Introduction

Cognitive deficits have been reported in people with schizophrenia. Deficits in memory, attention and executive functioning are most commonly reported, with lesser degree of dysfunction in perceptual and language processes. Cognitive deficits are present early in the course of the disorder and are stable over time, and may be heritable.

First-degree relatives of people with schizophrenia may show attenuated signs of the illness, such as similar cognitive deficits. If cognitive deficits found in people with schizophrenia are also found in their relatives, this may be suggestive of the presence of an underlying genetic basis. This is particularly informative in disorders that display complex inheritance patterns such as schizophrenia.¹

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. As part of a wider search for all topics included in the library, reviews on cognition in first degree relatives of people with schizophrenia were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. The decision to include or exclude reviews was conducted in duplicate by two independent reviewers with any disagreements settled by discussion. All quality assessments and data extraction have been completed in duplicate by two reviewers who were not masked to review authors.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (formerly the QUOROM statement) which describes a preferred way to present a meta-analysis.² Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. For instance, a low possibility of bias would be assigned to reviews checking over 66% of items, a medium possibility between 33 and 66% and a high possibility would be given to reviews checking less than 33%. Due to the increased number of reviews published since 2014, reviews reporting less than 50% of items have been excluded from the library, prior to this date we excluded reviews reporting less than 33% of items. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCT) may be downgraded to moderate, low or very low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the
intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

Results
We found eight reviews that met inclusion criteria.1, 4-10
Click on review ID for a link to the review’s abstract.
See PRISMA checklist for review quality assessments.

Conclusions
• High quality evidence shows a small to medium effect of poorer executive functioning, including tasks which also measure attention and language, in relatives compared to controls.
• High quality evidence also shows a small to medium effect of poorer visual and verbal memory, and short and long term episodic memory, in relatives compared to controls.
• Moderate to high quality evidence suggests a small to medium effect of poorer IQ and processing speed, and moderate quality evidence suggests poorer psychomotor and visuospatial ability in relatives compared to controls.
Cohen A.S. Brown L.A. and Auster, T.L.

Olfaction, “olfiction,” and the schizophrenia-spectrum: An updated meta-analysis on identification and acuity


View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Olfactory identification and acuity in people with a family history of schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>Moderate quality evidence (precise, direct, unable to assess consistency) suggests no impairment in olfactory performance</td>
</tr>
</tbody>
</table>

Olfactory performance

No significant differences were reported
9 studies, N = 517 (233 at risk, 284 controls)

\[ d = -0.21, 95\%\text{CI} -0.53 \text{ to } 0.12 \]

Consistency

Unable to assess

Precision

Precise

Directness

Direct

Dickinson D., Ramsey M.E., Gold J.M.

Overlooking the Obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia

Archives of General Psychiatry 2007. 64: 532-542

View review abstract online

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Cognitive functioning in relatives of people with schizophrenia vs. controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note</td>
<td>degree of relationship between relatives and schizophrenia patients is unclear</td>
</tr>
</tbody>
</table>
## Summary of evidence

Moderate to high quality evidence (direct, unable to assess consistency, precise) suggests a medium effect of poorer processing speed, and a small to medium effect of poorer sustained attention, episodic memory and executive functioning in relatives compared to controls.

Moderate to high quality evidence also suggests no difference in IQ, working memory and letter fluency.

