Overlooking the Obvious

A Meta-analytic Comparison of Digit Symbol Coding Tasks and Other Cognitive Measures in Schizophrenia

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Context: In focusing on potentially localizable cognitive impairments, the schizophrenia meta-analytic literature has overlooked the largest single impairment: on digit symbol coding tasks.

Objective: To compare the magnitude of the schizophrenia impairment on coding tasks with impairments on other traditional neuropsychological instruments.

Data Sources: MEDLINE and PsycINFO electronic databases and reference lists from identified articles.

Study Selection: English-language studies from 1990 to present, comparing performance of patients with schizophrenia and healthy controls on coding tasks and cognitive measures representing at least 2 other cognitive domains. Of 182 studies identified, 40 met all criteria for inclusion in the meta-analysis.

Data Extraction: Means, standard deviations, and sample sizes were extracted for digit symbol coding and 36 other cognitive variables. In addition, we recorded potential clinical moderator variables, including chronicity/severity, medication status, age, and education, and potential study design moderators, including coding task variant, matching, and study publication date.

Data Synthesis: Main analyses synthesized data from 37 studies comprising 1961 patients with schizophrenia and 1444 comparison subjects. Combination of mean effect sizes across studies by means of a random effects model yielded a weighted mean effect for digit symbol coding of $g=-1.57$ (95% confidence interval, −1.66 to −1.48). This effect compared with a grand mean effect of $g=-0.98$ and was significantly larger than effects for widely used measures of episodic memory, executive functioning, and working memory. Moderator variable analyses indicated that clinical and study design differences between studies had little effect on the coding task effect. Comparison with previous meta-analyses suggested that current results were representative of the broader literature. Subsidiary analysis of data from relatives of patients with schizophrenia also suggested prominent coding task impairments in this group.

Conclusion: The 5-minute digit symbol coding task, reliable and easy to administer, taps an information processing inefficiency that is a central feature of the cognitive deficit in schizophrenia and deserves systematic investigation.

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With evidence from hundreds of studies, cognitive impairment is now widely recognized as a critical and reliable feature of schizophrenia. Meta-analytic methods have been useful in distilling this enormous literature. In the first major synthesis, Heinrichs and Zakzanis[1] found evidence of significant impairment across the full range of traditional neuropsychological tests, with some evidence of disproportionate impairment in the area of verbal memory. Other meta-analyses have focused more specifically on episodic memory,[2,3] executive functioning,[4] the Wisconsin Card Sorting Test,[5,6] working memory,[7] and verbal fluency.[8,9] These meta-analyses—highlighting domains and measures associated with prefrontal and temporal brain regions—reflect the dominant thinking in cognitive research in schizophrenia during the past 2 decades. Much of this research has been motivated by the goal of identifying and isolating impairments that might be attributed to dysfunction in specific neural substrates, an emphasis that first developed in the clinical neuropsychology literature and accompanied the adoption and spread of neuropsychological methods in schizophrenia research.

One unintended consequence of the focus on potentially localizable impairments has been decreased interest in measures of processing speed. As used herein

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(following the work of Salthouse[10] on cognitive aging and the broader factor-analytic literature on intellectual abilities[11]), *processing speed* simply refers to the speed with which different cognitive operations can be executed. Psychometrically, processing speed is typically indexed by the number of trials of a simple task that a subject can complete during a brief interval, on the order of 60 to 120 seconds. For example, the Digit Symbol Substitution Test from the Wechsler intelligence scales[12] reflects speeded performance of a number of straightforward scanning, matching, switching, and writing operations, as subjects use a key of 9 digit-symbol pairings to enter the symbols associated with a lengthy series of digits. Despite the narrow measurement approach, we believe that this performance dimension represents a very general constraint on cognitive processing.[10] That is, many higher cognitive operations—including perceptual processes, encoding and retrieval operations, transformation of information held in active memory, and decision processes—involve internal dynamics that are speed-dependent to an important extent. The general importance of processing speed is reflected in the inclusion of these tasks in many standard measures of intelligence[12,13]

Coding tasks, such as the Wechsler digit symbol test, are sensitive to a wide array of neuropsychiatric conditions,[14,15] including schizophrenia, but they have not been linked to structure or function in specific brain systems. Two facts make the relative absence of coding tasks from the meta-analytic literature particularly noteworthy. First, there is no lack of published data involving the tasks—as shown subsequently, the measures have been used in dozens of schizophrenia studies published since 1990. Yet the measures were not included in the Heinrichs and Zakzanis review and were discussed as a matter of secondary interest in only 1 of the other reviews.[9] Second, notwithstanding the perennial focus of cognitive research in schizophrenia on memory, attention, executive, and working memory functions, impairments on coding tasks in schizophrenia are significantly more pronounced than impairments on measures from these other cognitive domains, as shown later (see also Henry and Crawford[9] and Dickinson and Gold[16]). In other words, the largest effect size documented in the clinical neuropsychology literature on schizophrenia has rarely been discussed as a central feature of the illness and has not been the focus of sustained experimental investigation.

The current meta-analysis was undertaken to address this important anomaly by testing the magnitude of the cognitive impairment on coding tasks in schizophrenia relative to other traditional cognitive instruments that are more widely used and discussed in the literature. Additional aims were to examine the effect of potential moderator variables on coding task performance, including clinical variables (eg, medication and chronicity) and study variables (eg, subject matching and sample size), and to place current results in the context of the existing meta-analytic literature comparing the cognitive performance of patients with schizophrenia with that of healthy comparison subjects. A subsidiary analysis compared coding tasks and other cognitive impairments in relatives of schizophrenia patients.

