Chapter 2

Memory impairment in schizophrenia

Summary
We present meta-analyses of the published literature on recall and recognition memory performance in patients with schizophrenia compared with normal controls. Tests of categorical models were used in analyses of potential moderators (clinical variables and study characteristics). Our findings (integrating the results of 70 studies) reveal a significant and stable association between schizophrenia and memory impairment. The composite effect size for recall performance was large, $d=1.21$. Recognition showed less, but still significant, impairment, $d=0.64$. The magnitude of memory impairment was not affected by age, medication, duration of illness, patient status, severity of psychopathology or positive symptoms. Negative symptoms showed a small, but significant relation with memory impairment. In conclusion, this meta-analysis documents significant memory impairment in schizophrenia. The impairment is stable, wide ranging and not substantially affected by potential moderating factors such as severity of psychopathology and duration of illness.


During the last decades, evidence has accumulated that schizophrenia is associated with significant impairment in cognitive functioning. Specifically, deficits in attention, memory and executive functions have been consistently reported in patients with
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schizophrenia (1-3). In contrast, formal assessment of perceptual processes and basic language functions does not show gross impairment (3). Memory has been regarded as one of the major areas of cognitive deficit in schizophrenia (4). Although the pioneers of schizophrenia research, Kraepelin (5) and Bleuler (6), considered memory functions to be relatively preserved in schizophrenia, numerous studies conducted in the second half of this century have shown patients with schizophrenia to perform poorly on a wide range of memory tasks (3, 7, 8). Recent studies indicate memory impairment in schizophrenia to be common and disproportionate to the overall level of intellectual impairment (9, 10). McKenna and colleagues (11) have even suggested the existence of a “schizophrenic amnesia”.

However, other authors consider the memory impairment to be relatively small in magnitude, or secondary to attentional dysfunction (12-15). In addition, the specificity of memory impairment in schizophrenia is unclear. It has been suggested that, in schizophrenia, some aspects of memory may be affected to a greater extent than others. This would be the case, for example, for active retrieval (free recall) of declarative information from long-term memory, which would be significantly more impaired in schizophrenics than retrieval from short-term memory, e.g. digit span (16). Also, some authors have proposed that encoding of information may be more affected than memory processes such as retrieval and recognition (17, 18). In contrast, other studies report that the memory deficit in schizophrenia encompasses a broad range of memory processes, as evidenced by poor scores in multiple task paradigms (7, 10, 19, 20). Other important issues regarding schizophrenia and memory performance which remain unclear are whether memory functioning in schizophrenia is stable over time, whether chronic patients exhibit greater memory impairment than acutely ill schizophrenics, and whether effects of medication may account for a significant portion of the observed memory impairment.

Meta-analysis represents a type of reviewing that applies a quantitative approach with statistical standards comparable to primary data analysis. A meta-analytical approach has several advantages above traditional narrative ways of reviewing. By quantitatively combining the results of a number of studies, the power of the statistical test is increased substantially. Also, studies are differentially weighted with varying sample size. Finally, by extracting information quantitatively from existing studies, meta-analysis allows one to examine more precisely the influence of potential moderators of effect size.

The aim of the present study was twofold. First, to determine the magnitude, extent and pattern of the memory impairment in schizophrenia by meta-analytically synthesizing the data from existing studies published during the past two decades. The second purpose was to examine the effect of potential moderator variables like clinical variables (e.g. age, patient status, medication) and study characteristics (e.g., matching
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of controls, year of publication) on the association between schizophrenia and memory impairment.

Method

Literature search

Articles for consideration were identified through an extensive literature search in PsycLIT and Medline, from 1975 through July 1998. Key words were ‘memory’ and ‘schizophrenia’. The search produced over 750 unique studies. Titles and abstracts of the articles were examined for possible inclusion in our analysis. Additional titles were obtained from the bibliographies of the obtained articles and a journal-by-journal search for all months of 1997 and the first half of 1998 of journals that to our perception most frequently publish articles in the targeted domain. This strategy was adopted in order to minimize the possibility of overlooking studies that may not yet have been included in the computerized databases. The journals included American Journal of Psychiatry, Archives of General Psychiatry, Journal of Abnormal Psychology, Psychological Medicine, Schizophrenia Bulletin, and Schizophrenia Research.

