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A Meta-Analysis of Cognitive Deficits in Adults with a Diagnosis of Schizophrenia

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This review identified 1275 studies examining cognitive deficits in people with schizophrenia, published between 1990 and 2003. Data from 113 studies (4365 patients and 3429 controls) were combined in a meta-analysis carried out on the five cognitive domains of IQ, memory, language, executive function, and attention. Studies were excluded where they lacked a suitable control group or failed to present complete information. In all five cognitive domains, analysis indicated a consistent trend for patients to perform more poorly than healthy controls, with significant heterogeneity across studies. Sources of heterogeneity were analyzed and a need to ensure more appropriate composition of patient and control groups and to adopt a more refined and methodologically correct, hypothesis-driven approach was identified.

KEY WORDS: schizophrenia; cognitive deficits; controlled studies; memory.

INTRODUCTION

Kraepelin's definition of dementia praecox (1971) identified schizophrenia as a disease of the brain characterized by intellectual and personality deterioration beginning in early adulthood. It was many years, however, before the relevance of Kraepelin's emphasis on the role of cognitive impairment in the clinical picture of schizophrenia was widely accepted. Today, various aspects of cognitive impairment are recognized as being among the most reliable distinguishing features of the diagnostic category of schizophrenia. However, since people with a diagnosis of schizophrenia tend, as a group, to show generally poorer performance on almost all tasks administered, this has been variously attributed to factors such as poor motivation, interference from psychotic thinking, institutionalization, or the effects of medication, rather than to any intrinsic underlying brain impairment (Seidman, 1983).

Most psychiatrists currently consider schizophrenia to be fundamentally a disease of the brain, and impaired cognitive functioning is viewed as one of the manifestations of the neuropathology of the illness (Gold and Harvey, 1993). Cognitive deficits in people with a diagnosis of schizophrenia, however, are still a matter of controversy. Some studies suggest that cognitive deficits are present throughout the disorder, including the pre-morbid stages, and that they remain evident between psychotic episodes in those patients who have a remitting course (Asarnow and MacCrimmon, 1978; Harvey et al., 1990). However, pre-morbid stages are not well defined.

Attention and memory emerge as the principal focus of interest in studies of cognitive impairment in people with a diagnosis of schizophrenia. Various procedures for assessing attention have identified impairments in sustained attention (Neuchterlein and Dawson, 1984; Neuchterlein et al., 1991) and slowed post-perceptual processing (Braff and Saccuzzo, 1982) among people with schizophrenia. In general, clinical findings suggest that people with schizophrenia show impairments in selective attention (the ability to selectively attend to relevant information while ignoring distractors), sustained attention (the ability to sustain concentration in continuous effort-demanding situations), and reaction time, including the ability to maintain the speed of perceptual and cognitive

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processing (Mirsky et al., 1986). From the earliest studies of reaction time, people with schizophrenia have consistently shown a slower than normal response to simple stimuli.

Based on these findings, many authors tend to consider impaired attention as the fundamental cognitive deficit in people with schizophrenia. In synthesis, all these results suggest that the study of neurobiological mechanisms of attention may provide a means of better understanding the symptoms of schizophrenia, but at the same time, they have not produced a consensus concerning the characteristics of disordered attention specifically evidenced by people with schizophrenia. Many hypotheses have been offered, including defective filtering or screening of incoming information, information loss in short-term memory, disordered control and maintenance of selective processing strategies, reduced processing capacity, and impaired effortful or controlled processing (Neuchterlein and Dawson, 1984; Hemsley and Richardson, 1980; Callaway and Naghdi, 1982).

Where memory functioning has been assessed by objective measures, the majority of people with schizophrenia score lower than normal (McKenna et al., 1990). Some authors have attributed the poor memory performance of these patients to impairments in encoding and retrieval processes, or to a broader impairment encompassing encoding, retrieval, and recognition functions (Gold and Harvey, 1993). A quantitative review of previous neurocognitive literature based on comparative studies with healthy controls (Heinrichs and Zarkanis, 1998) concluded that "schizophrenia is characterized by a broadly cognitive impairment, with varying degrees of deficit in all ability domains measured by standard clinical tests."

The development of neuropathological and neuroimaging techniques has generated new interest in studying memory impairment in people with a diagnosis of schizophrenia. Structural abnormalities in the medial temporal lobe, in the frontal cortex, and in the diencephalon of these individuals have been associated with memory impairments. A critical review (Zarkanis and Heinrichs, 1999) of structural and physiological brain system deficits in patients with schizophrenia concluded that a single model of impairment (i.e., one based on frontal lobe dysfunction) is not sufficiently comprehensive to include all the variance of evidence emerged from the imaging studies in schizophrenia.

The increasing number of studies published each year that focus on cognitive impairment in people with a diagnosis of schizophrenia led us to attempt to explore the available data systematically using the method of meta-analysis. The aim of our review was to identify all the relevant data concerning differences between individuals with a diagnosis of schizophrenia and healthy controls on measures of cognitive efficiency and to verify the stability of results as described in the previous quantitative review published in 1998 by Heinrichs and Zarkanis. Furthermore, our goal was to investigate the heterogeneity of the evidence for the generalized impairment in cognitive functioning for people affected by schizophrenia and the sources contributing to the observed heterogeneity.

According to Higgins and Thompson (2002) "the extent of heterogeneity in a meta-analysis partly determines the difficulty in drawing overall conclusions." A meta-analysis carried out without considering the heterogeneity of its results is incomplete and may not be useful for an in-depth interpretation of results. This type of analysis is based on the diversity of the studies included and the lack of information concerning the amount of variability due to specific sources and not to chance alone (heterogeneity) does not allow a generalization of meta-analytic results and limits it to a description of what was found in the studies included in the analysis. For this reason we planned to evaluate both effect size and heterogeneity indices in our review.

Studies were eligible for inclusion if they involved assessment of cognitive functioning in people with schizophrenia and if they included a healthy control group. Data from the included studies were subjected to meta-analysis in order to identify areas of systematic concordance and methodological homogeneity among studies in the various domains of cognitive assessment where persons with schizophrenia have been compared to healthy controls.

METHOD

Studies were considered for inclusion if they reported comparative evaluations of cognitive functioning in individuals with a diagnosis of schizophrenia and healthy controls of comparable age. A perusal of the studies found in the literature evidenced the existence of a diverse range of criteria and modalities used to select the patient groups in the included studies. Participant groups included either outpatients or inpatients or an unspecified mixture of both, and these might be people with differing clinical forms of schizophrenia. Studies adopted different definitions of chronicity, and in many cases no attempt was made to control for age, sex or educational level. Consequently, it was not possible to subdivide the participants in most of these studies into separate homogeneous clinical types of patients labeled under the general term "schizophrenia."

Database Analysis

A bibliographic search covering the period from January 1990 to December 2003 was conducted using three different databases—Psychlit, Psychiatry, and Medline—in order to identify all studies concerned with cognitive impairments in people with a diagnosis of schizophrenia. Any association of the following two keywords was used to select potentially relevant studies: "Schizophrenia" and "Cognit*." The latter represents the common source of terms such as "cognition," "cognitive," etc. In the first screening phase, this search identified a list of 1275 papers. Two researchers independently examined all the bibliographic information collected in the database search and independently rated the papers regarding their suitability for inclusion. Disagreements between the raters were resolved by discussion. Studies were excluded if they lacked a control group of healthy individuals. Subsequently, those studies which included no formal objective assessment of cognitive functioning, or which did not present their results in full in detailed tables containing separate numerical data for the patient and control groups, were also excluded. In total, 113 papers were found to meet the inclusion criteria for this review and to have numerical data available. The actual number of studies represented in the analysis is 117 as some papers reported multiple studies. Where data were obtained from controlled clinical trials, only data from the baseline evaluation, after washout, were considered for inclusion in the review.

Studies that were not included in this analysis fell into the following categories: comparative clinical studies in which two or more groups of psychiatric patients were compared but there was no healthy control group (37% of the total number of studies not included); pre-post treatment studies without a control group (15%); studies with no available data in numerical form (16%); reviews or other non-experimental studies (30%). Only 10 (2%) of the papers potentially suitable for inclusion were not included because a copy of them was not made available to the reviewers.

The criteria for inclusion of studies in this meta-analysis were chosen with the aim of identifying all possible sources of scientific information available in the literature in the form of controlled studies. Our aim was not focused on specific hypotheses such as the evaluation of utility or prevalence of use of specific measures in assessing cognitive deficits in patients with schizophrenia. Instead we set out to examine the full body of scientific data available in this field in order to extract useful conclusions about the research work carried out prior to the date of this meta-analysis.

Participant Selection Criteria

The studies under review used a diverse range of criteria when selecting participants. Seven studies (involving a total of 134 patients) used research diagnostic criteria (RDC), two studies (involving a total of 328 patients) adopted ICD criteria, one study (involving 31 patients) used the Present State Examination, one study (involving 47 patients) used Diagnostic Criteria for Schizophrenia, and one study (involving 14 patients) used the SANPS. Three studies (involving a total of 205 patients) provided no indication of the specific criteria used to select participants. The remaining studies adopted DSM III, III-R, or IV criteria. No study specified a particular clinical form of schizophrenia as a requirement for selection of participants.

This lack of a systematic and organized procedure for identifying and classifying participants meant that we could not differentiate the included studies into separate clinical domains along similar lines to those proposed for the cognitive variables (see Table 1).

Description of Participants

The total number of cases included in this meta-analysis comprises 4365 people with a diagnosis of schizophrenia (patients) and 3429 controls. The patients were 2647 men and 1369 women (F/M ratio = .52). The healthy control groups included 1683 men and 1354 women (F/M ratio = .80). Gender was not specified for the remaining individuals. The mean age of the patients ranged from 16.05 to 73.71 years. In eight studies an age range was given instead of the mean age, and here the youngest participants were 16 years of age. Mean educational level was reported in all but 72 studies, and ranged from 4.9 to 17.7 years of schooling. The National Adult Reading Test (NART) was used to give an estimate of premorbid or optimal IQ in 294 patients (mean 108.9, *SD* 10.1). Mean duration of illness ranged from 1.3 to 30.9 years. Mean age at first hospitalization ranged from 20.24 to 27.10 years, but this information was offered in seven studies only. Mean length of stay in a psychiatric ward (82.5 months) was indicated for only 30 patients.

