed) and the other two to control groups (attention-working memory and motor skills). The four domains with a relationship between study country and ES heterogeneity (nonverbal memory, language, executive functioning, and social cognition) all showed smaller ESs in studies conducted outside of the United States. Higher educational levels were associated with larger ESs in the control group for the language domain, and in both control and FE groups for the motor skills domain. Although mean age of FE and/or control groups and diagnostic composition of FE samples would be considered potentially important moderator variables, each of these variables influenced ES heterogeneity of only two domains. With respect to age, larger ESs were observed with studies documenting older control samples in the social cognition domain as well as with older control and younger FE groups in the motor domain. This may be due, in part, to the fact that age-based norms are available for many of the tests included in other domains, but are not as readily available or up-to-date for tests used in the social cognition and motor domains. For diagnosis, smaller ESs were shown in publications with fewer FE patients diagnosed with schizophrenia (compared to schizophreniform disorder, or mixed samples of schizophrenia, schizoaffective, and schizophreniform disorders) in the attention-vigilance domain, but with higher proportions of FE patients diagnosed with schizophrenia in the immediate verbal memory domain. Range restrictions on these variables may have contributed to their relative nonsignificance.

Lastly, of the five domains revealing associations between the percentage of FE samples on antipsychotic medications and the magnitude of FE-control sample performance differences (nonverbal memory, language, EF, social cognition, and motor skills), all except motor skills showed smaller ESs in studies with higher percentages of FE participants on antipsychotic medication. Given that these FE studies often explicitly tested the effects of antipsychotic medications or attempted to study persons in a medication-free state, it can be inferred that these medications tended to have some small, aggregate positive effect on neurocognition in FE schizophrenia, consistent with Harvey and Keefe (2001).

Limitations and Recommendations

Our results should be interpreted in the context of the limitations of meta-analytic procedures. As with many meta-analyses, our ability to determine the influence of sample characteristics on the magnitude of the ESs was constrained by the failure of many studies to report information on essential demographic and clinical variables. For example, despite emerging research documenting differences in cognition among symptom profile subgroups (e.g., "deficit syndrome"; Cohen et al., 2007; Kirkpatrick et al., 2000), few studies included sufficient information to contribute to moderator variable analyses on these illness dimensions. Overall, our efforts at moderator variable analysis were limited and underscore the need for improvements in researchers' reporting practices to include demographic and clinical characteristics of samples of particular theoretical relevance in schizophrenia research (e.g., see Table 1). In addition, characterizing samples with novel indices of defeatist beliefs may contribute to a broader biopsychosocial understanding of sources of variability in cognitive performance among individuals with schizophrenia (Grant & Beck, in press).

Another limitation of this meta-analysis is that it was comprised of studies that included FE participants often vaguely described as in the "early stages" of schizophrenia, making inferences about stage difficult to specify sufficiently; in fact, there is no clear consensus in the field about what constitutes, in operational terms, the FE of psychosis or schizophrenia. Another important issue is that only 14 studies followed FE participants longitudinally to confirm their primary diagnosis of schizophrenia. Fourth, nearly all of the studies included in this meta-analysis relied on a wide variety of traditional, multifactorial clinical neuropsychological measures to characterize cognition, a strategy that complicates the interpretation of results across studies. Future studies should seriously consider inclusion of the consensus-based Measurement of Treatment Effects on Cognition in Schizophrenia (MATRICS; Nuechterlein et al., 2008) to ensure a common core battery across studies, putative neurocognitive endophenotypes for schizophrenia (see Glahn et al., 2007), measures of social and emotional processing, and/or a cognitive neuroscience-based approach to permit measurement of specific cognitive processes that may also lend support to a growing translational science (e.g., Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia [CNTRICS]; Carter & Barch, 2007; see also Barch, 2005). Fifth, our rank ordering of domain and test ESs is intended as a convenient organizational method, and caution against reification of differential ESs should be exercised. The specific relationships among ESs and wide-ranging neurobiological substrates (e.g., gray and white matter abnormalities) implicated in schizophrenia remains an area of active empirical study, relationships

that are likely moderated by the construct validity and other psychometric properties of the measures themselves (Chapman & Chapman, 1973, 1978, 1979). Such relationships might be most productively explored with putative neurocognitive endophenotypes and cognitive neuroscience-based approaches. These latter approaches are likely to yield more precisely defined relationships between cognitive and neural abnormalities.

Lastly, because meta-analyses are based on group differences, they identify reliable central tendencies and to some extent mask within-group variability (e.g., heterogeneity of the illness phenotype), which is itself deserving of more focused research. In fact, a challenge for the field as a whole is to better understand heterogeneous patterns of neuropsychological performance in subgroups of individuals and among individuals themselves. There are a paucity of studies that have classified neurocognitive performance by clinical symptom profiles (e.g., paranoid, nonparanoid; deficit, nondeficit) or by attempts to evaluate clusters of individuals by their neuropsychological profiles. The former approach depends on thorough clinical characterization, and is well within the capacity of most investigators, if they recognize that such characterization and subcategorization may be meaningful. The latter approach, attempting to cluster individuals using a neuropsychological analysis (Kremen et al., 2004; Palmer et al., 1997), is more ambitious and relatively uncharted. This approach requires a priori conceptual approaches to neuropsychological syndrome definition. This method is based on the original goal of neuropsychologists to cluster individuals into meaningful groups to facilitate a better understanding of brain-behavior relationships. This approach may ultimately provide more refined information regarding treatment-relevant (e.g., cognitive) interventions and responses, and may also elucidate the course of neurocognitive function over time in different subgroups.

In conclusion, this quantitative review of the literature underscores that neurocognitive deficit in the FE (or relatively short duration of illness) is a reliable finding. Our meta-analytic results revealed moderate to large ES across all cognitive domains, and the magnitude and pattern of these deficits approximates those documented in older and more chronic samples. Our findings also indicate that the impairments in general cognitive ability (IQ) present in the FE is meaningfully greater than that observed before frank illness onset (including premorbid and prodromal phases), suggesting that substantial decline in cognition likely occurs between the premorbid and FE phases. The magnitude of neurocognitive deficits in FE schizophrenia shows considerable variability across studies, and the most potent sources of variability that might help to explain between-study FE-control group differences remain uncertain. Moreover, despite the extensive volume of studies that have attempted to engage the question of illness course, most, with few exceptions (e.g., Rund, 1998), have been cross-sectional. This area of research is in need of well-designed and sufficiently powered developmental-longitudinal studies of well-characterized samples (e.g., Bilder et al., 2000) to determine the course of cognitive deficits in schizophrenia, and the extent to which course(s) is related to sex, illness subtype differences, and other putatively important demographic and clinical variables.

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