METHODS

STUDY AND VARIABLE SELECTION

Our analysis focused on individual measures rather than on broader cognitive constructs (eg, executive functioning and attention). Although this approach results in a large number of variables for comparison and fewer studies for each effect size calculation, it avoids inconsistent assumptions about the structure and constituents of broader cognitive abilities.[1,17]

As a means to anchor the analysis to coding tasks, we considered studies for inclusion only if they compared individuals with schizophrenia and healthy controls on the Wechsler digit symbol test or a close variant, such as the written version of the Symbol Digit Modalities Test.[18] (The group of tests is referred to as "coding tasks" and "digit symbol coding" hereafter.) To allow comparison of effect sizes among various measures, we also required that the studies report results from measures of at least 2 other cognitive domains. In practice, most of the studies that were included used broad selections of measures that could be described as "full neuropsychological batteries." Two approaches were used to locate articles for the meta-analysis. First, articles were identified through a series of searches of the MEDLINE and PsycINFO electronic databases with combinations of key words *schizophreni*, cogniti*, neuropsychologi*, digit symbol, processing speed, perceptual speed,* and *psychomotor speed.* The searches were conducted for the period from 1990 through April 2006. The beginning date was selected as a point by which relatively current diagnostic criteria (eg, *DSM-III-R*, issued in 1987)[19] were in wide use. Second, we searched the reference lists from these articles to identify additional publications.

The following criteria were used to select studies for review: (1) The study must have reported results for a digit symbol coding task and results for at least 2 other cognitive tasks representing different cognitive performance domains. (2) The study must have contrasted cognitive performance in schizophrenia patients and healthy controls. (3) The study must have based schizophrenia diagnoses on contemporary diagnostic criteria (eg, *DSM-III-R*, *DSM-IV*, or *International Classification of Diseases, Ninth Revision* [*ICD-9*] or later). (4) Results must have been reported with sufficient detail to allow calculation of effect sizes. (5) Finally, the study must have been reported in English. More than 2000 studies were identified through the overlapping database searches. In the first instance, abstracts and titles were reviewed to eliminate studies that obviously failed to meet criteria. One hundred eighty-two articles were retained for examination in greater detail. Of these, 81 did not include a coding task. In 24 studies, a coding task was included as part of a composite variable but not reported individually. Seventeen studies did not include a healthy comparison sample. Six studies did not include an adequately characterized schizophrenia sample. Two studies reported coding task results but not results for other measures. In 6 further studies, the data were insufficient for calculation of effect sizes. The 46 remaining studies were checked for sample overlap. Where studies appeared to use the same or overlapping samples, we used data from only 1 of the studies. Six studies were eliminated on this basis, leaving 40 studies that met all inclusion criteria for the meta-analysis.[20-59]

Digit symbol coding tasks were tracked for meta-analysis across all studies. Other cognitive variables were tracked if they appeared in at least 3 included studies. In sum, 36 cognitive variables in addition to the coding tasks were analyzed. They were grouped into 9 familiar cognitive domains for presentation. Notably, although our general approach was to combine data on an individual test by individual test basis, we combined data across very similar tests in some instances. For example, studies reporting the written Symbol Digit Modalities Test and other digit symbol coding variants were combined with the Wechsler digit symbol studies to calculate the overall digit symbol coding effect size. We also combined data across different word list learning tests and across different sets of prompts for letter and category fluency tasks. Full-battery IQ scores and estimates based on IQ battery short forms were combined, as were word reading scores from the Wide Range Achievement Test and National Adult Reading Test (specific citations for the cognitive measures referred to in this article are available in standard neuropsychological reference works[60]).

We recorded information about a number of potential moderator variables. The clinical variables included severity/chronicity of illness, the presence and dose of antipsychotic medication, symptom severity, and education. Study characteristics included whether the Wechsler digit symbol test or a variant was used, whether schizophrenic and comparison subjects were matched on age and education, whether studies included larger or smaller schizophrenia samples, and whether the studies were published recently or longer ago. Moderator variables were inconsistently reported. In the case of symptomatology, for example, enough studies reported Brief Psychiatric Rating Scale data to allow an examination of the relationship of total symptomatology to cognitive performance. However, too few studies reported data on positive and negative symptoms to permit meaningful analysis.

DATA ANALYSIS

All analyses were performed using the Comprehensive Meta-analysis software package.[61] Effect sizes for each cognitive variable from each study were calculated as the mean difference between schizophrenia and healthy control performance divided by the pooled standard deviation and adjusted for small sample bias (Hedges *g*).[62] The direction of these numerous effect sizes was almost uniformly negative, reflecting worse performance by schizophrenia patients than by comparison subjects. These values were weighted and combined for each variable by means of a random effects model, rather than the more commonly used fixed effects model.[63,64] This conservative estimation method yields more generalizable parameter estimates than would be derived with a fixed effects model, most clearly evident in larger standard errors and confidence intervals and smaller *z* scores.[63] We also calculated 95% confidence intervals and a χ^2 statistic, Q, indicating the homogeneity of effect sizes across studies.[64] To explore possible publication bias, we calculated Orwin's fail-safe N,[65] which is the number of unpublished studies with null effects that would be needed to reduce the obtained effect size to a negligible level (set at 0.2 for the present analysis). We also examined publication bias graphically, with a funnel plot.[66] The funnel plot graphs the effect size point estimate for individual studies (here, Hedges g) against the precision of the estimate (here, standard error). A lack of symmetry around the overall effect size, especially an imbalance favoring large effects among the lower-precision studies, may indicate publication bias.

Our hypothesis was that the coding task effect size would be larger than the effect sizes for other variables. We conducted these tests within groups of studies; that is, the comparison for each cognitive variable was made within the subset of studies in which both the coding task and the comparator variable were reported, to ensure that exactly the same subjects were being compared on the measures of interest.[9] Specifically, for each individual study, we calculated "difference" effect sizes and standard errors comparing the coding task with every other cognitive variable. These difference scores were then combined, comparator variable by comparator variable, by means of a random effects model, and the resulting combined effect sizes were assessed by *z* tests. Each significant result therefore indicated that the coding task effect size was reliably larger than the effect size for the comparator variable within the matched group of studies and subjects.

