

Memory tests in first-degree adult relatives of schizophrenic patients: a meta-analysis

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ABSTRACT

Background: Memory deficits have been clearly demonstrated in schizophrenic patients. However, studies of memory performances in their relatives compared to normal controls provide conflicting results. A meta-analysis was carried out to synthesize all the published data. Unlike previous meta-analyses, which were based on composite scores, we analyzed each memory test separately. This prevents theoretically questionable choices in grouping variables, leads to results with clearer implications for applied research (e.g. the best choice of a test according to its sensitivity) and is more productive in suggesting explanatory hypotheses.

Method: We initially selected 77 potentially relevant articles, but only 16 met our inclusion criteria. These articles provided data on eight different tasks, from five different memory tests: four tests from the Wechsler Memory Scale (WMS) and the California Verbal Learning Test (CVLT). For each task, we assessed data homogeneity, and then estimated effect sizes and tested publication bias using funnel plots.

Results: Adult relatives of schizophrenic patients were significantly impaired on most, but not all, tasks. The largest deficits were observed for the verbal paired associates test, the digit span forward test and the digit span backward test. We found no significant differences in tasks of delayed recall, when deficits in immediate conditions (reflecting encoding) were taken into account.

Conclusions: Adult relatives of schizophrenic patients have wide but not severe memory impairments. The size of estimated effects suggests that encoding processes are impaired, whereas storage and retrieval processes are relatively unaffected.

Keywords: Schizophrenia, Relatives, Memory, Endophenotypes.

1. Introduction

Cognitive dysfunctions are considered core deficits in schizophrenia (Seidman *et al.*, 1992). The study of these dysfunctions can be used to understand the etiopathogeny of schizophrenia (Andreasen, 2000). Although the strict demonstration of specific deficits in schizophrenia is limited by psychometric considerations (Chapman and Chapman 1973, 2001; Strauss, 2001) it is generally agreed that memory is one of the most impaired cognitive domains in schizophrenic patients (McKenna *et al.*, 1995, Stip, 1996). Meta-analytical studies have corroborated this view (Aleman *et al.*, 1999; Heinrichs and Zakzanis, 1998), showing that schizophrenic patients suffer wide ranging memory deficits.

Numerous studies have explored cognition in the relatives of schizophrenic patients to try to determine the origins of cognitive deficits in schizophrenia. These studies not only allow the influence of familial factors to be revealed but also avoid the influence of confusion factors present in patients (for example treatment, hospitalization, etc.). The studies of memory performance in relatives of schizophrenic patients carried out to date have shown conflicting results; some studies showed significant impairments whereas others demonstrated no significant difference between relatives and controls (Table 1).

Two meta-analyses have already been published (Snitz *et al.*, 2003; Sitskoorn *et al.*, 2004). Snitz *et al.* (2003) published their study as an abstract only and, consequently, their results are difficult to interpret because the meta-analytical methodology, articles included and memory tests analyzed were not given in sufficient detail. Sitskoorn *et al.* (2004) presented their meta-analytical results as composite scores for wide domains of memory (e.g. verbal memory, visual memory). This approach, which combines data from tests exploring different memory processes (e.g. immediate and delayed recall, cued and free recall, etc.), gives results with questionable theoretical relevance. As previously shown (Szöke *at al.*, 2005), even for tests

that are supposed to measure the same cognitive function, differences between relatives and controls may vary widely.

Therefore, we decided to conduct a meta-analysis of studies on memory impairments in adult relatives of schizophrenic patients, with separate analyses for each memory test. This approach should enable us to identify the most impaired memory processes as well as the most sensitive tests. This should make these analyses more theoretically and practically useful.

Our study had three aims: 1. to determine, by meta-analysis, the existence and magnitude of impairment in memory tests in relatives of schizophrenic patients; 2. to identify the tests most sensitive to memory deficits in relatives ; and 3. to identify factors that significantly affect the magnitude of differences between relatives and controls.

2. Method

Here, we summarize the methodology used in this meta-analysis, although more details can be found elsewhere (Szöke *et al.*, 2005).