The identified studies had to meet the following inclusion criteria. First, each study had to include valid measures of explicit memory performance. We included the following paradigms: digit span (forward and backward), cued and free list recall and word list recognition, paired-associate recall, prose recall, and nonverbal (visual pattern) recall and recognition. Second, studies had to compare performance of a healthy normal control group with performance of patients with schizophrenia. Studies with a control group consisting of nonpsychotic subjects with a higher risk for schizophrenia (e.g. first degree relatives or subjects with schizotypal traits) were not included in the analyses. Finally, studies had to include sufficient data for the computation of a d value, which implies that means and SDs, exact p values, t values or exact F values and relevant means should be reported. We obtained 70 studies (refs. 21-84) that met the criteria for inclusion in our meta-analysis.

Data collection and analysis

By comparing measures of free recall, cued recall and recognition, we examined the effect of retrieval support on memory performance in schizophrenic patients compared to normal controls. In free recall measures, retention is measured in the absence of any cues, while in cued recall tests a portion of the encoding context is presented at the time of retrieval. In recognition, the target material is presented along with distracters, and the subject is required to differentiate between target material and distracters. The learning curve refers to the increase in recall of information with different learning trials. Furthermore, we investigated the influence of the nature of
the stimuli used in the memory tasks (verbal vs. nonverbal). Finally, we evaluated the role of retention interval, which could be immediately after presentation of the to-be-learned material, or after a delay.

From the data reported in each study, we calculated effect sizes for the difference in memory performance between schizophrenic patients and normals. The effect size estimate used was Hedges $g$ (85), the difference between the mean of the schizophrenic group and the mean of the control group, divided by the pooled standard deviation. From these $g$'s an unbiased estimation, $d$, was calculated, to correct for upwardly biased estimation of the effect in small sample sizes (85, 86). The direction of effect size was positive if the performance of schizophrenic patients on memory measures was worse than that of controls.

The combined $d$ value is an indication of the magnitude of associations across all studies. In addition to $d$, we calculated another statistic, Stouffer's $Z$ weighted by sample size, with a corresponding probability level (86). This statistic provides an indication of the significance of the difference between memory performance in the schizophrenic and the control group, and thus indicated whether the results could have arisen by chance. We also calculated a chi-square statistic, $Q$, indicating the homogeneity of results across studies (87). Significance of the $Q$-statistic points to heterogeneity of the set of studies, in which case a further search of moderator variables is needed. In the moderator analyses, $Q_W$ denotes heterogeneity of studies within categories. The $Q_B$-statistic refers to a test of differences between categories. This between-group homogeneity statistic is analogous to the $F$ statistic. All analyses were performed with the statistical package META (88).

When more than one dependent measure was used as an indication of memory performance, a pooled effect size was computed in order to prevent data from one study from dominating the outcome of the overall meta-analysis. For example, in studies reporting data on free and cued recall of verbal and nonverbal stimuli, for each study a combined $d$ was calculated for inclusion in the overall analysis. However, in subsequent analyses, we only included the data pertaining to the specific category of our aim. Thus, for example, in the meta-analysis of differences between schizophrenic patients and controls in cued recall performance, only data of cued recall measures were included in the analysis. In a similar way, when a study reported data for subgroups like first-episode versus chronic schizophrenic patients, in the overall analysis the $d$'s were pooled, but in the moderator analysis of duration of illness the $d$'s were included separately in the analysis.

In the case of twin studies (e.g. Goldberg et al. [44]) the patients were compared with normal control twins. Thus, the unaffected siblings of identical twins discordant for schizophrenia were not included in the analyses. Furthermore, in studies wherein data were reported for different subgroups (e.g., male/female, paranoid/nonparanoid), data
were pooled across subgroups, which were then compared as one group with performance of the control group.