A subsidiary analysis examined the coding task effect size in relatives of individuals with schizophrenia. None of the 5 existing meta-analyses of cognitive deficits in relatives of schizophrenia patients[17,67-70] addressed digit symbol coding. However, 7 studies[30,35,39,41-43,59] identified in our search included a relatives sample as well as a schizophrenia sample. All of the relative groups had mean ages greater than 32 years, past the age of greatest risk of illness. Although this set of relative samples was obtained incidentally to our main literature search, it nevertheless provided an indication of how the coding task effect size compared with other cognitive effect sizes in relatives at low risk of developing schizophrenia.

We tested the effects of moderator variables on coding task performance by means of categorical models. For quantitative moderator variables, we used a median split to divide the studies into subgroups. We calculated the homogeneity statistics Q_w and Q_{bet}. The Q_w statistic denotes the homogeneity or heterogeneity of studies within moderator variable subgroups. The Q_{bet} statistic tests the significance of differences in effect size magnitude between moderator variable subgroups, analogously to the F statistic.[71]

To place current findings in the context of other pertinent meta-analytic work, we compiled findings from meta-analyses that have addressed the same or comparable cognitive variables in this population.[1,2,4,5,7-9,72] Although doubtless overlapping to a degree with the current analysis, the very different objectives and study selection criteria used across different reviews ensure that different study and subject samples underlie their results. The compiled results from these analyses served as a check on the generalizability of findings of the current analysis. (The Johnson-Selfridge and Zalewski analysis[4] used nonstandard effect size calculations and was not included in the compilation.)

RESULTS

Supplementary tables providing clinical, demographic, and variable-by-variable effect sizes for each study are available on request from the corresponding author.

MAIN META-ANALYSIS

An initial meta-analysis with all 40 studies yielded a coding task effect size (random effects model) of $g=-1.59$. A significant Q statistic ($Q_{39}=96.7$, $P<.001$) indicated heterogeneity among the studies beyond what would be expected on the basis of sampling variation. Examination of the distribution of effect sizes suggested that coding task effect size outliers might account for this heterogeneity. All coding task effect sizes for the 40 studies fell within a range of less than 1 effect size unit (from $g=-1.05$ to $g=-2.02$), with 3 exceptions (values of $g=-0.63$,[23] $g=-2.68$,[34] and $g=-2.63$[73]). Apart from the divergent coding tasks effects, there was nothing remarkable about these 3 studies. Their elimination from the analysis had a negligible effect on the obtained coding task effect size (reduction from $g=-1.59$ to $g=-1.57$) but left a group of 37 studies that was homogeneous with respect to the digit symbol coding variable ($Q_{36}=40.7$, $P=.21$). To enhance

Table 1. Results of Meta-analyses of Differences in Digit Symbol Coding and Other Cognitive Variables Between Schizophrenia Patients and Healthy Comparison Subjects

							z Score*	
Cognitive Domain/Measure	k	SZn	HCn	ES	SE	95% CI	ES Different From 0?	Variable ES<Matched Digit Symbol Coding ES?
Processing speed								
Digit symbol coding	37	1961	1444	−1.57	0.05	−1.66 to −1.48	−34.73	. . .
Trail Making Test part A	19	1081	689	−0.88	0.07	−1.01 to −0.75	−12.98	8.06
Stroop word-reading condition	3	135	77	−0.97	0.15	−1.26 to −0.67	−6.46	3.24
Episodic memory								
Word list learning	21	1254	853	−1.25	0.10	−1.44 to −1.05	−12.66	2.31 (*P* = .02)
Word list learning delayed	16	871	645	−1.09	0.08	−1.25 to −0.93	−13.37	5.43
Story memory	12	863	656	−1.19	0.11	−1.40 to −0.98	−10.96	3.45
Story memory delayed	10	671	530	−1.29	0.11	−1.51 to −1.07	−11.56	2.16 (*P* = .03)
Verbal paired associates	6	399	235	−1.12	0.26	−1.62 to −0.61	−4.36	0.99 (*P* = .33)
Visual reproduction	9	544	297	−0.82	0.10	−1.02 to −0.62	−7.92	4.07
Visual reproduction delayed	8	486	272	−0.78	0.09	−0.95 to −0.61	−8.89	5.67
Figure recall	5	280	349	−1.03	0.13	−1.28 to −0.77	−7.89	2.13 (*P* = .03)
Executive functioning								
WCST categories	20	1018	858	−1.00	0.10	−1.19 to −0.81	−10.31	7.65
WCST perseverative errors	23	1295	929	−0.81	0.07	−0.94 to −0.67	−11.64	10.94
Trail Making Test part B	21	1190	754	−0.92	0.05	−1.02 to −0.82	−18.30	8.72
Stroop color-word condition	8	422	470	−0.99	0.14	−1.26 to −0.72	−7.28	5.04
Working memory								
Letter-number sequencing	4	273	146	−0.85	0.11	−1.06 to −0.63	−7.87	5.00
Digit span forward	4	175	117	−0.73	0.18	−1.08 to −0.38	−4.07	5.20
Digit span backward	4	107	81	−0.86	0.14	−1.14 to −0.59	−6.20	3.36
Digit span total	17	845	757	−0.71	0.06	−0.82 to −0.59	−11.84	11.25
Arithmetic	9	612	335	−1.18	0.10	−1.38 to −0.98	−11.70	3.01
Sustained attention								
AX CPT	4	265	178	−1.13	0.36	−1.83 to −0.42	−3.14	1.55 (*P* = .12)
Degraded stimulus CPT	5	96	153	−0.66	0.16	−0.98 to −0.35	−4.11	3.34
Identical pairs CPT	4	260	173	−0.86	0.14	−1.13 to −0.58	−6.14	5.72
Conners CPT	5	218	298	−1.02	0.15	−1.31 to −0.73	−6.95	4.16
Motor speed								
Finger tapping dominant	9	571	502	−0.68	0.11	−0.90 to −0.46	−5.95	4.85
Finger tapping nondominant	9	571	502	−0.52	0.09	−0.71 to −0.34	−5.57	6.27
Grooved pegboard dominant	7	483	245	−0.92	0.08	−1.09 to −0.75	−10.85	4.07
Grooved pegboard nondominant	6	437	211	−0.98	0.10	−1.17 to −0.79	−10.31	3.22
Fluency								
Category fluency	8	462	236	−1.41	0.11	−1.62 to −1.19	−12.78	0.17 (*P* = .86)
Letter fluency	22	1213	894	−0.83	0.06	−0.96 to −0.71	−13.49	9.32
Intellectual/verbal ability								
IQ/estimated IQ	15	863	508	−1.19	0.15	−1.48 to −0.90	−8.03	2.22 (*P* = .03)
Vocabulary	10	608	586	−0.90	0.13	−1.15 to −0.65	−7.03	4.26
Information	8	638	492	−0.82	0.10	−1.01 to −0.64	−8.54	6.02
Similarities	8	480	458	−1.01	0.08	−1.16 to −0.86	−13.32	4.89
WRAT or NART reading	10	715	450	−0.59	0.11	−0.81 to −0.37	−5.21	5.55
Perceptual/problem solving								
Block design	10	693	607	−0.84	0.12	−1.06 to −0.61	−7.24	5.03
Line orientation	6	372	252	−0.62	0.16	−0.94 to −0.30	−3.77	5.51
Overall weighted ES	. . .	. . .	. . .	−0.98	. . .	. . .	. . .	. . .