Most of the studies did not explicitly mention whether patients were assessed in an acute or chronic clinical phase. Where specific details were given, 1498 were said to be inpatients, and of these 552 were described as being in a chronic phase and 164 in an acute phase when assessed. A further 1132 were described as outpatients. Only few of the patients considered in this review were experiencing their first episode of illness.

Table 1. A Meta-Analysis of Cognitive Deficits in Adults with a Diagnosis of Schizophrenia

	Characteristics of included studies		
Study ID	Methods	Participants	Outcomes described in the studies
Arango C.	Patient selection according to DSM III R. All chronic outpatients, clinically stable, mostly medicated.	85 patients (60 males, 25 females) and 36 controls (24 males, 12 females). Patients' mean age 35.89 years (*SD* 7.7), and years of education 12.3 (*SD* 2.3); controls' mean age 35.13 years (*SD* 7.4), and years of education 14.3 (*SD* 2.1).	Verbal fluency; category fluency; Wechsler Memory Scale-revised, logical memory subscale.
Besche C.	Patient selection according to DSM III R. Patients were diagnosed as thought-disordered schizophrenics. All chronic inpatients, medicated.	24 patients (17 males, 7 females) and 20 controls (15 males, 5 females). Patients' mean age 35.4 years (*SD* 10.0), and years of education 11.1 (*SD* 1.7); controls' mean age 26.6 years (*SD* 11.6), and years of education 12.1 (*SD* 2.6).	Vocabulary; reaction time during a semantic lexical decision task.
Braff D.L.	Patient selection according to DSM III R and SCID. All chronic outpatients, mostly medicated.	40 patients (30 males, 10 females) and 40 controls (30 males, 10 females). Patients' mean age 29.7 years (*SD* 7.9), and years of education 13.3 (*SD* 1.7); controls' mean age 29.7 years (*SD* 7.6), and years of education 13.9 (*SD* 1.8).	WCST (categories achieved); verbal IQ (WAIS-R); Tactual Performance Test, memory (TPT).
Brankovic S.B.	Patient selection according to DSM IV. All chronic inpatients, medicated.	29 patients (15 males, 14 females) and 35 controls (10 males, 25 females). Patients' mean age 33.1 years (*SD* 8.4), and years of education 13.0; controls' mean age 29.8 years (*SD* 7.2), and years of education 15.2.	Reasoning task.
Brazo P.	Patient selection according to DSM IV. All outpatients, clinically stable for at least 4 months, medicated.	35 patients and 35 controls. Patients' mean age 34,9 years (*SD* 9.9); controls' mean age 35 years (*SD* 9.5). Mean age at first hospitalization was 22.3 (*SD* 4.7), mean length of disease was 10.9 (*SD* 9.3).	WAIS-R; WCST (categories); category fluency; TMT (B-A); CVLT.
Brebion G.	Patient selection according to DSM IV. All inpatients, medicated.	50 patients (32 males, 18 females) and 40 controls (26 males, 14 females). Patients' mean age 32.8 years (*SD* 10.6), and years of education 12.4 (*SD* 2.5); controls' mean age 37.0 years (*SD* 9.9), and years of education 13.2 (*SD* 1.9). Mean age at first hospitalization was 22.2 (*SD* 7.7), mean length of disease was 11.4 years (*SD* 9.9).	Global memory efficiency.
Broerse A.	Patient selection according to DSM IV and SCAN criteria. Both acute and chronic, mostly medicated.	24 patients (18 males, 6 females) and 20 controls (15 males, 5 females). Patients' mean age 26.54 years (*SD* 8.47); controls' mean age 20.95 years (*SD* 2.80).	CPT; verbal fluency; Rey complex figure.
Buckley P.F.	Patient selection according to DSM III R. Both acute and chronic, in and outpatients, mostly medicated.	27 patients (15 males, 12 females) and 20 controls (10 males, 10 females). Patients' mean age 30.8 years (*SD* 7.0), and years of education 13.6 (*SD* 2.1); controls' mean age 30.1 years (*SD* 7.8), and years of education 14.1 (*SD* 2.1). Mean length of disease was 7.8 years (*SD* 6.5).	Wechsler Memory Scale-revised, general memory.
Cadenhead K.S.	Patient selection according to DSM IV and SCID. Both in and outpatients, mostly medicated.	20 patients (8 males, 12 females) and 20 controls (8 males, 12 females). Patients' mean age 34.8 years (range 19–53), and years of education 13.8 (range 10–18); controls' mean age 35.8 years (range 20–59), and years of education 14.5 (range 12–18).	WCST-categories; Recognition Memory Test; WAIS-R, vocabulary.

Cantor G.E.	Patient selection according to DSM III R and on the basis of a structured clinical interview and medical records. All acute patients, mostly not medicated.	14 patients (8 males, 6 females) and 14 controls. Patients' mean age 36 years (range 21–59), and years of education 11.2 (range 7–19). Controls were individually case-matched to the patients on the basis of gender, age and level of educational attainment. Mean length of disease was 6.6 years (range 6 months to 30 years), 4 patients had a disease length of less than 2 years.	WAIS, vocabulary subtest; paired associate and (immediate recall) Verbal Memory Test; Reaction Time Test.
Carter C.S.	Patient selection according to DSM III R and SCID. All outpatients, mostly not medicated.	13 patients (10 males, 3 females) and 11 controls (9 males, 2 females). Patients' mean age 32.5 years (*SD* 4.3), and years of education 13.4 (*SD* 2.0); controls' mean age 31 years (*SD* 6.1), and years of education 14.5 (*SD* 2.1). Mean length of disease was 10.07 years (*SD* 6.13).	Stroop color naming task (neutral word).
Chey J.	Patient selection according to DSM IV. Mostly outpatients, all medicated.	15 patients (9 males, 6 females) and 16 controls (10 males, 6 females). Patients' mean age 33.0 years (*SD* 8.9), and years of education 12.7 (*SD* 2.7); controls' mean age 32 years (*SD* 8.2), and years of education 12.8 (*SD* 2.6).	Spatial delay response (delay and immediate).
Clare L.	Patient selection according to Research Diagnostic Criteria. All chronic patients, medicated.	12 patients (7 ma1es, 5 females) and 12 controls. Patients' mean age 42.7 years (range 21–70), mean of premorbid IQ was 105.7 (range 91–122) estimated in 11 patients using the National Adult Reading Test (NART). Controls mean age 43.2 years (range 17–75), IQ mean, estimated from NART scores in 11 subjects, was 109.9 (range 94–125).	Warrington's Recognition Memory Test.
Cohen J.D.	Patient selection according to DSM III R and SCID. Both in and outpatients, all medicated.	53 patients (27 males, 26 females) and 31 controls (19 males, 12 females). Patients' mean age 36.3 years (*SD* 8.7), and years of education 12.7 (*SD* 2.3); controls' mean age 33.2 years (*SD* 7.7), and years of education 14.0 (*SD* 2.4). Mean age at first hospitalization was 22.90 years (*SD* 6.5).	Short-term memory, word span.
Conklin H.M.	Patient selection according to DSM IV and SCID. All inpatients.	39 patients (23 males, 16 females) and 56 controls (22 males, 34 females). Patients' mean age 37.8 years (*SD* 8.2), and years of education 13.1 (*SD* 1.8); controls' mean age 33.9 years (*SD* 12.9), and years of education 15.9 (*SD* 2.5).	IQ (prorated); RAVLT.
Corrigan P.W.	Patient selection according to DSM III R. All inpatients, medicated.	30 patients (23 males, 7 females) and 15 controls (10 males, 5 females). Patients' mean age 34.0 years (*SD* 7.6), and years of education 11.5 (*SD* 1.6); controls' mean age 31.7 years (*SD* 10.4), and years of education 14.1 (*SD* 1.9). Mean interval from first hospitalization was 14.30 years (*SD* 6.5).	Component recognition.
Crespo-Facorro B.	Patient selection according to Scale for the Assessment of Negative and Positive Symptoms. All inpatients, not medicated.	14 patients (10 males, 4 females) and 13 controls (6 males, 7 females). Patients' mean age 30.7 years (*SD* 11.3), and years of education 13.2 (*SD* 2.2); controls' mean age 28.6 years (*SD* 7.2), and years of education 14.7 (*SD* 1.5). Mean length of disease was 10.60 years (*SD* 12.2).	Rey auditory verbal learning test.
Danion J.M.	Patient selection according to DSM IV. All outpatients, clinically stable, medicated.	48 patients (31 males, 17 females) and 24 controls (15 males, 9 females). Patients' mean age 34.1 years (*SD* 6.4), and years of education 11.8 (*SD* 3.1); controls' mean age 33.7 years (*SD* 5.9), and years of education 12.1 (*SD* 3.0). Mean length of disease was 10.6 years (*SD* 6.0).	IQ (WAIS); verbal fluency.