2.1. Literature search

We used three approaches to identify potentially relevant articles. Firstly, we searched the Medline database using the following search parameters: (schizo* OR psychotic) AND (relatives OR children OR parents OR sib*) AND (memory) limited to: Human, Adult and Publication Date from 1978 to 2003. Secondly, we obtained additional articles from the reference lists of these articles. Finally, we carried out a manual search in medical journals considered relevant for our study (Schizophrenia Research, Archives of General Psychiatry,

The American Journal of Psychiatry, The British Journal of Psychiatry and Journal of Psychiatric Research)

2.2. Selection of articles included in meta-analysis

We included articles meeting the following criteria:

- a) diagnosis of schizophrenia in patients (according to RDC, DSM-III, IIR or IV, ICD-9 or 10);
- b) inclusion of groups of first-degree relatives and of controls in the studies;
- c) age of subjects being over 18 years;
- d) results being reported separately for each test (i.e. not only as composite scores);
- e) possibility of converting statistics to effect size;
- f) data for relatives and controls being independent from the other articles included in our meta-analysis.

2.3. Recorded variables

For each study we retained the following variables (see table 1):

- a) name of the first author and year of publication;
- b) the tests used;
- c) proband diagnosis (i.e. only schizophrenic or schizophrenic and other psychotic disorders);
- d) exclusion or not of controls with psychotic first-degree relatives;
- e) exclusion criteria based on psychiatric diagnosis in relatives and controls;
- f) type of first degree relatives (i.e. siblings, parents, twins, mixed);
- g) differences in age, sex or education level between relatives and controls;
- h) results of tests (mean and SD).

We included only the study with the largest sample size for studies having non-independent populations.

2.4. Meta-analytical procedure

Based on the data reported in each study we estimated the effect size as Hedges' unbiased g (Hedges & Olkin, 1985); positive effects reflecting better performances in controls. We tested the homogeneity of effect sizes as described by Hedges (1994). For heterogeneous data, we used a one-factor fixed effect model to determine the causes of heterogeneity and to identify homogenous sub-samples. When this proved unsuccessful, we used the sample adjusted meta-analytic deviancy (SAMD) and a scree plot (Arthur *et al.*, 2001) to identify outliers. A global effect size was calculated for homogenous data. Finally, we used funnel plots as described by Sterne and Egger (2001) to assess publication bias.

3. Results

3.1. Selection of articles to be included in our meta-analysis

We found 77 potentially relevant studies of which only 16 met our inclusion criteria. The selection process is described in a flow diagram (Fig 1). Several studies reported results from more than one memory test. Therefore, these were included in more than one analysis. For five tests (4 tests derived from the Wechsler Memory Scale and the California Verbal Learning Test), the results were reported in at least three studies each, making meta-analytical synthesis possible.

The studies included in our meta-analysis and their characteristics are summarized in Table 1

Fig.1. Flow diagram describing the selection process of the articles included in the meta-analysis