Abbreviations: AX, the AX version of the continuous performance test (CPT); CI, confidence interval; ES, effect size; HCn, healthy comparison group sample size; k, number of studies; NART, National Adult Reading Test; SZn, schizophrenia sample size; WCST, Wisconsin Card Sorting Test; WRAT, Wide Range Achievement Test; ellipses, not applicable.

*$P \leq .01$ unless otherwise indicated.

the generalizability of findings, further analyses were restricted to these 37 studies.

Across these studies, cognitive results were analyzed for 1961 schizophrenia patients and 1444 healthy comparison subjects. The sample-weighted mean age for the schizophrenia patients was 31.5 years (range of study means, 15.4-44.9 years), compared with 30.2 years for the controls (range, 15.1-48.9 years). For 22 studies that reported level of education in patients, the mean was 12.3 years (range, 9.5-14 years). In 20 studies reporting education in controls, the comparable value was 13.7 years (range, 11.4-15.2 years). Duration of illness varied widely among the studies (range, 0.1-16.2 years), averaging 9.1 years for 24 studies that reported this information. **Table 1** displays

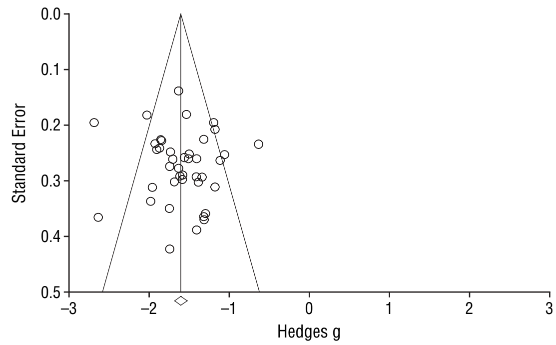

Figure. Funnel plot of effect size against standard error for the meta-analysis of digit symbol coding in 40 studies comparing schizophrenia patients with healthy controls. Each circle represents a single study. The vertical line, rising from the diamond on the x-axis, indicates the mean weighted coding task effect size. The slanted lines encompass ±1 effect size unit at the base of the funnel. Excepting 3 outliers,[23,34,55] the studies are closely and symmetrically grouped around the overall effect size.

the results of meta-analyses of schizophrenia and comparison group differences in performance on digit symbol coding and 36 other cognitive measures.

Cohen's criteria—0.20 for a small effect, 0.50 for a medium effect, and 0.80 for a large effect—provide a guide to interpretation of the obtained effect sizes.[74] As shown in Table 1, cognitive performance is significantly impaired in schizophrenia across performance domains, with a grand mean weighted effect size of $g = -0.98$. Analyses of each cognitive measure yielded a significant z value for the difference between patients and comparison subjects. The largest effect size obtained was $g = -1.57$ for digit symbol coding, nearly double Cohen's convention for a large effect. These effect sizes also can be interpreted in terms of the percentage of nonoverlap between the distributions of test scores for the schizophrenia and healthy control groups.[74] The grand mean effect size denotes approximately 55% nonoverlap between the schizophrenia and control distributions. The digit symbol coding effect indicates 73% nonoverlap between distributions. Orwin's fail-safe N indicated that 281 studies with null effects would have to have been performed but not published to reduce the coding task effect size to 0.20. Examination of the funnel plot (**Figure**) showed that, excepting the coding task outliers, most studies were grouped tightly and symmetrically around the overall effect, with no imbalance between small and large effect size studies at lower levels of precision.

A large proportion of the other obtained effect sizes fell between $g = -0.80$ and $g = -1.20$, close to the grand mean effect size. Verbal memory measures collected around $g = -1.20$, as did IQ. Executive functioning measures were near $g = -1.00$. Visual episodic memory, working memory, and motor speed measures were typically near or below $g = -0.90$. The smallest value was a medium effect size of $g = -0.52$ for finger tapping with the nondominant hand.