Table 1. Continued

Davidson M.	Patient selection according to DSM III R. All chronic patients, mostly medicated.	66 patients (26 males, 40 females) and 66 controls (25 males, 41 females). Patients' mean age 73.28 years (*SD* 5.56), and years of education 10.33 years (*SD* 2.13); controls' mean age 73.30 years (*SD* 5.80), and years of education 14.30 (*SD* 2.50).	Verbal serial learning delayed recall.
Docherty N.M.	Patient selection according to DSM IV. All outpatients, clinically stable.	43 patients (38 males, 5 females) and 23 controls (11 males, 12 females). Patients' mean age 33.00 years (*SD* 7.00), and years of education 12.00 (*SD* 2.00); controls' mean age 62.00 years (*SD* 9.00), and years of education 13.00 (*SD* 3.00).	Communication disturbances index.
Earle Boyer E.A.	Patient selection according to DSM III and on the basis of Schedule for Affective Disorders and Schizophrenia (SADS). All medicated.	17 patients (10 males, 7 females) and 19 controls (10 males, 9 females). Patients' mean age 31.64 years (*SD* 8.80), and years of education 12.5 (*SD* 1.34); controls' mean age 28.40 years (*SD* 8.32), and years of education 13.80 (*SD* 1.88). Mean age at first admission was 20.24 (*SD* 4.93).	CPT-stimuli; visual task, lexical stimuli.
Egan M.F.	Patient selection according to SCID. All outpatients, medicated.	120 patients (100 males, 20 females) and 43 controls (16 males, 27 females). Patients' mean age 35.9 years (*SD* 8.2), and years of education 13.4 (*SD* 2.3); controls' mean age 33.3 years (*SD* 8.8), and years of education 15.1 (*SD* 2.3).	IQ; working memory (WCST-CAT); language production/retrieval; declarative memory.
Elvevag B. (a)	Patient selection according to Research Diagnostic Criteria (RDC) and on the basis of a clinical interview. All patients clinically stable, medicated.	28 patients (22 males, 10 females) and 48 controls (20 males, 28 females). Patients' mean age 36.0 years (*SD* 9.0); controls' mean age 43.0 years (*SD* 8.0).	NART IQ; cued spatial location task.
Elvevag B. (b)	Patient selection according to DSM IV and SCID. All inpatients, clinically stable, medicated.	20 patients (18 males, 2 females) and 30 controls (15 males, 15 females). Patients' mean age 35.7 years (*SD* 9.17); controls' mean age 29.7 years (*SD* 7.37).	WAIS IQ; CPT (latency time).
Elvevag B. (c)	Patient selection according to DSM IV and SCID. All inpatients, clinically stable, medicated.	24 patients and 29 controls. Patients' mean age 35.00 years (*SD* 9.70); controls' mean age 32.00 years (*SD* 9.80).	WAIS-R IQ.
Frith C.D.	Patient selection according to ICD-9 classification. Both in and outpatients, all medicated.	283 patients (153 males, 130 females) and 35 controls. Patients' mean age 45.0 years (*SD* 12.5) and mean of premorbid IQ was 109.0 (*SD* 10.1) using the National Adult Reading Test (NART). Controls mean age 40.3 years (*SD* 15.4) and IQ mean, estimated from NART scores, was 108.1 (*SD* 9.9).	Quick test for IQ; verbal fluency task (odd responses); forced-choice recognition memory for single words.
Fucetola R. (study 1)		20 older patients and 20 controls of comparable age.	Visual CPT (reaction time).
Fucetola R. (study 2)		20 younger patients and 20 controls of comparable age.	Visual CPT (reaction time).
Giovannetti T.	Patient selection according to research Diagnostic Criteria for Schizophrenia. All inpatients, medicated.	47 patients (27 males, 20 females) and 31 controls (21 males, 20 females). Patients' mean age 25.76 years (*SD* 6.77), and years of education 13.26 (*SD* 1.95); controls' mean age 25.2 years (*SD* 6.07), and years of education 15.0 (*SD* 1.48).	IQ (WAIS-R); trail making test (Trails-B); Boston naming test..
Glann D.C.	Patient selection according to DSM IV and SCID. 16 patients were at the first episode of illness, mostly medicated.	62 patients (31 males, 31 females) and 62 controls (32 males, 30 females). Patients' mean age 29.60 years (range 17–66), and years of education 13.0 (*SD* 2.30); controls' mean age 27.20 years (range 18 to 62 years), and years of education 15.6 (*SD* 1.10). Mean age at onset of disease was 22.70 (*SD* 6.00).	WAIS-R (vocabulary); digit span (forward); WCST (categories); controlled oral word association task; trial making test.

Gold J.M.	Patient selection according to DSM III R. All outpatients, medicated.	37 patients and 20 controls. Patients' mean age 40.9 years (*SD* 7.34), and years of education 12.81 (*SD* 2.17); controls' mean age35.8 years (*SD* 7.4), and years education 14.9 (*SD* 1.33).	Wide range achievement test (WRAT 3), conditional associative learning (CAL) correct responses on the unique task.
Goldberg T.E. (a)	Patient selection according to DSM III R and SCID. Mostly outpatients, mostly medicated.	16 patients (8 males, 8 females) and 7 controls (3 males,4 females). Patients mean age 32 years (range 24–44 years), and years of education 15.6; controls' mean age 31 years (range 19–44 years), and years of education 16.6. Mean length of disease was 9.1 years (range 3 to 16 years).	WAIS-R (vocabulary and full scale IQ); Wechsler Memory Scale (memory quotient); CPT stimuli (reaction time); WCST (categories).
Goldberg T.E. (b)	Patient selection according to DSM III R and SCID. All inpatients, medicated.	23 patients (18 males, 5 females) and 23 controls (13 males, 10 females). Patients' mean age 35.00 years (*SD* 14.40); controls' mean age 35.50 years (*SD* 8.50). Mean length of disease was 17.1 years (*SD* 8.60).	Wide range achievement test-R for IQ, Peabody picture vocabulary test, WCST (categories).
Goldstein J.M.	Patient selection according to DSM III R. All outpatients, medicated.	31 patients (17 males, 14 females) and 27 controls (13 males, 14 females). Patients' mean age 39.1 years (*SD* 7.0), and years of education 13.2 (*SD* 1.9); controls' mean age 38.32 years (*SD* 8.77), and years of education 14.18 (*SD* 2.3). Mean length of disease was 17.8 years. (*SD* 9.10).	Wide range achievement test-R for IQ.
Gooding D.C.	Patient selection according to DSM IV and SCID. All outpatients, clinically stable, all medicated.	57 patients (34 males, 23 females) and 30 controls (16 males, 14 females). Patients' mean age 38.89 years (*SD* 9.09); controls' mean age 35.03 years (*SD* 10.29). Mean length of disease was 17.20 years. (*SD* 8.38).	IQ (WAIS –R).
Gras-Vicendon A.	Patient selection according to DSM III R. Mostly chronic inpatients, all medicated.	24 patients (13 males, 11 females) and 24 controls (13 males, 11 females). Patients' mean age 28.2 years (*SD* 6.4), and years of education 14.1 (*SD* 1.7); controls' mean age 26.7 years (*SD* 5.9), and years of education 15.0 (*SD* 2.0). Mean length of disease was 7.4 years (*SD* 6.3).	Wechsler Memory Scale free recall (number of words).
Grillon C.	Patient selection according to Research Diagnostic Criteria and on the basis of the Schedule for Affective Disorders and Schizophrenia, Lifetime version. Mostly medicated.	15 patients (12 males, 3 females) and 15 controls (matched for gender to the patients). Patients' mean age 31.6 years (*SD* 6.7); controls' mean age 29.1 years (*SD* 6.7).	Auditory reaction time task (distraction condition).
Gur R. C.	Patient selection according to DSM IV and SCID-P. All patients clinically stable, mostly medicated.	53 patients (34 males, 19 females) and 71 controls (41 males, 30 females). Patients' mean age 34.1 years (*SD* 11.1), and years of education 13.4 (*SD* 2.3); controls' mean age 31.2 years (*SD* 9.7), and years of education 15.9 (*SD* 2.0). Mean age at first hospitalization was 22.5 (*SD* 5.4), mean length of disease was 10.4 years (*SD* 9.5).	Attention (Trail B); logical memory delayed recall; language ability (LAN); WCTS (categories).
Hartman M.	Patient selection according to DSM IV and SCID-P. All inpatients, all medicated.	16 patients (12 males, 4 females) and 16 controls (12 males, 4 females). Patients' mean age 34.6 years (*SD* 11.2), and years of education 13.4 (*SD* 2.1); controls' mean age 31.9 years (*SD* 10.9), and years of education 14 (*SD* 2.53). Mean age at first hospitalization was 21.4 (*SD* 6.5), mean length of disease was 13.8 years (*SD* 10.1).	Memory (cognistat); delayed match sample (DMTS).
Harvey P.D. (a)	Patient selection according to DSM III and on the basis of Schedule for Affective Disorders and Schizophrenia. All inpatients, medicated.	38 patients (16 males, 16 females) and 25 controls (11 males, 14 females). Patients' mean age 32.5 years (*SD* 8.6), and years education 11.9 (*SD* 2.1); controls' mean age 30.6 years (*SD* 10.2), and years of education 13.1 (*SD* 1.3).	Word span encoding task (neutral, length 8 words).
Harvey P.D. (b)		165 patients (66 males, 99 females) and 165 controls (66 males, 99 females). Patients' mean age 73.71yrs (*SD* 8.34), and years of education 11.21 (*SD* 2.51); controls' mean age 73.59 years (*SD* 8.76), and years of education 11.34 (*SD* 2.60). Mean age at the first diagnosis was 27.10 years (*SD* 10.83).	MMSE, CERAD (delayed recall score, animal naming fluency).