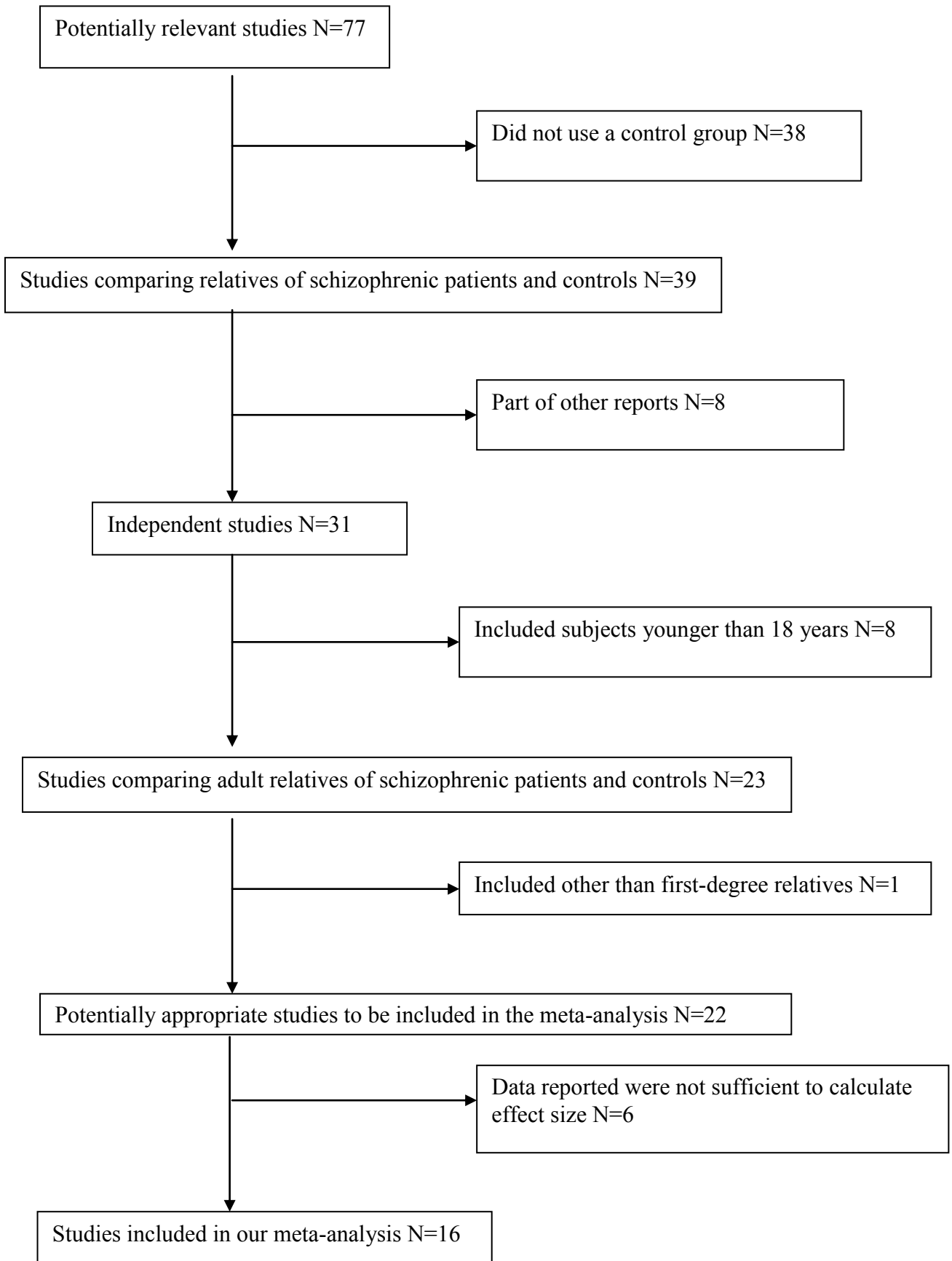


Table 1 : Characteristics of studies included in the meta-analysis

Study (first author, year)	Diagnostic in probands ^a	Type of relatives ^b	Exclusion of controls with psychotic first- degree relatives	Exclusion criteria based on psychiatric diagnosis ^c		Differences between groups on demographic variables	Logical Stories ^{d,e}		Paired Associates ^e	Visual Reproduction ^{d,e}		Digit span ^e		CVLT ^e
				Relatives	controls		I	D		I	D	forward	backward	
1	Appels (2003)	1	P	YES	1	2	NO					S	NS	S
2	Chen (2000)	1	S	YES	3	3	NO					NS	S	
3	Egan (2001)	2	S	YES	0	1	NO	NS	NS		NS	NS		NS
4	Faraone (1996)	1	M	YES	1	1	NO	NS	NS		NS			
5	Faraone (2000)	1	M	YES ^f	1	1	NO	S	S		S	S		
6	Franke (1999)	2	S	NO	4	4	NO					S		
7	Goldberg (1993)	2	T	NO	2	4	NO	S	NS	NS	NS	S		
8	Harris (1996)	1	P	YES	0	0	NO							NS
9	Ismail (2000)	1	S	YES	2	2	YES						NS	NS
10	Keri (2001)	1	S	YES	4	4	NO						NS	NS
11	Laurent (1999)	1	M	YES	4	3	NO	S	NS	S	NS	NS	S	S
12	Laurent (2000)	1	M	YES	3	3	NO	S	NS	S	NS	NS	S	S
13	Lyons (1995)	1	M	NO	0	0	NO							NS
14	O'Driscoll (2001)	1	M	YES	2+3	2+3	NO	NS	S					
15	Shedlack (1997)	2	S	NO	2	4	YES	NS	NS		NS	NS	NS	NS
16	Toulpoulou (2003)	2	M	YES	1	1	YES	S	NS	S	S	NS		