In matched comparisons, the coding task effect size was significantly larger than effect sizes obtained for 33 of the 36 other cognitive variables. Effect sizes for 2 of the variables not found to differ significantly (verbal paired associates, $g = -1.12$; AX continuous performance test, $g = -1.13$) were considerably smaller than the coding task effect size. However, these estimates were quite imprecise because of limited degrees of freedom and significant study-to-study effect size heterogeneity (verbal paired associates, $Q_5 = 39.1$; AX continuous performance test, $Q_3 = 26.5$; both $P < .001$), explaining the nonsignificant results. Category fluency was the only comparator variable that was both estimated from a homogeneous group of studies ($Q_7 = 10.0$, $P = .19$) and close to digit symbol coding in magnitude ($g = -1.41$). Thus, the effect size for digit symbol coding is the largest documented in this body of studies.

META-ANALYSIS OF RELATIVES OF SCHIZOPHRENIA PATIENTS

In many respects, the findings from the main meta-analysis were recapitulated in the subsidiary analysis comparing relatives of schizophrenia patients with healthy controls (**Table 2**). Of 9 widely reported cognitive variables represented by 3 or more studies in this subset, relatives showed significant impairment relative to controls on 6, despite low meta-analytic power. The level of cognitive deficit among relatives was intermediate between schizophrenia patients and comparison subjects, reflected in a grand mean effect of $g = -0.43$. The obtained effect size for digit symbol coding was $g = -0.62$, and this was a reliable estimate, based on a homogeneous group of studies ($Q_6 = 2.51$, $P = .87$). This effect compares with the largest effect sizes reported in earlier meta-analyses of cognition in relatives of schizophrenia patients.[17,67-70]

MODERATOR VARIABLE ANALYSES

Further analyses considered whether important clinical and study moderator variables had influenced the coding task findings. In general, as shown in **Table 3**, the effect of moderator variables was limited. An analysis of subsets of studies characterized by different degrees of illness chronicity and severity showed that, except for patients with very early onset and poor prognosis, younger patients with a short duration of illness performed significantly better on the coding tasks than older, more chronically ill patients ($g = -1.44$ vs $g = -1.62$). The patients with very early onset performed worst of the 3 groups ($g = -1.72$). (Deleting the 4 early-onset studies[38,48,50,56] in an alternative analysis reduced the coding task effect size minimally, from $g = -1.57$ to $g = -1.56$.) Despite the differences among the chronicity/severity groups, the coding task effect size indicated profound impairment in all groups and, even in the least impaired, was larger than effect sizes calculated for all other cognitive variables. None of the other clinical moderators, including medication status, symptom severity, and education, resulted in a significant between-group difference. The lack of an antipsychotic medication effect, in particular, helps exclude iatrogenic treatment effects on psychomotor functioning. Of 218 schizophrenic subjects from 6 studies that were included in this analysis, 172 were first-episode patients who were drug-naive or had had minimal antipsychotic exposure. Excluding the remaining medication-free subjects (chronically ill patients who were not

Table 2. Results of Meta-analyses of Differences in Digit Symbol Coding and Other Cognitive Variables Between Relatives of Schizophrenia Patients and Healthy Comparison Subjects

Cognitive Domain/Measure	k	SZn	HCn	ES	SE	95% CI	z Score: ES Different From 0?
Processing speed							
Digit symbol coding	7	203	301	−0.62	0.09	−0.80 to −0.43	−6.54*
Trail Making Test part A	3	80	113	−0.51	0.15	−0.80 to −0.21	−3.36*
Episodic memory							
Word list learning immediate	3	80	113	−0.45	0.15	−0.72 to −0.13	−2.80*
Executive functioning							
WCST categories	4	111	158	−0.26	0.13	−0.50 to 0.00	−1.99*
Trail Making Test part B	3	80	113	−0.54	0.15	−0.82 to −0.23	−3.48*
Working memory							
Digit span total	4	92	143	−0.23	0.14	−0.50 to 0.03	−1.71
Sustained attention							
Degraded stimulus CPT	3	78	93	−0.39	0.16	−0.70 to −0.08	−2.45*
Fluency							
Letter fluency	3	79	145	−0.22	0.14	−0.49 to 0.05	−1.58
Intellectual/verbal ability							
IQ/estimated IQ	4	139	176	−0.20	0.12	−0.43 to 0.04	−1.66
Overall weighted effect size	. . .	. . .	. . .	−0.43	. . .	. . .	. . .

Abbreviations: CI, confidence interval; CPT, continuous performance test; ES, effect size; HCn, healthy comparison group sample size; k, number of studies; SZn, schizophrenia sample size; WCST, Wisconsin Card Sorting Test; ellipses, not applicable.

*$P \leq .05$.

Table 3. Analyses of Potential Moderators of Digit Symbol Coding Effect Size in 37 Studies Comparing Cognitive Performance in Schizophrenia Patients and Healthy Controls