Table 1. Continued

Haskins B.	Patient selection according to DSM III R. All chronic inpatients, medicated.	47 patients (26 males, 21 females) and 51 controls (22 males, 29 females). Patients' mean age 34 years (*SD* 6.5); controls' mean age 36.3 years (*SD* 7.8). Mean length of disease was 16.1 years (*SD* 6.8).	Emotional Blunting Scale.
Hazlett E.A.	Patient selection according to DSM IV and on the basis of Comprehensive Assessment of Symptoms and History (CASH).	20 patients (14 males, 6 females) and 32 controls (25 males, 7 females). Patients' mean age 38.3 years (*SD* 14.1); controls' mean age 41.8 years (*SD* 12.1).	Serial verbal learning test (SVLT) (number of correct recalls).
Heaton R.	Patient selection according to DSM III R and on the basis of a semi-structured intake evaluation based on DSM III R. Both in and outpatients, all medicated.	35 patients (31 males, 4 females) and 38 controls (13 males, 25 females). Patients age 55.9 years (*SD* 9.1), and years of education 12.9 (*SD* 2.4); controls' mean age 65.7 years (*SD* 8.5), and years of education 13.7 (*SD* 2.2). Mean length of disease was 28.0 years (*SD* 12.1).	WAIS-R
Hirt M.	Patient selection according to Research Diagnostic Criteria and on the basis of the Present State Examination. All chronic inpatients, medicated.	10 patients (all males) and 10 controls (all males). Patients' mean age 31.5 years (*SD* 10.33); controls' mean age 29.4 years (*SD* 9.26). Mean length of disease was 8.2 years (*SD* 3.39).	Reaction times at a visual task.
Hoff A.L. (a)	Patient selection according to DSM III R. All chronic patients, medicated.	26 patients (16 males, 10 females) and 25 controls (16 males, 9 females). Patients' mean age 31.1 years (*SD* 8.5), and years of education 13.0 (*SD* 2.0); controls' mean age 26.1 years (*SD* 6.0), and years of education 14.6 (*SD* 2.1).	Logical memory; WCST(categories); Boston naming test; cancellation test.
Hoff A.L. (b)	Patient selection according to DSM III R. First episode and chronic patients.	32 patients (92 males, 40 females) and 74 controls (56 males, 18 females). Patients' mean age 32.51 years (*SD* 7.91); controls' mean age 30.18 years (*SD* 8.69). Mean age at the onset of disease was 21.31 (*SD* 5.35).	Verbal IQ; WCST (categories); associate learning; concentration and speed test.
Hoffman R.E.D.	Patient selection according to DSM IV. All inpatients, included immediately after an acute episode, mostly medicated.	21 patients (10 males, 11 females) and 26 controls (11 males, 15 females). Patients' mean age 32.9 years (*SD* 10.3), and years of education 14.0 (*SD* 2.1); controls' mean age 32.9 years (*SD* 10.3), and years of education 13.9 (*SD* 1.5). Mean age at first hospitalization was 22.6 years (*SD* 6.3).	CPT (hit rate).
Huges C.	Patient selection according to DSM IV. All outpatients, medicated.	62 patients (39 males, 23 females) and 25 controls (15 males, 15 females). Patients' mean age 37.7 years (*SD* 10.27), and years of education 12.8 (*SD* 2.5); controls' mean age 34.9 years (*SD* 13.0), and years of education 15.2 (*SD* 3.3). Mean length of disease was 19.3 years (*SD* 9.3).	IQ (full scale); WCST categories; delayed verbal memory; CPT reaction time.
Javitt D.C. (a)	Patient selection according to DSM III R. Mostly inpatients, mostly medicated.	31 patients (27 male, 4 females) and 11 controls (6 males, 5 females). Patients' mean age 36.2 years (*SD* 8.8); controls' mean age 38.3 years (*SD* 9.73).	Quick Test; auditory mean CPT (reaction time).
Javitt D.C. (b)	Patient selection according to DSM III R. All chronic patients.	20 patients and 19 controls. Patients' mean age 38.7 years (*SD* 2.0); controls' mean age 36.8 years (*SD* 8.7).	Tone memory performance.
Joyce E.	Patient selection according to DSM IV. All outpatients, medicated.	136 patients (107 males, 29 females) and 81 controls (49 males, 32 females). Patients' mean age 25.74 years (*SD* 7.99); controls' mean age 26.12 years (*SD* 5.19).	IQ (NART); spatial working memory.
Kiefer M.	Patient selection according to ICD-10 and on the basis of the Brief Psychiatric Rating Scale. All inpatients, medicated.	24 patients (11 males, 13 females) and 24 controls (11 males, 13 females). Patients' mean age 34.5 years (*SD* 10.33), and years of education 10.3 (*SD* 1.46); controls' mean age 34.2 years (*SD* 8.33), and years of education 10.2 (*SD* 1.96). Mean length of disease was 10.75 years.	Working memory tasks (digit span backward); category fluency.

Kim M.S.	Patient selection according to DSM IV and SCID. Mostly outpatients, medicated.	22 patients (14 males, 8 females) and 21 controls (16 males, 5 females). Patients' mean age 29.55 years (*SD* 7.57), and years of education 13.68 (*SD* 2.21); controls' mean age 27.624 years (*SD* 9.21), and years of education 14.62 (*SD* 2.52).	IQ; delay recall (Rey-Osterrieth complex figure); Trail Making Test (trails-B); COWA (category); WCST.
Kircker T.T.J.	Patient selection according to DSM IV. All acute inpatients, medicated.	6 patients (all males) and 7 controls (all males). Patients' mean age 34.3 years (*SD* 11.5) and years of education 11.7 (*SD* 1.7); controls' mean age 34.0 years (*SD* 7.9) and years of education 11.3 (*SD* 2.7).	IQ (NART); continuous performance
Krabbendam L.	Patient selection according to DSM IV and on the basis of the Composite International Diagnostic Interview. All outpatients, medicated.	27 patients (13 males, 14 females) and 19 controls (9 males, 10 females). Patients' mean age 35.9 years (*SD* 8.6); controls' mean age 36.0 years (*SD* 9.4).	Groningen intelligence test (GIT), IQ.
Kravariti E.	Patient selection according to DSM IV and SCID. All inpatients, medicated.	20 patients (13 males, 7 females) and 21 controls (12 males, 9 females). Patients' mean age 16.5 years (*SD* 1.2), and years of education 11.0 (*SD* 1.1); controls' mean age 16.2 years (*SD* 1.2), and years of education 11.2 (*SD* 1.2).	IQ; general memory.
Kurachi M.	Patient selection according to DSM III R. All outpatients, medicated.	12 patients (6 males, 6 females) and 12 controls (6 males, 6 females). Patients' mean age 23.3 years (*SD* 5.4); controls' mean age 25.9 years (*SD* 3.4). Mean length of disease was 3.3 years (*SD* 2.5).	Picture Completion Test of WAIS (response time).
Landro N.I.	Patient selection according to DSM III R and SCID. Mostly chronic, all inpatient, mostly medicated	30 patients (21 males, 9 females) and 18 controls (10 males, 8 females). Patients' mean age 34.4 years (*SD* 10.0), and months of education 115.8 (*SD* 28.3); controls' mean age 32.4 years (*SD* 10.2), and months of education 120.7 (*SD* 28.4). Mean duration of hospitalization was 82.5 months (*SD* 75.1).	Short-Term Memory Test.
Lanser M.G.	Patient selection according to DSM III R. All inpatients, medicated.	39 patients (27 males, 12 females) and 36 controls (25 males, 11 females). Patients' mean age 31.66 years (*SD* 8.46); controls' mean age 32,4 years (*SD* 8,4).	Verbal intelligence; visuo-perceptual memory; Semantic Clustering (CVLT).
Laplante L.	Patient selection according to DSM III and on the basis of Brief Psychiatric Rating Scale. All inpatients, medicated.	10 patients and 35 controls. Patients' mean age 33 years, and years of education 11; controls' mean age 32 years, and years of education 12.7.	Reaction time.
MacDonald A. W.	Patient selection according to DSM IV and SCID. Mostly outpatients, medicated.	24 patients (13 males, 11 females) and 36 controls (15 males, 21 females). Patients' mean age 36.8 years (*SD* 9.2), and years of education 14.0 (*SD* 2.4); controls' mean age 33.6 years (*SD* 8.4), and years of education 15.6 (*SD* 2.8).	WRAT III (raw score).
Miller M.B.	Patient selection according to DSM III R. All outpatients, mostly medicated.	30 patients (24 males, 6 females) and 27 controls (23 males, 4 females). Patients' mean age 33 years, and years of education 11; controls' mean age 32 years, and years of education 12.7.	Hard anagrams.
Mirsky A.F.	Patient selection according to DSM III R and SCID. Mostly medicated..	23 patients (16 males, 7 females) and 43 normal subjects (22 males, 21 females). Patients' mean age 44.9 years (*SD* 10.7), and years of education 9.5 (*SD* 1.7); controls' mean age 48.9 years (*SD* 12.1), and years of education 11.2 (*SD* 2.7).	WCST(Categories); Vocabulary of WAIS-R; CPT (reaction time)
Morice R.	Patient selection according to DSM III and on the basis of Diagnostic Interview Schedule (DIS). All chronic, in and outpatients, medicated.	60 patients (46 males, 14 females) and 34 controls (21 males, 13 females). Patients' mean age 32.0 years (*SD* 9.1); controls' mean age 29.0 years (*SD* 10.6). Educational level was fairly uniform across the groups except that of 10 (17%) schizophrenics had only completed primary education. Mean length of disease was 9.6 years (*SD* 9.4).	Vocabulary and similarities subtest of WAIS-R and IQ.

Table 1. Continued

Moritz S.	Patient selection according to DSM IV. All inpatients, mostly medicated.	20 patients (8 males, 12 females) and 20 controls (8 males, 12 females). Patients' mean age 33.0 years (*SD* 9.1), and years of education 11.5 (*SD* 1.5); controls' mean age 31.8yrs (*SD* 9.5), and years of education 11.5 (*SD* 1.6). Mean length of disease was 8.7 years (*SD* 8.6).	Prime presentation time with mask (250 ms).
Morrison-Stewart S.L	Patient selection according to DSM III and SCID. Mostly outpatients, all medicated.	20 patients (16 males, 4 females) and 30 controls (24 males, 6 females). Patients' mean age 31.9 years (*SD* 8.52); controls' mean age 30.3 years (*SD* 8.15).	Wonderlic Personnell Test (IQ.)
Myles-Worsley W.M.	Patient selection according to DSM III R and Research Diagnostic Criteria. All inpatients, medicated.	20 patients (11 males, 9 females) and 20 controls (9 males, 11 females). Patients' mean age 28.9 years (*SD* 7.5), and years of education 11.8 (*SD* 1.9); controls' mean age 31.5 years (*SD* 9.2), and years of education 12.1 (*SD* 2.4).	Attentional task with verbal response.
Nestor P.G.	Patient selection according to DSM III R and SCID. All inpatients, medicated.	18 patients and 21 controls. Patients' mean age 44.0 years (*SD* 9.5); controls' mean age 39.9 years (*SD* 11.4). Mean length of disease was 23.2 (*SD* 10.2).	Cued associative recall.
Neufeld R.W.J.	Patient selection according to Research Diagnostic Criteria. All inpatients, medicated.	15 patients (7 males, 8 females) and 16 controls (9 males, 7 females). Patients' mean age 31.73 years (*SD* 7.88), and years of education 12.07 (*SD* 2.99); controls' mean age 25.31 years (*SD* 4.55), and years of education 14.88 (*SD* 1.54).	Number Named (spatial memory).
Ober B.A.	Patient selection according to DSM III R. All chronic, outpatients, mostly medicated.	19 patients (17 males, 2 females) and 22 controls (10 males, 12 females). Patients' mean age 31.58 years (*SD* 5.35), and years of education 12.63 (*SD* 1.46); controls' mean age 20.14 years (*SD* 2.73), and years of education 13.31 (*SD* 1.09).	Lexical decision task (reaction time).
Ojeda N.	Patient selection according to DSM IV. All chronic, inpatients, medicated.	11 patients (10 males, 1 female) and 10 controls (7 males, 3 females). Patients' mean age 27.55 years (*SD* 9.4), and years of education 12.93 (*SD* 1.90); controls' mean age 26.10 years (*SD* 6.95), and years of education 14.67 (*SD* 2.71). Mean length of disease was 17.73 years (*SD* 4.7).	WCST (categories); FAS (verbal fluency); CPT (reaction time).
Okada A	Patient selection according to DSM IV. All inpatients, medicated.	22 patients (15 males, 7 females) and 22 controls (12 males, 10 females). Patients' mean age 41.6 years (*SD* 9.3), and years of education 12.2 (*SD* 2.2); controls' mean age 40.6 years (*SD* 7.6), and years of education 14.0 (*SD* 2.6). Mean length of disease was 14.1 years (*SD* 6.2).	IQ (WAIS-R).
Papageorgiou C.	Patient selection according to DSM IV. All inpatients, mostly medicated.	9 patients (4 males and 5 females) and 11 controls (5 males and 6 females). Patients' mean age 34.9 years (*SD* 7), and years of education 12.9 (*SD* 2.7); controls' mean age 34.2 years (*SD* 6.8) and years of education 13.2 (*SD* 2.5).	Digit span.
Parellada E.	Patient selection according to DSM III R. All inpatients, neuroleptic-naive.	6 patients (all females) and 6 controls (all females). Patients' mean age 22.7 years (*SD* 5.2), and years of education 12.7 (*SD* 3.5); controls' mean age 25.2 years (*SD* 2.8) and years of education 17.7 (*SD* 0.4). Mean length of disease was 15.5 months (*SD* 13.4).	WCST (categories).