When we encountered different studies in which data were reported concerning the same sample of subjects, only one of the studies was included in the analysis, in order to avoid the problem of dependent data (i.e. to prevent one sample from dominating the outcome). For example, in the study by Goldberg et al. (89) the same subjects were included as in Goldberg et al. (44). We only included Goldberg et al. (44) in the analysis, because the sample in this study contained more subjects than the sample in Goldberg et al. (89).

Publication bias
In order to examine the possibility of publication bias, we computed a fail-safe N (90, 86). Publication bias implies that studies with no effect may not get published and remain in file drawers, and may pose a threat to the stability of the obtained effect size. The fail-safe N statistic indicates the number of studies with null effects that must reside in file drawers before the results of the obtained effect sizes are reduced to a negligible level (which we set at 0.2). Publication bias can also be inspected graphically in a funnel plot (91). The total sample size of each study is plotted with its effect size. As larger studies will more influence the population effect size, small studies should be randomly scattered about the central effect size of the larger studies. Thus, scatter will increase when study size decreases, which gives rise to an inverted funnel appearance. When the portion of the funnel near effect size 0 is not present, this may be an indication of publication bias due to studies with nonsignificant effects and small samples not being published.

Moderator variables
The literature suggests a number of variables that may affect memory performance of schizophrenic patients. We evaluated the potential influence on effect size of several such factors using categorical models. The moderator variables we studied can be divided in two groups: clinical variables and study characteristics. The clinical variables included age of subjects, patient status (inpatient or outpatient), medication status, duration of illness, severity of psychopathology and the influence of positive and negative symptoms. For the analysis of severity of psychopathology we only included studies reporting Brief Psychiatric Rating Scale (BPRS) scores. Other psychopathology measures such as the Positive and Negative Syndrome Scale (PANSS) were not included because of a lack of studies. For positive and negative symptoms the scales included in the analysis were the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS), respectively. The groups were divided by means of a median split.
Study characteristics were year of publication (before and after 1986, the median of the period covered in the literature search), sample size, and whether schizophrenic and control groups were matched for age and level of education. Unfortunately, sex differences, differential performance of diagnostic subgroups (e.g., paranoid/nonparanoid), task difficulty and reliability, and moderating effects of attentional dysfunction could not be studied, due to the very small number or total lack of studies reporting exact results for these parameters.

Results
Table 1 displays the results of meta-analyses on schizophrenia/control differences in performance on several memory measures: verbal and nonverbal, cued and free recall, delayed and immediate; verbal and nonverbal recognition; short-term memory (digit span) and encoding (learning curve).

**Combined schizophrenia-memory effect sizes**
As can be seen in table 1, memory is significantly impaired in schizophrenia. All analyses yielded highly significant Z-values for the difference in memory performance between patients with schizophrenia and controls. The magnitude of the overall effect size of the composite long-term recall measures was large, $d=1.21$. In this overall analysis, 60 studies were included with a total sample size of 3315 (with study sample ranging from $N=16$ to $N=254$). Effect sizes ranged from 0.44 to 3.10. The homogeneity statistic showed significant heterogeneity among studies. The funnel plot (figure) demonstrates the characteristic inverted funnel. However, the lower left portion of the funnel is less pronounced than the right part, suggesting some bias in not publishing small studies with no effect. The fail-safe $N$, at a critical $d$ of 0.20, was 303. This implies that 303 unpublished null-effect studies are necessary to reduce our effects to a size of 0.20. Fail-safe $N$’s for the other analyses were also large enough to lend credence to our findings.
Analyses of short-term memory (digit span) and encoding also revealed significant memory impairment, although to a considerable lesser degree than for recall measures. The difference between forward ($d=0.71$) and backward ($d=0.82$) digit span was not significant ($Q_B=0.6$, $df=1$, $p>0.10$).

**Effects of task characteristics**

**Level of retrieval support.** Schizophrenic patients show significantly better memory performance when retrieval cues are provided, as evidenced by the $d$ of 1.20 in delayed free recall versus a $d$ of 0.78 in cued recall ($Q_B=11.6$, $df=1$, $p<0.001$). However, the difference in performance on cued recall measures between normals and schizophrenics remains considerable. Recognition also showed significant less impairment than recall ($Q_B=58.1$, $df=1$, $p<0.0001$), but the difference with control performance remains substantial ($d=0.64$). As can be seen in table 1, the $Q_W$ statistics indicate homogeneous within group $d$ values.