^a **1**=schizophrenia ; **2**=schizophrenia and schizoaffective disorder and/or schizophreniform disorder

^b **P**=parents ; **S**=siblings ; **M**=mixed, **T**=twins.

^c Exclusion criteria based on diagnosis : **0**=no exclusion; **1**=psychosis; **2**=psychosis + schizotypal personality disorder; **3**=all DSM Axis I diagnosis; **4**=all DSM Axis I and II diagnosis

^d **I**=immediate, **D**=delayed

^e **S**=significant difference between relatives and controls, **NS**=non-significant difference between relatives and controls

^f Based on data from Faraone *et al* 1995

3.2. Analysis of effect sizes

3.2.1. *Memory tests from the Wechsler Memory Scale (Wechsler, 1987; Lichtenberger et al., 2002):*

3.2.1.1. *Paired Associates*

This is a cued recall test of verbal memory. The score represents the number of words recalled during five trials; four immediate and one delayed trial.

We identified four studies comparing Paired Associates performances in relatives of schizophrenic patients and controls. Data from these studies were homogeneous ($p=0.69$) and showed better results in controls (estimated effect = 0.53; 95% CI 0.32 to 0.74).

3.2.1.2. *Digit span*

Digit span forward is considered as a measure of short-term memory. The eight studies that used Digit span forward provide homogeneous data ($p=0.40$) and an estimated effect of 0.48 (95% CI 0.32-0.64) with controls performing better than relatives.

Digit span backward: This test requires mental manipulation of numbers, and is considered as a measure of working memory (Lichtenberger and Kaufman, 2002). Results from the seven studies that used Digit span backward were homogeneous ($p=0.64$) and the estimated effect is 0.46 (95% CI 0.28-0.64).

3.2.1.3. *Logical Stories*

This test is used to evaluate the immediate and delayed free recall of verbal information.

Logical Stories–immediate recall: The nine studies that used this test provided homogenous data ($p=0.71$) and showed that controls performed better than relatives: estimated effect 0.41 (95% CI 0.26 to 0.55).

Logical Stories–delayed recall: The results for this test were presented as raw scores in some studies and as percentages of information retained in others. There were five homogenous studies ($p=0.28$) that presented results as raw scores, with the estimated effect being 0.43 (95% CI 0.23 to 0.62) and with controls obtaining better results than relatives. In four other studies, the results were presented as percentages of immediate recall. This variable is thought to reflect more specifically the retention of successfully encoded material. These four studies presented homogenous data ($p=0.21$), with the estimated effect being 0.09 (95% CI -0.13 to 0.30).

3.2.1.4. Visual Reproduction

This test evaluates the immediate and delayed recall of geometric designs.

Visual Reproduction–immediate recall: There were eight studies on Visual Reproduction – immediate recall, with the data provided being heterogeneous ($p=0.02$). We tried to identify potential factors explaining this heterogeneity by tabulating the study characteristics after sorting them for the size of the estimated effect (Table 2). However, we could not find any potential explanation. Furthermore, the studies that provided the most extreme results (Faraone *et al.*, 1996, Faraone *et al.*, 2000) came from the same research group and were studies that were very similar in design. The first author of these studies revealed (personal communication) that the only difference between the two studies was the age of participants (subjects older than 60 years in the Faraone *et al.*, 1996 study). Therefore, we used a one factor fixed effect model to investigate whether age could explain the heterogeneity of the studies. However, age did not significantly influence the effect sizes ($p=0.59$) and the studies

remained heterogeneous ($p=0.01$). We then tried a sample-adjusted meta-analytic deviancy (SAMD) analysis and scree plot, as described by Arthur *et al.*, (2001), to detect any outliers but found no clearly identified study as contributing to the heterogeneity. Therefore, we did not estimate a global effect size for Visual Reproduction – immediate recall.