Park S.	Patient selection according to DSM III R and SCID. All chronic, outpatients, not medicated.	18 patients (gender composition not defined) and 18 controls (gender composition not defined). Patients' mean age 34.6 years (*SD* 8.7), and years of education 14.2 (*SD* 2.1); controls' mean age 29.4 years (*SD* 8.6), and years of education 14.7 (*SD* 2.8).	Memory task (reaction time).
Paulsen J.S.	Patient selection according to DSM III R and SCID. All inpatients, medicated.	20 patients (14 males, 6 females) and 30 controls (8 males, 22 females). Patients' mean age 56.9 years (*SD* 8.0), and years of education 13.2 (*SD* 2.2); controls' mean age 62.7 years (*SD* 5.2), and years of education 13.7 (*SD* 2.1). Mean length of disease was 19.2 years (*SD* 18.3).	Verbal ability task; abstraction and cognitive flexibility task; memory task.
Penn D.L.	Patient selection according to the Present State Examination. All inpatients, medicated.	31 patients (18 males, 6 females) and 31 controls (15 males, 16 females). Patients' mean age years 20.6 years (*SD* 2.5); controls' mean age 26.6 years (*SD* 3.3).	Reaction time.
Perlstein W.M. (a)	Patient selection according to DSM IV and SCID. All inpatients, medicated.	55 patients (30 males, 25 females) and 24 controls (13 males, 11 females). Patients' mean age 38.5 years (*SD* 8.8), and years of education 11.9 (*SD* 1.6); controls' mean age 35.5 years (*SD* 5.4), and years of education 15.0 (*SD* 2.2). Mean length of disease was 20.5 years (*SD* 7.6).	Card stroop (color-word association); single trial stroop (reaction time).
Perlstein W.M. (b)	Patient selection according to DSM IV and SCID. All stable outpatients, medicated.	17 patients (11 males, 6 females) and 16 controls (10 males, 6 females). Patients' mean age 36.5 years (*SD* 7.5), and years of education 13.6 (*SD* 2.2); controls' mean age 36.5 years (*SD* 6.9), and years of education 15.0 (*SD* 2.4). Mean length of disease was 13.9 years (*SD* 8.4).	Working memory (reaction time and target-detection sensitivity).
Perry W. (study 1)	Patient selection according to DSM III-R and SCID. All stable inpatients, medicated.	50 patients (24 males, 26 females) and 50 controls (27 males, 23 females). Patients' mean age 35.8 years (*SD* 8.4), and years of education 12.6 (*SD* 2.2); controls' mean age 32.0 years (*SD* 10.2), and years of education 13.6 (*SD* 1.6). Mean length of disease was 21.9 years (*SD* 5.6).	Vocabulary performance; digit span (WAIS-R).
Perry W. (study 3)	Patient selection according to SCID III-R. Mostly inpatients, medicated.	40 patients (24 males, 26 females) and 40 controls. Patients' mean age 30.4 years (*SD* 7.4), and years of education 12.1 (*SD* 1.4); controls' mean age 33.5 years (*SD* 8.3), and years of education 12.0 (*SD* 1.7). Mean length of disease was 21.7 years (*SD* 5.9).	WCST (categories); vocabulary performance (WAIS-R).
Perry W. (study 4)	Patient selection according to DSM IV and SCID. Mostly outpatients, mostly unmedicated.	37 patients (21 males, 16 females) and 34 controls (25 males, 9 females). Patients' mean age 39.1 years (*SD* 8.7), and years of education 12.1 (*SD* 1.7); controls' mean age 36.6 years (*SD* 9.7), and years of education 14.0 (*SD* 2.4). Mean length of disease was 22.5 years (*SD* 5.9).	WCST (categories); NUMERICAL Attention Test (NAT).
Phillips M.L.	Patient selection according to DSM IV. Both in and outpatients.	27 patients (23 males, 4 females) and 18 controls (12 males, 6 females). Patients' mean age 35.15 years (*SD* 10.2); controls' mean age 36.0 years (*SD* 9.76).	National Adult Reading Test (NART) IQ.
Rief W.	Patient selection according to DSM III. All inpatients, medicated.	24 patients (12 male, 12 females) and 24 controls (12 males, 12 females). Patients' mean age 32.4 years (range 20–48); controls' mean age 33.4 years (range 20–51).	Visual task.
Riley E.M.	Patient selection according to DSM IV and SCID. First episode patients, all medicated.	40 patients and 22 controls. Patients' mean age 24.62 years (range 16–40), and years of education 12.00; controls' mean age 26.73 years; and years of education 15.38.	WCST(categories), verbal fluency (letters), long delay free recall, Trials A psychomotoric speed.
Ross R.G.	Patient selection according to DSM IV and SCID. All chronic, outpatients, clinically stable, mostly medicated.	10 patients and 10 controls. Patients' mean age 40.00 years (*SD* 7.00), and years of education 14.00 (*SD* 2.00); controls' mean age 38.00 years (*SD* 8.00), and years of education 15.00 (*SD* 2.00).	WAIS-R IQ; accuracy of the cue-location in visuo-spatial and other memory systems.
Sarfati Y.	Patient selection according to DSM III R. All acute, inpatients, medicated.	26 patients (21 males, 5 females) and 13 controls (11 males, 2 females). Patients' mean age 32.70 years (*SD* 11.61); controls' mean age 33.0 years (*SD* 9.7). Mean length of disease was 11.5 years (*SD* 10.69).	Character intention task (image condition and verbal condition).

Table 1. Continued

Sayers M.D.	Patient selection according to DSM III R and SCID. All inpatients.	27 patients (15 males, 12 females) and 19 controls (7 males, 12 females). Patients' mean age 30.32 years (*SD* 5.63), and years of education 12.04 (*SD* 1.95); controls' mean age 31.58 years (*SD* 6.74), and years of education 13.22 (*SD* 1.95). Mean age at the first hospitalization was 21.85 (*SD* 4.60).	IQ.
Schmand B.	Patient selection according to DSM III R criteria. All inpatients, medicated.	67 patients (38 males, 29 females) and 19 controls (7 males, 12 females). Patients' mean age 33.2 years (*SD* 10.9), and years of education 4.9 (*SD* 1.4); controls' mean age 37.3 years (*SD* 14.7), and years of education 4.2 (*SD* 1.6).	Verbal learning test (delayed recall).
Schreiber H.	Patient selection according to the criteria of International Classification of Diseases. All medicated.	21 patients (16 males, 5 females) and 22 controls (16 male, 6 female). Patients' mean age 34,0 years (*SD* 10.5); controls' mean age 37.3 years (*SD* 13.8). Mean length of disease was 8.8 years (*SD* 7.2).	Reaction time; IQ (WAIS),
Shuepbach D.	Patient selection according to DSM IV and SCID. All acute patients, medicated.	34 patients (17 males, 17 females) and 24 controls (15 male, 9 female). Patients' mean age 27.68 years (*SD* 8.81); controls' mean age 24.50 years (*SD* 5.98). Mean age at onset of illness was 23.91 (*SD* 7.76) length of disease was 1.30 years (*SD* 1.47).	Trail Making Test; verbal fluency; California Velbal Learning Test (CVLT).
Schwartz B.L.	Patient selection according to Research Diagnostic Criteria and on the basis of the Schedule for Affective Disorders and Schizophrenia. All patients clinically stable, medicated.	16 patients (15 males, 1 female) and 16 controls (15 male, 1 female). Patients' mean age 37 years (*SD* 8), and years of education 13.5 (*SD* 2.03); controls' mean age 34 years (*SD* 9), and years of education 17.1 (*SD* 2.67). Mean length of disease was 13.5 years (*SD* 7.24).	WCST (Categories).
Sereno A.B. (a)	Patient selection according to DSM III R and SCID. Mostly inpatients, all medicated.	17 patients (13 males, 4 females) and 14 controls (10 males, 4 females). Patients' mean age 33.2 years (*SD* 5.4); controls' mean age 32.3 (*SD* 5.2). Mean length of disease was 10.2 years (*SD* 4.3).	Reaction time.
Sereno A.B. (b)	Patient selection according to DSM III R and SCID. Mostly inpatients, all medicated.	17 patients (13 males, 4 females) and 14 controls (10 males, 4 females). Patients' mean age 33.2 years (*SD* 5.4); controls' mean age 32.3 (*SD* 5.2). Mean length of disease was 10.2 years (*SD* 4.3).	Reaction time in spatial selective attention tasks.
Shelley A.	Patient selection according to DSM III R. Mostly inpatients, all medicated.	11 patients (all males) and 13 controls (9 males, 4 females). Patients' mean age 32.6 years (range 26–48); controls' mean age 34.9 (range 24–50).	CPT (hit rate).
Silver H.	Patient selection according to DSM IV. Mostly inpatients, all medicated.	27 patients (all males) and 38 controls (16 male, 22 females). Patients' mean age 38 years (*SD* 13.5), and years of education 11.2 (*SD* 3.0); controls' mean age 42.4 years (*SD* 11.1), and years of education 15.2 (*SD* 1.6). Mean length of disease was 12.7 years (*SD* 10.5).	Digit span (WAIS-R); executive function; Benton Visual Retention Test.
Stirling J.D.	Patient selection according to DSM III R. All inpatients, all medicated.	40 patients (27 males, 13 females) and 36 controls (20 males, 16 females). Patients' mean age 36.42 years (*SD* 10.56) and years of education 12.75 (*SD* 1.77); controls' mean age 35.37 (*SD* 9.09) and years of education 13.55 (*SD* 2.14).	IQ (QT—Quick Test); RT (CPT).
Stone M.	Patient selection according to DSM III R and SCID. All inpatients, medicated.	18 patients and 15 controls. All males.	Listening span and word recognition.