Moderator Variable	k	SZn	HCn	Coding Task ES	95% CI	z Score*: ES Different From 0?	Q_w	Q_{bet}
Clinical Characteristics								
Chronicity/severity								
Age 18-27 y or illness duration <1 y†	10	544	500	−1.44	−1.63 to −1.25	−14.62	14.18	4.6§
Age >35 y or illness duration >10 y‡	17	865	573	−1.62	−1.77 to −1.47	−21.37	21.43	
Onset of illness and assessment before age 18 y	4	108	129	−1.72	−2.09 to −1.34	−9.01	4.39	
Medications								
No	6	218	377	−1.53	−1.72 to −1.34	−15.56	2.84	0.2
Yes	31	1743	1067	−1.58	−1.68 to −1.48	−30.05	37.64	
CPZ ≤410 mg	6	230	191	−1.58	−1.84 to −1.31	−11.68	6.72	0.38
CPZ >410 mg	7	496	268	−1.65	−1.91 to −1.40	−12.55	12.34§	
Symptom severity								
BPRS <34	6	333	213	−1.57	−1.78 to −1.36	−14.83	2.25	0.02
BPRS ≥34	5	218	128	−1.55	−1.81 to −1.30	−11.88	3.44	
Education ≤12 y	11	592	321	−1.60	−1.76 to −1.44	−19.69	9.21	0.37
Education >12 y	11	656	665	−1.53	−1.70 to −1.37	−18.18	14.53	
Study Characteristics								
Task variations								
Wechsler Digit Symbol	28	1482	1135	−1.59	−1.69 to −1.50	−31.65	29.10	0.66
Variant coding tasks	9	479	309	−1.50	−1.69 to −1.30	−15.07	10.43	
Coding task SS reported	19	986	638	−1.62	−1.75 to −1.49	−24.38	20.71	1.79
Coding task raw reported	7	341	213	−1.46	−1.66 to −1.27	−14.69	5.16	
Matching								
Age-matched	26	1327	1108	−1.64	−1.74 to −1.54	−32.00	26.24	4.37§
Not age-matched	10	538	316	−1.44	−1.60 to −1.28	−17.45	6.01	
Education-matched	11	504	351	−1.62	−1.78 to −1.45	−19.23	9.27	1.11
Not education-matched	16	1021	784	−1.62	−1.74 to −1.51	−28.07	14.02	
Schizophrenia n<50	19	500	547	−1.52	−1.66 to −1.38	−21.23	11.20	0.68
Schizophrenia n≥50	18	1461	897	−1.60	−1.73 to −1.46	−23.31	28.68§	
Date ≤1999	16	697	655	−1.54	−1.67 to −1.41	−22.87	11.37	0.29
Date >1999	21	1264	789	−1.59	−1.72 to −1.46	−24.33	28.96	

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CI, confidence interval; CPZ, chlorpromazine equivalents; ES, effect size; HCn, healthy comparison group sample size; k, number of studies; Q_{bet}, between–moderator subgroups homogeneity statistic; Q_w, within–moderator subgroup homogeneity statistic; SS, standard score; SZn, schizophrenia sample size.

*$P \leq .001$.

†Includes studies in which the overall sample met criteria, as well as information about subsamples that were reported separately in 4 studies.[20,21,33,46]

‡Includes studies in which the overall sample met criteria, as well as information about subsamples that were reported separately in 2 studies.[21,46]

§$P \leq .05$.

Table 4. Compilation of Effect Sizes From Different Meta-analyses Comparing Schizophrenia Patients and Healthy Controls on Widely Used Cognitive Variables*

Cognitive Domain/Meta-analysis	Study Variable	ES	k	SZn	TOTn
Grand mean ES					
Heinrichs[75]	Grand mean	−0.92	204	7420	13 285
Current	*Grand mean*	*−0.98*	*37*	*1961*	*3405*
Global cognitive					
Fioravanti et al[72]	IQ/broad cognitive ability	−1.01	74	. . .	6280
Heinrichs and Zakzanis[1]	IQ	−1.10	35	1018	2066
Laws[5]	IQ	−1.23	12	. . .	681
Henry and Crawford[9]†	IQ	−1.39	13	. . .	587
Current	*IQ*	*−1.19*	*15*	*863*	*1371*
Henry and Crawford[9]†	Premorbid IQ/reading	−0.54	15	. . .	1051
Current	*Premorbid IQ/reading*	*−0.59*	*10*	*715*	*1165*
Processing speed					
Henry and Crawford[9]†	Digit symbol coding	−1.46	18	. . .	1077
Current	*Digit symbol coding*	*−1.57*	*37*	*1961*	*3405*
Heinrichs and Zakzanis[1]	Trail Making Test part A	−0.70	12	1204	1800
Current	*Trail Making Test part A*	*−0.88*	*19*	*1081*	*1770*
Verbal memory					
Heinrichs and Zakzanis[1]	Broad verbal learning	−1.41	31	1088	2275
Aleman et al[2]	Broad verbal learning	−1.22	33	. . .	1734
Current	*Story memory learning*	*−1.19*	*12*	*863*	*1519*
Current	*Word list learning*	*−1.25*	*21*	*1254*	*2107*
Current	*Paired associates learning*	*−1.12*	*6*	*399*	*634*
Fioravanti et al[72]	Broad delayed verbal	−1.18	88	. . .	6628
Heinrichs and Zakzanis[1]	Broad delayed verbal	−0.90	7	559	1292
Aleman et al[2]	Broad delayed verbal	−1.20	35	. . .	1910
Current	*Story memory delayed*	*−1.29*	*10*	*671*	*1201*
Current	*Word list delayed*	*−1.09*	*16*	*871*	*1516*
Nonverbal memory					
Heinrichs and Zakzanis[1]	Broad nonverbal learning	−0.74	14	379	956
Aleman et al[2]	Broad nonverbal learning	−1.00	7	. . .	294
Current	*Visual reproduction learning*	*−0.82*	*9*	*544*	*841*
Aleman et al[2]	Broad delayed nonverbal	−1.09	11	. . .	800
Current	*Visual reproduction delayed*	*−0.78*	*8*	*486*	*758*
Current	*Figure recall*	*−1.03*	*5*	*280*	*629*

(continued)

taking medications at testing[26,57]) had no effect on the obtained effect size. Study characteristics—including the variant of digit symbol coding task, whether the patients and controls were education-matched, the size of the schizophrenia sample, and the vintage of the study—also did not significantly influence the coding task effect. Age matching was the only other moderator variable that significantly affected the overall effect, showing a somewhat smaller value in studies in which patients and controls were matched for age than in unmatched studies. Again, however, this subgroup difference was small relative to the digit symbol coding effect size advantage over other cognitive variables.