**Stimulus type** Verbal and nonverbal recall both show significant $d$ values ($p<0.0001$). Although impairment for verbal material in the delayed recall condition ($d=1.20$) seemed larger than for nonverbal material ($d=1.09$), this difference was not significant. This was also the case for the immediate condition. For the recognition measures, the reverse pattern was observed: retrieval of verbal material ($d=0.61$) appeared to be less impaired than retrieval of nonverbal material ($d=0.73$), but again the difference did not
Retention interval. The length of the retention interval did not affect the magnitude of d values. The difference between delayed (d=1.20) and immediate (d=1.22) verbal recall was not significant.

Table 1. Results of meta-analyses of schizophrenia/control differences in memory performance

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>N</th>
<th>d</th>
<th>Z*</th>
<th>95%CI</th>
<th>Q_w^b</th>
<th>Fail Safe-N</th>
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<td>60</td>
<td>3315</td>
<td>1.21</td>
<td>20.5</td>
<td>1.09-1.33</td>
<td>101.6</td>
<td>303</td>
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<td>35</td>
<td>1910</td>
<td>1.20</td>
<td>17.5</td>
<td>1.06-1.33</td>
<td>61.4^a</td>
<td>175</td>
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<td>free</td>
<td>33</td>
<td>1740</td>
<td>1.20</td>
<td>18.9</td>
<td>1.08-1.33</td>
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<td>165</td>
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<td>7</td>
<td>342</td>
<td>0.78</td>
<td>5.7</td>
<td>0.51-1.05</td>
<td>9.25^c</td>
<td>0</td>
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<td>1734</td>
<td>1.22</td>
<td>11.7</td>
<td>1.01-1.42</td>
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<td>168</td>
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<td>free</td>
<td>31</td>
<td>1666</td>
<td>1.27</td>
<td>11.3</td>
<td>1.05-1.48</td>
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<td>0.82-1.37</td>
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<td>49</td>
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<td>1.00</td>
<td>5.3</td>
<td>0.62-1.36</td>
<td>8.9^c</td>
<td>28</td>
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<td><strong>Total recognition</strong></td>
<td>17</td>
<td>1024</td>
<td>0.64</td>
<td>9.6</td>
<td>0.51-0.77</td>
<td>15.7^c</td>
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<td></td>
<td></td>
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<td>Hit rate</td>
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<td>0.61</td>
<td>7.8</td>
<td>0.45-0.76</td>
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<td>False alarm</td>
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<td>0.36-0.80</td>
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<td>Discriminability</td>
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<td>7.0</td>
<td>0.52-0.93</td>
<td>2.8^c</td>
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<tr>
<td>Hit rate</td>
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<td>347</td>
<td>0.73</td>
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<td>0.45-1.00</td>
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<td><strong>Digit Span</strong></td>
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<td>forward</td>
<td>18</td>
<td>881</td>
<td>0.71</td>
<td>9.2</td>
<td>0.56-0.86</td>
<td>17.8^c</td>
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<td>backward</td>
<td>7</td>
<td>306</td>
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<td>0.49-1.16</td>
<td>11.8^c</td>
<td>22</td>
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<td>Learning curve</td>
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<td>399</td>
<td>0.60</td>
<td>3.3</td>
<td>0.24-0.94</td>
<td>9.43^c</td>
<td>8</td>
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</table>

k=number of studies; N=total number of subjects; d=mean weighted effect size; Z=Stouffer's Z for significance of effect size; 95%CI=95% confidence interval; Q_w=within category homogeneity statistic; Fail-safe N=the number of unrecovered studies with null results that would be required to reduce d to 0.20. ^All Z values are significant, p<0.0001. ^df=k-1. ^Not significant. ^Significant, p<0.01. ^Verbal + nonverbal, hit-rate only.