Visual Reproduction–delayed recall: Of the seven studies providing data on the Visual Reproduction test in the delayed condition, three presented results as raw scores and four as percentages of retention. Both groups of studies were homogenous, with estimated effects of 0.17 (95%CI -0.04 to 0.38 N.S.) for the studies reporting raw scores and 0.16 (95% CI -0.05 to 0.37 N.S.) for the studies reporting percentages of retention.

Table 2 : Characteristics of studies that used Visual Reproduction Test (tabulated in ascending order of estimated effect)

Study (first author, year)	Diagnosis in probands ^a	Type of relatives	Exclusion of controls with psychotic first-degree relatives	Exclusion criteria based on psychiatric diagnosis ^b		Differences between groups on demographic variables	Effect Estimate (CI)
				Relative s	Controls		
1 Faraone (1996)	1	mixed	YES	1	1	NO	-0.26 (-0.93-0.42)
2 Shedlack (1997)	2	siblings	NO	2	4	YES	-0.16 (-0.87-0.55)
3 Egan (2001)	2	siblings	YES	0	1	NO	-0.01 (-0.35-0.32)
4 Goldberg (1993)	2	twins	NO	2	4	NO	0.00 (-0.57-0.75)
5 Laurent (2000)	1	mixed	YES	3	3	NO	0.19 (-0.21-0.59)
6 Laurent (1999)	1	mixed	YES	4	3	NO	0.27 (-0.19-0.73)
7 Toulpoulou (2003)	2	mixed	YES	1	1	YES	0.56 (0.24-0.87)
8 Faraone (2000)	1	mixed	NO	1	1	NO	0.73 (0.42-1.04)

^a 1=schizophrenia ; 2=schizophrenia and schizo affective disorder and/or schizophreniform disorder

^b Exclusion criteria based on diagnosis : **0**=no exclusion; **1**=psychosis; **2**=psychosis + schizotypal personality disorder; **3**=all DSM Axis I diagnosis; **4**=all DSM Axis I and II diagnosis

3.2.2. California Verbal Learning Test (Delis et al., 1987)

Although this test is frequently used for verbal memory evaluation, it primarily explores the interaction between verbal memory and conceptual ability (Lezak, 1995). Data from the four studies using the CVLT were homogenous ($p=0.66$), with the estimated effect being 0.34 (95% CI 0.13-0.55), with controls performing better.

Funnel plots did not suggest publication bias for any of the tests analyzed (not shown, available on request).

All the results of our analyses are summarized in Table 3

Table 3: Summary of findings in our meta-analysis

Test	Recall type	Number of studies included	Number of relatives	Number of controls	Estimated 95% CI
	Immediate vs Delayed				
Verbal Paired Associates	Immediate and Delayed	4	210	163	0.53 0.32 - 0.74
Digit span - forward	Immediate	8	292	329	0.48 0.32 - 0.64
Digit span - backward	Immediate	7	243	277	0.46 0.28 - 0.64
Logical Stories	Immediate	9	532	351	0.41 0.26 - 0.55
	Delayed (raw score)	5	322	188	0.43 0.23 - 0.62
	Delayed (% retained)	4	194	157	0.09 -0.13 - 0.30
Visual Reproduction	Immediate	8	512	437	heterogeneous sample
	Delayed (raw score)	3	280	160	0.17 -0.04 - 0.38
	Delayed (% retained)	4	199	157	0.16 -0.05 - 0.37

California Verbal Learning Test	Immediate and Delayed	4	309	128	0.34 0.13 - 0.55
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4. Discussion

In our study we used meta-analysis to synthesize previous research on memory impairments in relatives of schizophrenic patients. We found 77 potentially relevant studies, of which only 16 met the criteria for inclusion.