<table>
<thead>
<tr>
<th>Function</th>
<th>Evidence Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sustained attention</strong></td>
<td>A small effect size suggests relatives showed poorer sustained attention on the degraded stimulus CPT compared to controls. gram, N = 171, g = -0.39, 95%CI -0.70 to -0.08, p ≤ 0.05, Q p not reported</td>
</tr>
<tr>
<td><strong>Intelligence</strong></td>
<td>No difference IQ or estimated IQ. 4 studies, N = 315, g = -0.20, 95%CI -0.43 to 0.04, p &gt; 0.05, Q p not reported</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td>A small to medium effect size suggests relatives showed poorer episodic memory performance on the word list learning task compared to controls. 3 studies, N = 193, g = -0.45, 95%CI -0.72 to -0.13, p ≤ 0.05, Q p not reported. No difference in working memory performance on the digit span total. 4 studies, N = 235, g = -0.23, 95%CI -0.50 to 0.03, p &gt; 0.05, Q p not reported</td>
</tr>
<tr>
<td><strong>Fluency</strong></td>
<td>No difference in fluency performance on the letter fluency task. 3 studies, N = 224, g = -0.22, 95%CI -0.49 to 0.05, p &gt; 0.05, Q p not reported</td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td>Medium effect sizes suggest relatives showed poorer processing speed performance compared to controls on: Digit symbol coding: 7 studies, N = 504, g = -0.62, 95%CI -0.80 to -0.43, p ≤ 0.05 TMT-A: 3 studies, N = 193, g = -0.51, 95%CI -0.80 to -0.21, p ≤ 0.05, Q p not reported</td>
</tr>
<tr>
<td><strong>Executive functioning</strong></td>
<td>No different in executive functioning performance.</td>
</tr>
</tbody>
</table>
A small effect size suggests relatives showed poorer executive functioning on the WCST categories compared to controls

4 studies, N = 269, $g = -0.26$, 95%CI -0.50 to 0.00, $p \leq 0.05$, Q $p$ not reported

A medium effect size suggests relatives showed poorer executive functioning on the trail making test part B compared to controls

3 studies, N = 193, $g = -0.54$, 95%CI -0.82 to -0.23, $p \leq 0.05$, Q $p$ not reported

Consistency in results | Unable to assess
---|---
Precision in results | Precise
Directness of results | Direct

Jameson K.G., Nasrallah H.A., Northern T.G., Welge J.A.

Executive function impairment in first-degree relatives of persons with schizophrenia: A meta-analysis of controlled studies

Asian Journal of Psychiatry 2011. 4: 96
View review abstract online

Comparison

Executive functioning in first-degree relatives of people with schizophrenia vs. controls

Summary of evidence

Moderate quality evidence (inconsistent or imprecise, potential publication bias) suggests poorer executive functioning in first-degree relatives of people with schizophrenia compared to controls

Executive functioning

Measured by WCST

A small to medium effect suggests significantly less categories achieved and significantly more perseverative errors in relatives of people with schizophrenia compared to controls

Categories achieved: 17 studies (N = 1602), $d = -0.34$, 95%CI -0.50 to 0.18, $p$ value not reported

Authors report no heterogeneity ($p = 0.273$), but potential publication bias ($p = 0.08$)

Perseverative errors: 23 studies (N = 2173), $d = 0.26$, 95%CI 0.06 to 0.46, $p$ value not reported

Authors report significant heterogeneity ($p < 0.001$) and potential publication bias ($p = 0.06$)
Families – Cognition in First-Degree Relatives

Consistency | Consistent for categories, inconsistent for perseverative errors
---|---
Precision | Precise for perseverative errors, imprecise for categories
Directness | Direct

**Sitskoorn M., Aleman A., Ebishe S., Appels M., Kahn R.**

**Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis**


[View review abstract online]

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Cognitive functioning in first-degree relatives of people with schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (direct, consistent, precise) shows a small to medium effect of poorer executive functioning as measured by TMT-B, attention as measured by Stroop and TMT-A, and visual and verbal memory in first-degree relatives. Moderate to high quality evidence (inconsistent) also suggests poorer performance on executive functioning as measured by WCST, attention as measured by CPT, and verbal fluency</td>
</tr>
</tbody>
</table>

**Executive functioning**

*Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:*

- **TMT-B**: 12 studies, N = 1424, $d = 0.51$, 95%CI 0.36 to 0.67, $p < 0.0001$
  
  $Q = 12.9$, $p > 0.05$

- **WCST**: 19 studies, N = 860, $d = 0.29$ 95%CI 0.14 to 0.43 $p = 0.0001$
  
  $Q = 33.2$, $p < 0.05$

**Attention**

*Small effect sizes suggest first degree relatives performed significantly worse than controls on:*