Potential moderators of effect size

Clinical variables. Table 2 shows the influence of potential moderator variables. The Q_B statistic only reveals a significant effect of negative symptoms, Q_B=4.1, df=1, p<0.05. Negative symptoms affected memory performance negatively. Age was not associated with memory impairment in schizophrenia in the categorical analysis. We also examined the exact correlation between age and d values, which was nonsignificant, r=0.14,
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N=57, p>0.10. Although in the categorical analyses the two groups differed significantly in age (p<0.001), the range of the group as a whole was rather restricted (mean=32.4 years, SD=5; range from 15.7 to 42.8).

Table 2. Analyses of potential moderators of effect size, clinical variables

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>N</th>
<th>d</th>
<th>Z</th>
<th>95% CI</th>
<th>QW</th>
<th>QB</th>
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<td>&lt;30</td>
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<td>10.1</td>
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<td>16.9</td>
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<td>96.1e</td>
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<td>1.19</td>
<td>18.4</td>
<td>1.06-1.32</td>
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<td>7.5</td>
<td>0.98-1.67</td>
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<td>Duration of illness</td>
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<td>2 yrs</td>
<td>15</td>
<td>792</td>
<td>1.17</td>
<td>11.5</td>
<td>0.97-1.37</td>
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<td>&gt;2 yrs</td>
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<td>1.19</td>
<td>16.0</td>
<td>1.04-1.33</td>
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<td>15.4</td>
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<td>0.81-1.40</td>
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<td>1.16-1.55</td>
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<td>1.11</td>
<td>9.02</td>
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</table>

k=number of studies; N=total number of subjects; d=mean weighted effect size; Z=Stouffer’s Z for significance of effect size; 95%CI=95% confidence interval; QW=within homogeneity statistic, QB=between homogeneity statistic. aAll Z values are significant, p<0.0001. bdf=k-1. cdf=1. dNot significant. eSignificant, p<0.01. fP=0.04.

Medication status, duration of illness, severity of psychopathology and positive symptoms were not associated with memory impairment. For duration of illness it was not possible to calculate a correlation coefficient because a great number of studies did not report exact values, and studies differed in their definition of disease onset. For the other parameters, the number of studies was too small in order to interpret meaningfully the r value.

**Study characteristics.** Studies that did not match controls for age and education showed a greater association between schizophrenia and poor memory performance than matched-control studies, Q_B=5.7, df=1, p=0.02. Notwithstanding, the d for
matched-control studies remained considerable, \( d=1.17 \). For the other study characteristics, number of subjects and year of publication, no relation was found with \( d \) values (table 3).

| Table 3. Analyses of potential moderators of effect size, study characteristics |
|-------------------------------|--------|--------|------|--------|--------|--------|
|                               | \( k \) | \( N \) | \( d \) | \( Z \)  | 95% CI  | \( Q_W \) | \( Q_B \) |
| Matched controls              |        |        |      |        |        |        |
| Yes                           | 38     | 2290   | 1.17 | 19.2   | 1.05-1.29 | 51.6\(^d\) | 5.7\(^c\) |
| No                            | 16     | 780    | 1.39 | 9.4    | 1.10-1.86 | 36.2\(^d\) |        |
| Number of subjects            |        |        |      |        |        |        |
| \( N \leq 50 \)               | 33     | 1132   | 1.21 | 13.1   | 1.03-1.40 | 45.2\(^d\) | 0.1     |
| \( N > 50 \)                 | 20     | 1846   | 1.24 | 14.1   | 1.06-1.41 | 50.1\(^e\) |        |
| Year of publication           |        |        |      |        |        |        |
| 1985                          | 14     | 485    | 1.31 | 7.0    | 0.94-1.68 | 28.9\(^e\) | 0.99    |
| >1985                         | 45     | 2829   | 1.18 | 70.4   | 1.08-1.28 | 70.4\(^e\) |        |

\( k \)=number of studies; \( N \)=total number of subjects; \( d \)=mean weighted effect size; \( Z \)=Stouffer’s \( Z \) for significance of effect size; 95%CI=95% confidence interval; \( Q_W \)=within homogeneity statistic, \( Q_B \)=between homogeneity statistic. \(^a\)All \( Z \) values are significant, \( p<0.0001 \). \(^b\)df=\( k-1 \). \(^c\)df=1. \(^d\)Not significant. \(^e\)Significant, \( p<0.01 \). \(^f\)\( p=0.02 \).