Unlike previous studies, we analyzed the data for each test separately. Although separate analysis of each test results in diminished statistical power, we strongly recommend this method in further meta-analyses for a number of reasons. It prevents theoretically questionable choices when grouping variables, leads to results with clearer implications for applied research (e.g. the best choice of a test according to its sensitivity) and is more productive in suggesting explanatory hypotheses. We believe that statistical power will be increased not by grouping results from different tests but by accumulating new data.

We discuss our results in terms of their theoretical implications, their comparison with similar studies and their comparison with memory impairments in schizophrenic patients.

The largest estimated effects in our study were obtained for the Paired Associates test (effect = 0.53), the Digit span forward test (effect = 0.48) and the Digit span backward (effect = 0.46). This suggests that the tests most sensitive to memory dysfunctions in relatives of schizophrenic patients are those with the lowest absolute difficulty, that is, tests of cued and immediate recall.

Adequate memory performance is the result of three complementary processes: encoding, storage and retrieval. Impairment of immediate recall suggests that, for verbal memory at least, the encoding process is altered in relatives of schizophrenic patients.

For the Logical Stories and Visual Reproduction tests, delayed recall performance is expressed as a percentage of immediate recall performance. By eliminating the influence of the encoding performance on delayed recall, this variable allows the memory decay process to be specifically estimated (Cirillo and Seidman, 2003). When this variable was used for the logical stories and visual reproduction tests there was no significant difference between relatives and controls, suggesting that relatives of schizophrenic patients do not have an abnormal storage of successfully encoded material. This is supported by the results for the Logical Stories test, where the effect for the raw delayed recall score, which assesses both encoding and storage, was similar to immediate recall score, which is a measure of encoding only.

This pattern of performance, characterized by reduced learning without an abnormal rate of forgetting, is considered typical of memory disorders associated with frontal lobe dysfunction (Wheeler *et al.*, 1995).

Retrieval is generally assessed by comparing recognition or cued recall performances, which are not influenced by retrieval deficits, with free recall performances, which typically depend on retrieval (Cirillo and Seidman 2003). As no study provided data for comparing recognition or cued recall with free recall for the same test, we cannot draw any firm conclusions for the existence or not of retrieval deficits. The verbal paired associates test was the only cued task (i.e. the only task not influenced by retrieval performance) analyzed in this study. It gave the largest estimated difference between relatives and controls, suggesting that it is unlikely that deficits in the retrieval process can explain memory impairments in relatives of schizophrenic patients.

For the Visual Reproduction–immediate condition test, the results from individual studies were heterogeneous. We were unable to determine the origin of this heterogeneity using single categorical or continuous variables and we could not clearly identify any study as being an outlier. As a consequence, we could not calculate a global effect for this test that evaluates encoding of visual material. Therefore, we could not draw any conclusions concerning the presence or not of visual encoding deficits in relatives of schizophrenic patients. More data should eventually allow the testing of more complex models (with two or more factors) and/or help to identify outliers, thereby clarifying this issue.

It is difficult to compare our results with these of previous similar meta-analyses (Snitz *et al.*, 2003; Sitskoorn *et al.*, 2004) because the results of these studies were presented only as composite scores, this is, with data from the different tests being pooled. In these studies, there seems to be greater memory impairments in relatives of schizophrenic patients than in our findings. Snitz *et al.*, (2003) found small to moderate effects (0.50 - 0.79) for immediate and delayed memory measures. Unfortunately, there is insufficient information for this study concerning selection criteria and the statistical methods used to be able to determine the causes of discrepancy with our results.