Stratta P. (a)	Patient selection according to DSM III R and SCID. All acute, inpatients, medicated.	25 patients (16 males, 9 females) and 25 controls (17 males, 8 females). Patients' mean age 33.0 years (*SD* 9.6), and years of education 10.84 (*SD* 3.43); controls' mean age 27.84 (*SD* 4.78), and years of education 16.04 (*SD* 3.28). Mean length of disease was 21.59 years (*SD* 3.52).	Visual-manual delayed response task.
Stratta P. (b)	Patient selection according to DSM III-R. All outpatients, medicated.	25 patients (16 males, 9 females) and 35 controls (22 males, 13 females). Patients' mean age 33.0 years (*SD* 9.68), and years of education 10.84 (*SD* 3.43); controls' mean age 33.54 (*SD* 4.06), and years of education 13.65 (*SD* 4.06). Mean length of disease was 21.59 years (*SD* 3.52).	WCST (categories).
Strik W.K.	Patient selection according to DSM III R. Both in and outpatients.	22 patients (16 males, 6 females) and 22 controls (16 males, 6 females), Patients' mean age 35.4 years (*SD* 11.4); controls' mean age 31.6 (*SD* 12.6). Mean length of disease was 21.59 years (*SD* 3.52).	Oddball paradigm.
Sullivan E.V.	Patient selection according to DSM III R and SCID. Mostly medicated.	34 patients (all males) and 47 controls (all males). Patients' mean age 36.9 years (*SD* 7.8), and years of education 12.8 (*SD* 2.1); controls' mean age 37.9 (*SD* 9.2), and years of education 16.3 (*SD* 2.7). Mean length of disease was 12.7 years (*SD* 6.4).	National Adult Reading Test (IQ).
Tek C.	Patient selection according to DSM IV. All outpatients, clinically stable, all medicated.	30 patients (25 males, 5 females) and 20 controls (10 males, 10 females). Patients' mean age 42.9 years (*SD* 7.2), and years of education 12.8 (*SD* 1.8); controls' mean age 40.0 (*SD* 11.4), and years of education 13.8 (*SD* 1.7). Mean length of disease was 22.0 years (*SD* 8.1).	Working Memory Performance.
Tendolkar I.	Patient selection according to DSM IV. All medicated.	14 patients (7 males and 7 female) and 14 controls (8 males and 6 females). Patients' mean age 32.2 years (*SD* 61), and years of education 12.2 (*SD* 1.2); controls' mean age 29.39 (*SD* 36), and years of education 12.5 (*SD* 1.1).	AVLT (delayed recall); verbal fluency; WCST; CPT.
Thomas P.	Patient selection according to Research Diagnostic Criteria. All acute, inpatients, medicated.	38 patients and 16 controls. Patients' mean age 26.15 years (*SD* 8.08), (range 16–50). There were no differences between schizophrenics and controls in years of full time education or chronological age. All patients were within 2 years of the first appearance of psychotic symptoms.	Reverse Digit Span Test (working memory).
Van Den Bosch R.J.	Patient selection according to DSM III R. All medicated.	30 patients and 21 controls with no significant sex difference between groups. Patients' mean age 29.9 years (*SD* 8.8); controls' mean age 32.2 years (*SD* 8.3).	CPT (percentage correct responses and reaction time).
Verdoux H.	Patient selection according to DSM III R. Mostly inpatients, all medicated.	18 patients (12 males, 6 females) and 18 controls (12 males, 6 females). Patients' mean age 37.9 years (*SD* 10.8); controls' mean age 37.2 years (*SD* 9.7). Mean length of disease was 10.61 years (*SD* 7.3).	WCST (categories); Verbal fluency test; Rey complex figure test (Rey recall).
Vinogradov S.	Patient selection according to DSM IV and SCID-P. All outpatients clinically stable, medicated.	40 patients (29 males, 11 females) and 16 controls (10 males, 6 females), Patients' mean age 38 years (*SD* 9) and years of education 13 (*SD* 2); controls' mean age 33 (*SD* 8) and years of education 15 (*SD* 2).	WAIS-R (FSIQ); category fluency; lexical decision.
Weickert T.W.	Patient selection according to DSM III R and SCID.	117 patients (84 males, 33 females) and 27 controls (15 males, 12 females). Patients' mean age 33.61 years (*SD* 8.34); controls' mean age 26.7 years (*SD* 9.9). Mean length of disease was 11.56 years (*SD* 7.91).	WCST (categories); Verbal fluency test; Wechsler Memory Scale (logical memory II); WAIS (IQ).

Table 1. Continued

Weiss A.P.	Patient selection according to DSM IV and SCID-P. All outpatients, medicated.	40 patients (all males) and 32 controls (all males). Patients' mean age 44.25 years (*SD* 7.55) and years of education 11.35 (*SD* 2.33); controls' mean age 39,56 years (*SD* 11,81) and years of education 15.57 (*SD* 3.3). Mean length of disease was 21.8 years (*SD* 7.55).	Old/New Recognition Memory Test
Weiss K.M. (study 1)	Patient selection according to DSM III R and SCID. All inpatients, not medicated.	18 patients (all males) and 13 controls (all males). Patients' mean age 35.5 years (*SD* 5.5); controls' mean age 32.1 years (*SD* 5.6).	Two-flash fusion (critical duration).
Weiss K.M. (study 2)	Patient selection according to DSM III R and SCID. All inpatients, medicated.	40 patients (all males) and 32 controls (all males). Patients' mean age 44.25 years (*SD*); controls' mean age 32.1 years (*SD* 5.6).	Picture encording; recognition memory.
Wexler B.E.	Patient selection according to DSM III R and SCID. All outpatients, medicated.	36 patients (19 males, 15 females) and 30 controls (11 males, 19 females). Patients' mean age 42.9 years (*SD* 9.5), and years of education 13.1 (*SD* 2.4); controls' mean age 36.7 years (*SD* 12.3), and years of education 14.7 (*SD* 2.9).	Sixteen words immediate recall.
Wilk C.M.	Patient selection according to DSM IV. Mostly inpatients.	181 patients (122 males, 59 females) and 99 controls (28 males, 71 females). Patients' mean age 40.26 years (*SD* 9.51), and years of education 11.71 (*SD* 2.60); controls' mean age 64.46 years (*SD* 14.76), and years of education 15.43 (*SD* 2.83).	RBANS (language; delayed memory).
Woonings F.M.L.	Patient selection according to DSM III R. All inpatients, medicated.	44 patients (38 males, 6 females) and 79 controls (46 males, 15 females). Patients' mean age 30.7 years (*SD* 8.2); controls' mean age 32.7 years (*SD* 7.8). Mean length of disease was 8.7 years (*SD* 5.9).	Secondary verbal memory (RAVLT recall); WCST (categories).
Zorrilla L.T.E.	Patient selection according to DSM III R and SCID. All outpatients.	116 patients (90 males, 26 females) and 122 controls (45 males, 77 females). Patients' mean age 56.6 years (*SD* 9.9), and years of education 12.6 (*SD* 2.4); controls' mean age 64.6 years (*SD* 13.0), and years of education 13.3 (*SD* 2.6). Mean length of disease was 30.9 years (*SD* 11.3).	Mattis Dementia Rating Scale.
Zuffante P.	Patient selection according to DSM IV. Both in and outpatients. All medicated.	23 patients (all males) and 23 controls (all males). Patients' mean age 46.5 years (*SD* 4.2); controls' mean age 43.3 years (*SD* 9.6). Mean length of disease was 22.9 years (*SD* 8.8).	IQ (performance); spatial delay response task.

CPT: Continuous Performance Test; WAIS-R: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; CVLT: California Verbal Learning Test.

In most of the studies, cognitive assessment was carried out while patients were receiving some form of continuous psychopharmacological treatment. There was considerable variability in type, dosage, and number of different medications adopted in the various studies. Only a relatively small number of patients were receiving benzodiazepines and/or tricyclic antidepressants together with anti-psychotic drugs. Lithium therapy was used in only few cases. Fourteen of the studies did not specify whether participants were currently receiving medication. In a few studies, participants were assessed during a period when they were taking no medication; absence of medication arose for a variety of reasons.

Assessment of Cognitive Functioning

For the purposes of this review, studies were grouped according to the cognitive domain(s) investigated (see Table 2). This required an initial examination of the type of data presented and a subsequent subdivision by types of cognitive measures which would allow maximum commonality between data from different studies considered in the same category and maximum difference from the data considered in the other categories. The following outcome measures were utilized to cluster the data: measures of intelligence (IQ); measures of memory; measures of language; measures of executive function; and measures of attention. This classification reflects the traditional approach to assessment of cognitive deficits emerging from the current literature. There are formal and content differences in the way cognitive evaluation is performed in the different domains identified here. Some measures are based on time (see the attention domain where measures of reaction or response time were used for the analysis), others on production of correct answers such as recall scores for memory and scores used to calculate IQ, or categorical reasoning for executive function.

Assessment Measures

Patients and controls were assessed using various clinical and neuropsychological measures.

Assessment of Global Cognitive Functioning or IQ. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Mini Mental State Examination (MMSE) were used to assess current IQ or overall cognitive functioning, and the National Adult Reading Test (NART) was used to assess pre-morbid or optimal IQ level (in those studies which controlled for this variable).

Assessment of Memory Functioning. Memory was assessed using the Wechsler Memory Scale-Revised, the CERAD neuropsychological battery, the Rey Complex Figure Test, and specific tasks of episodic, semantic, procedural and implicit memory (only scores concerning delayed memory were included when explicitly indicated).