**Discussion**

The purpose of this study was to investigate whether and to what extent schizophrenia is associated with memory impairment and whether this association is influenced by potential moderator variables. The results of the meta-analysis indicate that schizophrenia and memory dysfunction are significantly associated, as evidenced by moderate to large effect sizes.

Our meta-analysis corroborates and extends the findings of a recent meta-analysis (92) in which performance on multiple measures of neurocognitive function was contrasted between schizophrenic patients and normal controls. With regard to differences in memory performance, Heinrichs and Zakzanis (92) also report moderate to large effect sizes for the memory variables they studied, which included verbal and nonverbal long-term memory.

The \( d \) for recall was 1.21, which indicates a large effect size according to the nomenclature of Cohen (93). Thus, performance of schizophrenic patients is more than 1 SD lower than that of normal controls on tasks of recall memory. A recent meta-analysis on memory impairment in depression (94) revealed a \( d \) of 0.56 (54 studies) for recall performance of depressive patients compared with normal controls. When comparing these results with our present analysis, the memory deficit in schizophrenia appears to be substantially greater than in depression. The \( d \) for recognition was 0.64, which can be considered a moderate effect size (93). The
difference in recall versus recognition performance may point to a retrieval deficit, in
addition to less effective consolidation of material.

Alternatively, the recall-recognition difference may be an artifact of the differences
in difficulty between recall and recognition tests. However, studies in which tasks were
matched for difficulty level also report greater impairment in recall than recognition
(33, 34). The finding of a considerable memory deficit in schizophrenia supports the
view that memory belongs to the cognitive domains which show major impairment in
schizophrenia(3, 4). However, the lack of difference between immediate and delayed
recall does not appear to be in accordance with schizophrenia as an “amnestic
syndrome” (11). Measures of short-term memory performance showed significant
impairment. This result appears to contradict the assertion by Clare et al. (40) that
short-term memory is preserved in schizophrenia. The divergence may result from the
fact that Clare et al. base their conclusion on one study only, while the present study
concerns a quantitative integration of multiple studies. Furthermore, our meta-analysis
provides evidence that the learning curve (which reflects explicit encoding of
information) is significantly affected in schizophrenia. The large difference between
recall of information after a delay (composite delayed recall, d=1.20) and learning
curve (d=0.60) suggests that the memory dysfunction in schizophrenia is not entirely
due to deficient learning processes (as has been argued by Heaton et al.[17]), but that
retrieval processes may also be affected. However, caution is needed in interpreting
this finding, considering that digit span and learning curve indices may not reflect all
“encoding” processes.

The results failed to reveal a difference in memory impairment for verbal and
nonverbal (visual pattern) stimuli. Thus, the memory impairment in schizophrenia does
not appear to be modality specific.

The present meta-analysis indicates memory impairment in schizophrenia to be
wide ranging and consistent across task variables such as level of retrieval support (free
recall, cued recall or recognition), stimulus type (verbal vs. nonverbal) and retention
interval (immediate vs. delayed). The extent of the memory impairment may appear
to be in accordance with a pattern of generalized dysfunction rather than a differential
deficit (95). However, our study was restricted to memory functions, whereas
conclusions regarding the generalized versus differential nature of neurocognitive
dysfunction in schizophrenia must also include evaluation of functioning in other
cognitive domains. Indeed, the recent meta-analysis by Heinrichs and Zakzanis (92) in
which schizophrenia versus control differences were indexed on multiple measures of
memory, attention, intelligence, executive function, language, and motor performance
indicated that schizophrenia is characterized by a broadly based cognitive impairment,
with varying degrees of deficit in the different ability domains.