Sitskoorn *et al.*, (2004) found differences between relatives and controls from 0.30 (for visual memory) to 0.54 (for verbal memory). For visual memory, we found that data were heterogeneous and so were unable to make any comparison with data from the study of Sitskoorn *et al.*, (2004). For digit span, our values (0.48) are somewhat higher than their values (0.35 in the cited study), whereas we obtained smaller effect sizes for the “verbal memory” tests (Logical Stories immediate and delayed, and CVLT), ranging from 0.18 to 0.53, compared to 0.54 obtained in their study. In our view, the main reason for this difference is the inclusion of different studies in the two different meta-analyses. We identified three principal sources for differences in the included studies. Firstly, we did not include data from

studies that reported the results of tests used in less than three studies (for example the RBMT in Byrne *et al.*, 1999, or the digit span used by Docherty and Gordinier, 1999). Secondly, we excluded studies that included subjects younger than 18 years of age (e.g. Cosway *et al.*, 2000). These two reasons concerned only very few articles and probably do not contribute much to the observed difference. However, the principal source of difference in the included articles was the exclusion from our meta-analysis of successive reports from the same study. Specifically, Sitskoorn *et al.* (2004) included data from the studies of Kremen *et al.* (1998), Toomey *et al.* (1998) and Faraone *et al.* (2000) which are successive reports from an ongoing study. In this study, the inclusion criteria and the screening processes for relatives and controls were different. Relatives were screened with the Structured Clinical Interview for DSM III R and the Structured Interview for DSM III R personality disorders. In the study of Faraone *et al.* (1995), the use of this screening process resulted in the exclusion of 6% of subjects due to psychotic disorders. In controls, Structured Interviews were not used. Instead, they were asked about past psychiatric hospitalizations or current major depression and substance abuse, which excluded 7.5 % of the controls. Also, in controls, the Minnesota Multiphasic Personality Inventory – 168 was used to exclude all subjects that demonstrated extreme values on any clinical or validity scale (except Masculinity-Feminity). This excluded another 16 % more of the controls. As the inclusion criteria for controls were more stringent than for relatives this potentially exaggerated differences between the two groups. As in all these successive reports the samples are relatively large and the potential bias effect is large, which could explain the difference between our results and the results of Sitskoorn *et al.* (2004).

Studies comparing memory performances in schizophrenic subjects and controls were synthesized by Aleman *et al.* (1999) in a meta-analysis, and by Cirillo and Seidman (2003) in a recent review. As expected, relatives are less impaired for memory functions compared to

schizophrenic patients. Aleman *et al.* (1999) found that effect size for recall performance was large but that recognition was relatively less impaired. This is consistent with the analysis of Cirillo and Seidman (2003), who found that memory impairments were largely accounted for by deficits in the encoding stage, although storage and retrieval were relatively unaffected. Similarly, in our study, we found evidence for a greater impairment of encoding compared to the storage process in first-degree relatives of schizophrenic subjects.

In the meta-analysis of Aleman *et al.* (1999), cued recall was found to be less impaired than free recall in schizophrenic patients, although in our meta-analysis, verbal paired associates — the only cued memory test — was the most impaired test. This suggests that cued recall tests (such as the paired associates test) are more suitable for using as an endophenotype, as they are sensitive to genetic loading and less influenced by factors linked to the illness.

We can also infer which tests are more sensitive to the genetic loading from studies on healthy relatives from multiplex families (i.e. families with more than one affected subject). This approach assumes that healthy relatives having only one first-degree relative with schizophrenia have a lower genetic loading than those having two or more relatives with schizophrenia (Faraone *et al.*, 2000). For tests that are more sensitive to genetic loading, we expect greater impairments in the relatives from multiplex families. We found only two such studies that met our inclusion criteria (Faraone *et al.*, 2000 and Shedlack *et al.*, 1997). Although Faraone *et al.* (2000) found evidence of more severe impairments in multiplex relatives, Shedlack *et al.* (1997) found no significant deficits in memory measures. Therefore, more data are needed to clarify this issue.

Overall, our meta-analysis results must be taken with caution because of the small number of studies included for each test.

In conclusion, the relatives of schizophrenic patients have impairments in most, but not all, memory tests compared to controls. Data suggest that the encoding process is impaired

although recall of successfully encoded material is relatively unaffected. The most sensitive tests seem to be those testing cued and immediate recall: the Paired Associates test and the Digit span test. These tests may be more suitable as endophenotypic markers in schizophrenia research. However, before firm conclusions are drawn, further research on memory performances of relatives of schizophrenic patients compared to control subjects is needed.

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