COMPARISON WITH PREVIOUS META-ANALYSES

Yoking study selection to the digit symbol coding variable potentially could limit the generalizability of findings from the current meta-analysis. To explore this issue, **Table 4** placed current results in the context of other meta-analyses comparing schizophrenia patients and healthy comparison subjects on widely used cognitive measures. The table illustrates that current results are consistent with results obtained by other investigators analyzing different (although overlapping) samples of studies. As in the current analysis, effect size values for past meta-analyses concentrated around $g=-1.00$, with few values smaller than $g=-0.80$ and few values larger than $g=-1.20$. The only other study that analyzed coding tasks[9] obtained a somewhat smaller effect size than the current estimate ($g=-1.46$, based on half as many studies and one third as many subjects), but it was still larger than effect sizes for any of the other cognitive variables reported in that or any of the other reviews. With one exception, the effect sizes for verbal memory measures reported across these meta-analyses were near or smaller than $g=-1.20$. The Heinrichs and Zakzanis[1] result for broad verbal learning was larger ($g=-1.41$) than that reported in other comparably powered syntheses (eg, Aleman et al[2]). Nonverbal memory, executive functioning, working memory, and sustained attention effect sizes were somewhat smaller than those reported for verbal memory across studies and specific measures. Notably, 2 studies that analyzed category fluency[8,9] obtained smaller effect size values than those obtained in the current analysis. The Henry and Crawford analysis[9] (which also reported a coding task effect of $g=-1.46$) was primarily focused on fluency measures. Its estimate of $g=-1.12$ was based on an extensive sample of studies and subjects

Table 4. Compilation of Effect Sizes From Different Meta-analyses Comparing Schizophrenia Patients and Healthy Controls on Widely Used Cognitive Variables* (cont)

Cognitive Domain/Meta-analysis	Study Variable	ES	k	SZn	TOTn
Executive functioning					
Heinrichs and Zakzanis[1]	Combined WCST	−0.88	43	1387	2540
Henry and Crawford[9]†	WCST categories	−1.06	40	. . .	2295
Laws[5]	WCST categories	−0.91	20	. . .	1064
Current	*WCST categories*	*−0.81*	*20*	*1018*	*1876*
Henry and Crawford[9]†	WCST perseverative errors	−0.98	43	. . .	2525
Laws[5]	WCST perseverative errors	−0.53	26	. . .	1516
Current	*WCST perseverative errors*	*−0.79*	*23*	*1295*	*2224*
Heinrichs and Zakzanis[1]	Stroop color-word condition	−1.11	6	179	309
Henry and Crawford[9]†	Stroop color-word condition	−0.98	20	. . .	1132
Current	*Stroop color-word condition*	*−0.99*	*8*	*422*	*892*
Heinrichs and Zakzanis[1]	Trail Making Test part B	−0.80	15	1372	2177
Current	*Trail Making Test part B*	*−0.92*	*21*	*1190*	*1944*
Working memory					
Lee and Park[7]†	Broad visuospatial WM	−0.98	59	. . .	. . .
Lee and Park[7]†	Broad verbal WM	−1.01	70	. . .	. . .
Current	*Arithmetic*	*−1.18*	*9*	*612*	*947*
Current	*Letter-number sequencing*	*−0.85*	*4*	*273*	*419*
Heinrichs and Zakzanis[1]	Digit span total	−0.61	18	440	841
Current	*Digit span total*	*−0.71*	*17*	*893*	*1704*
Aleman et al[2]	Digit span forward	−0.71	18	. . .	881
Current	*Digit span forward*	*−0.73*	*4*	*175*	*292*
Aleman et al[2]	Digit span backward	−0.82	7	. . .	306
Current	*Digit span backward*	*−0.86*	*4*	*155*	*260*
Fluency					
Heinrichs and Zakzanis[1]	Combined verbal fluency	−1.15	29	1020	1919
Bokat and Goldberg[8]	Letter fluency	−0.99	13	526	915
Henry and Crawford[9]†	Letter fluency	−0.95	30	. . .	1633
Current	*Letter fluency*	*−0.83*	*22*	*1213*	*2107*
Bokat and Goldberg[8]	Category fluency	−1.27	13	526	915
Henry and Crawford[9]†	Category fluency	−1.12	30	. . .	1633
Current	*Category fluency*	*−1.41*	*8*	*462*	*698*
Sustained attention					
Heinrichs and Zakzanis[1]	Combined CPT	−1.16	14	417	752
Current	*AX CPT*	*−1.13*	*4*	*265*	*443*
Current	*Degraded stimulus CPT*	*−0.66*	*5*	*96*	*259*
Current	*Identical pairs CPT*	*−0.86*	*4*	*260*	*433*
Current	*Conners CPT*	*−1.02*	*5*	*218*	*516*

Abbreviations: AX, the AX version of the continuous performance test (CPT); ES, effect size; k, number of studies; SZn, schizophrenia sample size; TOTn, total sample size including schizophrenia patients and comparison subjects; WCST, Wisconsin Card Sorting Test; WM, working memory; ellipses, not reported.

*Results for the current meta-analysis are presented in *italics*.

†ES values for 2 studies were reported as correlation coefficients.[7,9] These values were converted to mathematically equivalent standard deviation–style effect sizes.

and suggests that the current estimate of $g = -1.41$ may be somewhat inflated.

COMMENT

In this systematic review of widely used neuropsychological measures in schizophrenia, the 5-minute digit symbol coding task—a reliable, easy to administer, yet often overlooked instrument—showed a schizophrenia impairment that was both substantial ($g = -1.57$) and significantly larger than effects for often-studied measures of verbal memory (eg, word list learning), executive functioning (eg, card sorting), and working memory (eg, span tasks). A comparison of current results with past meta-analyses of schizophrenia cognitive deficits strongly suggested that our sample of included studies is representative of the broader literature. Thus, digit symbol coding yields the largest impairment documented in the schizophrenia clinical neuropsychology literature, yet it has rarely been the focus of theoretical discussion or experimental study. This empirical result has practical implications and raises questions about the nature of the underlying impairment that can only be addressed through further experimental research.