Assessment of Language. Language functioning was assessed by means of the Verbal Fluency Task, the Boston Naming Test, and the Reading Subtest of the Wide Range Achievement Test. These tasks were used either in full or in part. Some studies also aimed to evaluate language-based signs of thought disorder, whether positive, such as pressure of speech, derailment, tangentiality, incoherence and illogicality, or negative, such as poverty of speech and poverty of content.

Assessment of Executive Function. The Stroop Color-Word Naming Task, the standard Wisconsin Card Sorting Test (WCST, subtest categories), and the Trail Making Test were used in some studies to evaluate executive function.

Assessment of Attention. Reaction time was the dependent variable in all the different experimental tasks where attention was examined, coupled with either recording of event-related potentials or performance measures. In some instances saccadic and smooth pursuit eye movements were also recorded during performance of cognitive tasks (reaction time was the only variable included).

Assessment of Psychiatric Symptoms

Some studies included an assessment of patients' psychiatric symptoms. The Brief Psychiatric Rating Scale (BPRS), the Rockland-Pollin Scale (RP), a measure of psychiatric symptomatology (SANS), the AIMS (from the National Institute of Mental Health), the Present State Examination, and the Global Assessment Scale (GAS) were used to assess the overall level of psychopathology. In some instances the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) were administered to evaluate the presence and degree of positive and negative symptoms

Data Analysis

The main outcome of interest for each study was the comparison between patients and controls. All data extracted for the review were continuous data. A test for between-studies heterogeneity in the cognitive efficiency criteria was performed using a standard chi-squared

Table 2. Distribution of the Included Studies in the Different Cognitive Domains

Memory functioning					
Arango C. (1999)[b]	Cohen J.D. (1999)	Gras-Vincendon A. (1994)	Kiefer M. (2002)[a]	Perlstein W.M. (b) (2001)[b]	Thomas P. (1996)[b]
Braff D.L. (1991)[b]	Conklin H.M. (2002)[a]	Gur R.C. (2001)	Kim M.S. (2003)	Riley E.M. (2000)	Van Den Bosch R.J. (1991)
Brazo P. (2002)[b]	Crespo-Facorro B. (1999)[a]	Hartman M. (2003)[a]	Kravariti E. (2003)[a]	Ross R.G. (2000)[b]	Verdoux H. (1995)
Brebion G. (2001)[a]	Danion J. (2001)[b]	Harvey P.D. (b) (2000)[a]	Landro N.I. (1993)[a]	Schmand B. (1992)[a]	Weickert T.W. (2000)
Broerse A. (2001)	Davidson M. (1996)	Hazlett E.A. (2000)	Lanser M.G. (2002)[a]	Schuepbach D. (2002)	Weiss A.P. (2002)[b]
Buckley P.F. (1994)	Egan M.F. (2001)[b]	Hoff A.L. (a) (1992)	MacDonald A.W. (2003)	Silver H. (2003)	Wexler B.E. (1998)[b]
Cadenhead K.S. (1999)	Frith C.D. (1991)	Hoff A.L. (b) (1998)	Nestor P.G. (1998)[a]	Stone M. (1998)[a]	Wilk C.M. (2002)
Cantor G.E. (1995)	Glann D.C. (2000)	Hughes C. (2002)[b]	Neufeld R.W.J. (1995)[a]	Stratta P. (a) (1999)[a]	Woonings F.M.J. (2002)[a]
Chey J. (2002)	Goldberg, T. E. (a) (1990)	Javitt D.C (b) (1999)	Papageorgiou C. (2003)[a]	Tek C. (2002)[b]	
Clare L. (1993)	Gooding D.C. (2002)[b]	Joyce E. (2002)[b]	Park S. (1995)[b]	Tendolkar I. (2002)	
Global cognitive functioning					
Besche C. (1997)[a]	Elvevag B. (b) (2000)[a]	Goldstein J.M. (1998)[b]	Kim M.S. (2003)	Okada A. (2002)[a]	Silver H. (2003)
Braff D.L. (1991)[b]	Elvevag B. (c) (2001)[a]	Gooding D.C. (2002)[b]	Kircker T.T.J. (2001)[a]	Penn D.L. (1993)[a]	Stirling J.D. (2001)[a]
Brazo P. (2002)[b]	Frith C.D. (1991)	Harvey P.D. (b) (2000)[a]	Krabbendam L. (2000)[b]	Perry W. (Study 1) (2001)[a]	Sullivan E.V. (1994)
Cadenhead K.S. (1999)	Giovannetti T. (2003)[a]	Heaton R. (1994)	Kravariti E. (2003)[a]	Perry W. (Study 3) (2001)	Vinogradov S. (2002)[b]
Conklin H.M (2002)	Glann D.C. (2000)	Hoff A.L. (b) (1998)	Lanser M.G (2002)[a]	Phillips M.L. (2000)	Weikert T.W. (2000)
Danion J. (2001)[b]	Gold J.M. (2000)	Hughes C. (2002)[b]	Macdonald A.W. (2003)	Ross R.G. (2000)[b]	Zorrilla L.T.E. (2000)[b]
Egan M.F. (2001)[b]	Goldberg T.E. (1990)	Javitt D.C. (a) (1995)	Morice R. (1990)	Sayers M.D. (1995)[a]	Zuffante P. (2001)
Elvevag B. (a) (2000)	Goldberg T.E. (b) (1998)	Joyce E. (2002)[b]	Morrison-Stewart S.L. (1991)	Schreiber H. (1995)	
Language					
Arango C. (1999)[b]	Earle Boyer E.A. (1991)	Goldberg T.E. (b) (1998)[a]	Hoffmann R.E. (1999)	Myles-Worsley W.M. (1991)	Stone M. (1998)[a]
Braff D.L. (1991)[b]	Egan M.F. (2001)[b]	Gur R.C. (2001)	Kiefer M. (2002)[a]	Ojeda N. (2002)[a]	Tendolkar I. (2002)
Broerse A. (2001)	Frith C.D. (1991)	Harvey P.D. (a) (1990)	Kim M.S. (2003)	Paulsen J.S. (1994)	Verdoux H. (1995)
Cantor G.E. (1995)	Giovannetti T. (2003)[a]	Harvey P.D. (b) (2000)[a]	Miller M.B. (1995)	Riley E.M. (2000)	Vinogradov S. (2002)[b]
Davidson M. (1996)	Glann D.C (2000)	Haskins B. (1995)	Mirky A.F. (1995)	Sarfati Y. (1999)	Weickert T.W. (2000)
Docherty N.M. (1999)	Goldberg T.E (a) (1990)	Hoff A.L. (a) (1992)	Morice R. (1990)	Schuepbach D. (2002)	Wilk C.M. (2002)
Executive function					
Arango C. (1999)[b]	Egan M.F. (2001)[b]	Gur R.C. (2001)	Morice R. (1990)	Rief W. (1991)	Verdoux H. (1995)
Braff D.L. (1991)[b]	Elvevag B. (a) (2000)	Hoff A.L. (1992)	Ojeda N. (2002)[a]	Riley E.M. (2000)	Weickert T.W. (2000)
Brankovic S.B. (1999)	Glann D.C. (2000)	Hoff A.L. (b) (1998)	Parellada E. (1994)	Sarfati Y. (1999)	Woonings F.M.J. (2002)[a]
Brazo P. (2002)[b]	Gold J.M. (2000)	Hughes C. (2002)[b]	Paulsen J.S. (1994)	Schwartz B.L. (1991)	
Cadenhead K.S. (1999)	Goldberg T.E (a) (1990)	Kim M.S. (2003)	Perlstein W.M. (a) (1998)[a]	Shelley A. (1996)	
Cantor G.E. (1995)	Goldberg T.E. (b) (1998)[a]	Lanser M.G. (2002)[a]	Perry W. (Study 3) (2001)	Silver H. (2003)	
Corrigan P.W. (1991)	Gooding D.C. (2002)[b]	Mirsky A.F. (1995)	Perry W. (Study 4) (2001)	Stratta P. (b) (2001)	
Attention					
Besche C. (1997)[a]	Fucetola R. (b) (1999)	Hirt M. (1991)[a]	Laplante L. (1992)[a]	Perlstein W.M. (a) (1998)[a]	Stirling J.D. (2001)[a]
Brazo P. (2002)[b]	Giovannetti T. (2003)[a]	Hoff A.L. (1998)	MacDonald A.W. (2003)	Perlstein W.M. (b) (2001)[b]	Stratta P. (a) (1999)[a]
Broerse A. (2001)	Glann D.C. (2000)	Hoff A.L. (a) (1992)	Mirsky A.F. (1995)	Perry W. (Study 4) (2001)	Strik W.K. (1993)
Cantor G.E. (1995)	Goldberg T.E (a) (1990)	Hughes C. (2002)[b]	Moritz S. (2001)[a]	Riley E. M. (2000)	Tek C. (2002)[b]
Carter C.S. (1992)[b]	Gooding D.C. (2002)[b]	Javitt D.C. (a) (1995)	Ober B.A. (1995)[b]	Schreiber H. (1995)	Van Den Bosh R.J. (1992)
Chey J. (2002)	Grillon C. (1990)	Kim M.S. (2003)	Ojeda N. (2002)[a]	Schuepbach D. (2002)	Weiss K.M. (1992)[a]
Elvevag B. (b) (2000)[a]	Gur R.C. (2001)	Kircker T.T.J. (2001)[a]	Park S. (1995)[b]	Sereno H. (a) (1995)	Zuffante P. (2001)
Fucetola R. (A) (1999)	Hartman M. (2003)[a]	Kurachi M. (1994)[b]	Penn D.L. (1993)[a]	Sereno H. (b) (1996)	

[a] Studies with cases as inpatients. [b] Studies with cases as outpatients.

analysis. When a significant index of heterogeneity was evident, a Random Effects Model was adopted for the meta-analysis. A between-group analysis was performed separately for each cluster of cognitive data using the Standardized Mean Difference (SMD) method. A further index of heterogeneity was the I^2 or index of Inconsistency, expressed as the percentage of the variability due to heterogeneity rather than to chance alone (Higgins and Thompson, 2002).

Heterogeneity was analyzed by a meta-regression method. The SMD of each individual study was the dependent variable and the corresponding patient group sample size, control group sample size, and SMD standard error were the independent or explanatory variables. Further analyses were carried using meta-regression in order to assess the impact of patient status (inpatients vs. outpatients), age, and educational level (expressed in years of schooling) on the SMD of the various cognitive domains.