On the basis of our results, it is not possible to establish the cause or underlying
mechanism of the memory impairment in schizophrenia. For example, we were not able to examine moderating effects of attentional dysfunction. However, given the magnitude and extent of the memory impairment revealed by the meta-analysis, the possibility that the memory impairment may be secondary to attentional dysfunction does not seem very plausible. Moreover, in case of an important attentional contribution to the memory impairment, one would expect performance on the backward digit span test to show a significant greater impairment than the forward digit span test. This was not the case, however. Our findings are in agreement with the study by Kenny and Meltzer (55), who controlled for the influence of attention by analysis of covariance. Controlling for attention had very little effect on the differences in performance on long-term memory recall between schizophrenic patients and controls.

Although the meta-analysis did not address the relation between memory impairment and brain pathology in schizophrenia, the pattern of impairment may be indicative of specific brain dysfunction. Impairments in encoding and consolidation have been associated with hippocampal and temporal lobe dysfunction (96, 97). Brain imaging studies have provided evidence for pathology or reduced volume of these structures in schizophrenia (98). In addition, frontal lobe systems, which may also be affected in schizophrenia, have been shown to be involved in active retrieval of declarative memories (99, 100). More research into the relation between brain dysfunction and memory impairment in schizophrenia is needed before firm conclusions can be drawn on this issue.

Of the potential moderator variables, only negative symptoms affected the schizophrenia-memory association. Although this effect was rather small, it is consistent with previous research examining the relation between negative symptoms and cognitive function in schizophrenia (101, 102). Specifically, negative symptoms have been associated with more pronounced frontal lobe dysfunction, which may account for larger retrieval deficits (102). No relation was found between age and the magnitude of memory impairment. Unfortunately, as all subjects included in the analyses were less than 45 years old, no conclusions can be made regarding the relation between cognitive aging and memory in schizophrenia.

Clinical variables such as medication, duration of illness, patient status, severity of psychopathology and positive symptoms did not appear to influence the magnitude of memory impairment. Thus, the memory impairment in schizophrenia is of a considerable robustness and is not readily moderated by variables that may seem relevant. This is an important finding, as a number of authors have emphasized the role of medication, symptom severity, and chronicity in memory performance of schizophrenic patients (8, 26). Frith (103) even suggested that medication may principally account for the memory deficits observed in schizophrenia. It is instructive to note that our meta-analysis does not address the relation between medication and
memory performance directly, but compares performance of unmedicated samples with medicated samples. Differences in medication status may be due to unspecified differences in clinical factors. Our results are consistent, however, with studies examining this relation directly by experimentally controlling for medication (104, 105). It must be emphasized that medication in the studies in our analysis consisted of conventional neuroleptics. Evidence is emerging that novel antipsychotics may have beneficial effects on memory function (106).

As the present meta-analysis demonstrates, there is no evidence of progressive decline associated with age or duration of illness in schizophrenia. Our failure to find an effect of chronicity on memory impairment is in accordance with the view of cognitive deficits in schizophrenia as a "static encephalopathy" (107). The fact that schizophrenic patients with a long duration of illness do not perform worse than more acutely ill patients on memory tasks implies that the concept of "dementia praecox" (5) may not be accurate in the sense of progressive deterioration during the long-term course of the illness. On the other hand, considering the substantial memory deficit in schizophrenia revealed by our analysis, the term dementia praecox may be even more appropriate than Kraepelin himself may have anticipated.

The findings of our meta-analysis have important clinical implications. The substantial memory deficit in schizophrenia is likely to have repercussions on therapy and rehabilitation. A thorough understanding of the cognitive deficits in schizophrenia may prevent future treatment failures (108). For example, insight-related or other therapies that require advanced learning and memory functions are almost certain to turn out ineffective.

The extent and stability of the association between schizophrenia and memory impairment suggest that the memory dysfunction may be a trait rather than a state characteristic. Hypothetically, some degree of memory dysfunction may already be present in subjects at risk for schizophrenia. Future research must concentrate on this issue in order to explore the possible implications with regard to prescreening for schizophrenia.

There is evidence that verbal memory is a rather strong predictor of functional outcome in schizophrenia (109). Improving memory may result beneficial for every day functioning. Therefore, given the considerable memory impairment revealed by our meta-analysis, research focusing on pharmacological treatment and rehabilitation strategies in order to improve memory functioning in patients with schizophrenia is necessary.
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