At a practical level, these results demonstrate that digit symbol coding tasks are useful tools in quantifying a form of cognitive impairment that is a central, reliable feature of the illness, and are more discriminating of diagnostic group status than cognitive measures that have been the focus of the recent schizophrenia literature. Thus, these tasks may be appropriate for use in a much wider range of clinical and research contexts than previously appreciated, ranging from clinical screening to assessment of treatment effects.

The subgroup and moderator variable analyses suggested that the coding task "signal" is quite strong. Of the original set of 40 studies, 37 formed a statistically homogeneous group with coding task effect sizes in the range from $g = -1.05$ to $g = -2.02$. Moderator analyses indicated that the impact of chronicity/severity groupings on the coding task impairment was significant. However, in all of these subgroups the coding task effect size remained higher than those obtained for other cognitive variables. The results were not sensitive to medication status. Neither a contrast of medicated and medication-free samples nor a contrast of low- vs high-dose antipsychotic treatment samples produced a statistically reliable effect size difference. Consistent with this, prospective, longitudinal studies have shown fairly stable digit symbol coding impairments early in the course of illness, with a very modest positive response to treatment.[32,57] Thus, it does not appear that the coding task effect is primarily attributable to either chronicity/severity or medication. Although reported in only 11 studies from the current study sample, symptom severity rated with the Brief Psychiatric Rating Scale was not related to coding task effect size. The coding task effect size also did not vary as a function of key study characteristics, including coding task variant, sample size, and year of study publication. However, moderator variable analyses were based on broad classifications of study characteristics, and it is certainly possible that subtle effects were not detected.

Digit symbol coding is not simply a marker of illness-related cognitive deficit. The subsidiary analysis of the 7 studies from the current study sample that included data from older relatives of schizophrenia patients showed a coding task effect size comparable to the largest effect sizes reported in other meta-analyses of cognitive deficits among relatives of schizophrenia patients. Other studies have shown coding task deficits in relatives still at high risk of developing illness.[76,77] Niendam et al[78] reported a premorbid coding task effect. In that study, based on retrospective testing data available from age 7 years, digit symbol coding and 2 other Wechsler subtests differentiated probands and their unaffected siblings from controls. However, only coding task performance distinguished individuals who would go on to develop schizophrenia years later from their own siblings who would not develop the disease. As noted, the measure distinguished patients with poor prognosis and early onset in the current analysis. Digit symbol coding also indexes the degree of functional disability that results from illness. Brekke et al[79] found coding task performance related to independent living. Stratta and colleagues[55] found the measure associated with scores on a scale measuring the level of performance in expected community roles. In short, this simple measure has a graded relationship with illness risk, severity, and disability in schizophrenia. It differentiates people with schizophrenia from healthy controls, low- and high-risk relatives of people with schizophrenia from healthy controls, and also unaffected relatives from schizophrenic probands. Furthermore, it appears to index poor prognosis and functional disability within the patient group. In sum, as an assessment tool, digit symbol coding tasks produce a robust impairment signal in schizophrenia that is related to risk for the illness, presence of the illness, and functional outcome.

Like nearly every measure in the clinical neuropsychology literature, coding tasks involve multiple component operations. Therefore, the robust effect size documented herein leaves critical questions unanswered: What subprocesses are involved in coding tasks? Are all of these subprocesses slowed by some relatively constant amount, or are particular operations severely slowed, constraining the whole assembly of operations? A few studies have addressed these issues,[80,81] but a more concerted program of experimental research will be needed to improve our understanding. The current results and the broader meta-analytic literature may help to guide that work. For example, it is intriguing that the coding task effect size is substantially larger than that observed for part A of the Trail Making Test or the word reading condition from the Stroop Color-Word Interference Test, which are other putative processing speed measures. At the same time, the coding effect did not differ significantly from the effect size for category fluency (ie, speeded word generation) in the current analysis (but see Henry and Crawford[9]). Careful task analyses would likely show that the Trails and Stroop tasks are operationally simpler than digit symbol coding and category fluency. The coding and fluency tasks involve very different subprocesses but share the requirement to rapidly and smoothly coordinate a complex assembly of elementary operations. Poor performance thus might implicate deficient coordination, or failures of effective connectivity among distributed brain networks, more so than specific subprocesses.

The meta-analysis did not address the relationship between the digit symbol coding impairment and brain pathology. However, one of the included studies[52] found significantly reduced gray (but not white) matter volumes in bilateral prefrontal cortex, whole temporal lobe, and superior temporal gyrus in schizophrenia patients relative to controls. Multiple regression analyses of brain structure–cognitive performance relationships highlighted digit symbol coding from among a large battery of cognitive measures. Better performance on coding was generally associated with larger gray matter volumes in bilateral prefrontal cortex, bilateral hippocampus, and left superior temporal gyrus. Findings in each of these regions accounted for more than 50% of between-group variance. In contrast, associations for word memory, cognitive flexibility, and verbal fluency measures were regionally more confined and accounted for 15% to 27% of between-group variance. The relative strength of the association of slower coding task performance with broadly reduced prefrontal and temporal gray matter volumes in schizophrenia patients relative to controls suggests that the measure taps a core neurobiological feature of the illness. At the same time, the widely distributed nature of the pathology may be consistent with the hypothesis that coding and fluency tasks require the rapid assembly and coordination of a series of elementary cognitive operations that are likely represented in distributed networks.

The current review and other recent work sharpen the hypothesis that the kind of slowed information processing tapped by digit symbol coding is a central feature of the cognitive impairment seen in this illness. The stable, traitlike qualities of digit symbol coding within patient groups, the relationship of the measures to prognosis and functional outcome, their high heritability,[82] and the presence of the same impairment in relative groups qualify coding tasks for consideration as a cognitive endophenotype.[83] The appearance of this impairment in premorbid and young, high-risk groups suggests that it may serve as a predictor of illness. In addition, the association of these measures with prognosis and functional outcome among those diagnosed as having schizophrenia supports increased effort to develop pharmacologic and remediation techniques to address the impairment.

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