RESULTS

Each of the cognitive domains investigated in this review yielded significant differences, indicating that there is a consistent trend across studies differentiating the performance of people with a diagnosis of schizophrenia from that of healthy controls of comparable age. Memory shows the highest mean difference between patients and controls (SMD −1.18 [−1.31, −1.05] $p < 0.00001$) and language (SMD −1.01 [−1.18, −.85] $p < .00001$) or IQ (SMD −1.01 [−1.13, −.89] $p < .00001$) the lowest. All domains evidenced a SMD greater than one.

Data based on IQ (74 studies for 6280 participants), memory (88 studies for 6628 participants), language (36 studies for 3111 participants), executive function (38 studies for 2671) and attention (72 studies for 3649 participants) showed significant heterogeneity across studies (respectively $\chi^2(46) = 185.07$, $\chi^2(57) = 303.23$, $\chi^2(35) = 127.70$, $\chi^2(37) = 81.89$, $\chi^2(47) = 111.18$, all p at least $<.0001$). These results show that all the domains traditionally considered in studies of cognitive impairment in people with a diagnosis of schizophrenia are highly sensitive to interference from the variability in measures and/or experimental designs adopted, and consequently cross-study comparisons have a very poor reliability. On the other hand, this heterogeneity cannot be attributed to changing patterns in results, since there are no findings of groups of patients performing better than groups of controls in any domain of cognitive functioning.

The high heterogeneity among the studies cannot even be related, for any of the variables considered in this analysis, to a chronological bias, since there is no change in the pattern of results when studies are plotted in a chronological order. On the contrary, a funnel plot analysis shows that there are considerable differences between variables when the effect of sample size is considered. Only the heterogeneity in IQ differences shows no relationship with the size of the single studies but seems to be a structural characteristic of the sampling method used by each study to identify the patients included. In general, IQ is a descriptive variable in almost all the studies. It is incidentally recorded and it is neither an independent nor a dependent variable in the study design defined according to inclusion/exclusion criteria.

Effect sizes for memory functioning, language, and attention, which were dependent variables in all studies, show a specific pattern of relationships with the control group sample size and with the SMD standard error. The respective partial correlations of control sample size and SMD standard error are −.59 and −.83 for memory functioning −.68 and −.71 for language and .58 and .79 for attention. These correlations indicate that when the number of control cases is reduced and/or the standard error is small the effect size tends to be larger. No relationship is found with the number of patients. Conversely, the number of patients and the standard error are negatively correlated with effect size in the studies where executive functioning was evaluated (respectively −.51 and −.49).

The two domains of executive function and language did not show any relationship with patient status (inpatient or outpatient), or with age or educational level of patients and controls. On the contrary, for measures of memory functioning, IQ and attention, patient status had a very strong influence on the heterogeneity between studies. In fact, when inpatients are plotted alone for these variables (16 studies with 886 participants, 464 patients vs. 422 controls for memory functioning; 15 studies with 1137 participants, 577 patients vs. 560 controls for IQ; 14 studies with 645 participants, 339 patients vs. 307 controls for attention) the results show that the proportion of variance due to heterogeneity is 41.8, 83.5, and 87.5%, respectively. For outpatients, the corresponding figures are 86.3% for memory (14 studies with 1151 participants, 711 patients vs. 440 controls), 42.2% for IQ (13 studies with 1194 participants, 710 patients vs. 484 controls) and 27.2% for attention (10 studies with 485 participants, 280 patients vs. 205 controls). The SMD is respectively −1.00 [−1.19. −.80] for inpatients and −1.38 [−1.76, −1.00] for outpatients in memory functioning studies, −1.13 [−1.47, −.79] and −.87 [−1.04, −.69] in IQ studies, and 1.53 [1.01, 2.06] and .70 [.47, .92] in attention studies; these values are all statistically significant ($p < .00001$) (see Table 3).

Table 3. Analysis of Cofactors of Heterogeneity

	Significant partial correlations between cognitive domains and sample size or effect size			Percentage of heterogeneity (I^2) in samples defined by type of patients.	
	Control group sample size[a]	Patient group sample size[a]	SMD SE[a]	Inpatients[b]	Outpatients[b]
Memory functioning	−.59		−.83	41.8	86.3
Language	−.68		−.71		
Attention	.58		.79	87.5	27.2
Executive functioning		−.51	−.49		
IQ				83.5	42.2

[a] Significant partial correlations between cognitive domains and sample size or effect size.
[b] Percentage of heterogeneity (I^2) in samples defined by type of patients.

These results show that in studies of memory functioning the imbalance between the number of patients and controls can be seen as a possible source of differences in heterogeneity between studies with inpatients and those with outpatients. Differences due to age and education level of patients and controls are other possible sources for the variations in heterogeneity (mean age of inpatients is 32.44, *SD* 5.87 while mean age of outpatients is 36.71, *SD* 5.08; $t = -2.09$, $p < .05$; mean years of schooling for inpatients are 11.25, *SD* 2.46 while mean years of schooling for outpatients are 12.97, *SD* .88; $t = -2.18$, $p < .05$). For memory functioning, heterogeneity is higher in outpatient studies, while for IQ and attention it is higher in inpatient studies. In all cognitive domains, when heterogeneity is higher the SMD tends to increase. Heterogeneity seems to be related in both IQ and attention studies to patient status, while differences in educational level also seem to contribute to this effect (respectively for IQ and attention mean years of schooling are 12.08, *SD* .79 for inpatients, and 12.99, *SD* .61, for outpatients; $t = -2.84$, $p < .05$, and 12.04, *SD* .97 for inpatients and 13.20, *SD* .56 for outpatients; $t = -2.85$, $p < .05$). Mean duration of illness also contributes to heterogeneity in IQ studies (21.45 years., *SD* 13.23, for inpatients, and 17.78, *SD* 7.40 for outpatients; the Beta weight in a regression equation with SMD is −.68).

DISCUSSION OF RESULTS

In synthesis, this meta-analysis of results from the recent-past scientific literature confirms the previous evidence for a consistent finding of generalized cognitive impairment in people with a diagnosis of schizophrenia when compared to controls. However, all domains were associated with a high level of heterogeneity between studies and this problem has never been pointed out in previous reviews. While these findings emphasize the importance of exploring the relevance and the characteristics of cognitive impairment associated with schizophrenia, they also demonstrate the pressing need for a more co-ordinated and methodologically sound approach in undertaking this type of research.

Some sources of heterogeneity seem to derive from the methods used in the individual studies. These mainly include differences in patient characteristics (for example, duration of illness, patients' chronological age, treatment history, and presence and type of ongoing pharmacological treatment) which affect overall intellectual efficiency and constitute a great source of clinical diversity among studies.

The way in which patients are matched with controls is another great source of heterogeneity, with most of the studies, especially those done exclusively with inpatients, not even trying to match the size, the age and the composition by sex of the control group with that of the patient group. This methodological diversity among studies derives also from the lack of generalized attempts to match according to other individual characteristics, such as educational level or NART score.

Our analysis of heterogeneity indicates that there has been a widespread failure to consider the multidimensional nature of this patient population (Clark et al., 1995). In fact, results from several recent studies have confirmed that the multidimensional nature of the patient population accounts for most of the variance due to within-group differences among patients (Arndt et al., 1991; Lenzenweger et al., 1991; Andreasen and Carpenter, 1993). These multifactorial solutions, albeit preliminary in nature, suggest that it is important to consider different qualitative hypotheses when choosing which specific cognitive variables to assess in people with schizophrenia (Surgulazde and David, 1998). Part of the heterogeneity found in some domains in the present review, especially that observed for executive function, could be due

to variations in the sensitivity of the measures employed to different factors across studies, but a definite hypothesis about specific measures or models of measuring cognitive functioning in this type of patients should be addressed in a more efficient way only after the suppression of the other non-essential sources of heterogeneity.

CONCLUSIONS

The evidence of heterogeneity in this meta-analysis has highlighted the importance of considering the methodological shortcomings of the studies examined. One problem that was found in a number of studies rejected from this review was the provision of incomplete information, in particular the failure to present precise numerical data and the tendency to substitute verbal descriptions, graphs and so on. This resulted in an unnecessary restriction in the amount of information available, and should be avoided in the future. Other problems concern the imbalance between the number of patients and normal controls, and the differing ratios of males and females within these groups, which are common to most of the comparative studies. The total number of patients included in this review is much larger than the total number of controls, and furthermore the male/female ratio in the patients and control samples is completely different. This is a peculiar finding that is very difficult to justify, given its extent, especially as many of the original studies are based on limited numbers and consequently lack statistical power.

Future studies in this field should aim to eradicate these methodological limitations in order to allow a more systematic and reliable exploration of the "true" characteristics of the cognitive impairment experienced by people with a diagnosis of schizophrenia. The impact of factors such as sex, type of diagnosis, age of onset, length of disease, interactions with types of treatment, pre-clinical educational and socio-economic status, and the clinical status of patients has already been addressed in some of the studies examined. Nevertheless, the effects of these factors need to be systematically considered in the future. Another specific warning rising from this meta-analysis concerns the composition of the patient group. It seems that a mixture of inpatients and outpatients in the same study should be avoided. Inpatients tend to be more acute and outpatients more chronic, and the two groups tend to vary in duration of illness. Even the composition by sex tends to be different in the two groups, and educational level is usually lower in hospitalized patients. There is also a clear need for the identification of specific and standardized methods of cognitive assessment.

Given the present state of the literature in this area, the possibility that the relative cognitive impairment of persons with schizophrenia can be attributed to generic factors such as poor motivation, inattentiveness to instructions, effects of institutionalization and/or medication, etc., cannot be discounted. There is a need for further systematic studies that can address the emerging hypotheses regarding specific neuropsychological impairments – for example, lower premorbid IQ as a risk factor, semantic memory deficits, the specific role of the hippocampus as distinct from that of frontal cortex in working memory, and the role of subcortical structures, in particular the frontostriatal pathways.

It has been already pointed out that "No longer is it sufficient to merely demonstrate deficits in a group of patients compared with control individuals" (Rossell and David, 1997, p. 28). Instead, a more clearly defined and hypothesis-driven approach is needed, especially as the results of such studies could assist in the clinical identification of specific groups of patients, and in the development of remedial procedures for use in rehabilitation programmes.

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