- **CPT**: 11 studies, N = 951, $d = 0.33$, 95%CI 0.09 to 0.57, $p = 0.006$
  
  $Q = 27.6$, $p < 0.01$
### Families – Cognition in First-Degree Relatives

**Stroop:** 8 studies, $N = 1689$, $d = 0.28$, 95%CI 0.06 to 0.50, $p = 0.01$

- $Q = 11.8$, $p > 0.05$

**TMT-A:** 10 studies, $N = 843$, $d = 0.38$, 95%CI 0.23 to 0.53, $p < 0.0001$

- $Q = 9.3$, $p > 0.05$

### Language function

A small effect size suggest first degree relatives performed significantly worse than controls on:

**Verbal fluency:** 13 studies, $N = 887$, $d = 0.35$, 95%CI 0.14 to 0.56, $p = 0.001$

- $Q = 30.6$, $p < 0.01$

### Memory

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

**CVLT/WMS verbal memory:** 15 studies, $N = 997$, $d = 0.54$, 95%CI 0.43 to 0.66, $p < 0.0001$

- $Q = 12.3$, $p > 0.05$

**WMS visual reproduction:** 8 studies, $N = 1148$, $d = 0.30$, 95%CI 0.10 to 0.50, $p = 0.003$

- $Q = 11.2$, $p > 0.05$

**Digit Span:** 10 studies, $N = 630$, $d = 0.35$, 95%CI 0.19 to 0.50, $p < 0.0001$

- $Q = 4.4$, $p > 0.05$

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Consistent apart from language, CPT and WCST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Snitz B., MacDonald III A. and Carter C.**

**Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes**

**Schizophrenia Bulletin 2006. 32(1): 179-194**

[View review abstract online](#)

| Comparison | Cognitive functioning in first-degree relatives of people with schizophrenia vs. healthy controls |
Summary of evidence

Moderate quality evidence (direct, large sample, unable to assess consistency or precision) suggests a small to medium effect of poorer executive functioning, verbal and visual memory, psychomotor ability and IQ, and poorer performance on some attention, language and visuospatial tasks (see below) in relatives compared to controls.

### Executive functioning

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

- **Wisconsin Card Sorting Task (categories)**: 17 studies, N = 1114, $g = 0.38, p < 0.05$
- **Wisconsin Card Sorting Task (total errors)**: 8 studies, N = 635, $g = 0.39, p < 0.05$
- **Wisconsin Card Sorting Task (perseverative errors/responses)**: 19 studies, N = 1572, $g = 0.40, p < 0.05$

### Attention

Small to medium effects sizes suggest first degree relatives performed significantly worse than controls on:

- **Spatial delayed response (accuracy)**: 4 studies, N = 236, $g = 0.55, p < 0.05$
- **CPT-AX/IP false alarms**: 5 studies, N = 450, $g = 0.54, p < 0.05$
- **CPT-AX/IP d prime**: 8 studies, N = 805, $g = 0.53, p < 0.05$
- **Stroop test- colour naming**: 3 studies, N = 200, $g = 0.44, p < 0.05$
- **CPT-X d prime**: 8 studies, N = 687, $g = 0.43, p < 0.05$
- **Trails B (time)**: 16 studies, N = 1364, $g = 0.41, p < 0.05$
- **Visual cancellation test (accuracy)**: 4 studies, N = 418, $g = 0.39, p < 0.05$
- **Stroop test- colour-word naming**: 5 studies, N = 326, $g = 0.33, p < 0.05$
- **CPT-X hits/omission errors**: 3 studies, N = 240, $g = 0.33, p > 0.05$
- **Trails A (time)**: 11 studies, N = 912, $g = 0.31, p < 0.05$
- **Antisaccade (percentage errors)**: 6 studies, N = 599, $g = 0.25, p < 0.05$
- **Span of apprehension (accuracy)**: 6 studies, N = 419, $g = 0.23, p < 0.05$
- **Antisaccade (reaction time)**: 6 studies, N = 599, $g = 0.19, p < 0.05$

However, there was no significant difference between groups on:

- **Prosaccade (reaction time)**: 6 studies, N = 599, $g = -0.00, p > 0.05$
Families – Cognition in First-Degree Relatives

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Studies</th>
<th>N</th>
<th>g</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroop test- word reading</td>
<td>4</td>
<td>284</td>
<td>0.07</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Spatial delayed response task (reaction time)</td>
<td>4</td>
<td>236</td>
<td>0.24</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Spatial span forward</td>
<td>3</td>
<td>251</td>
<td>0.25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>CPT-AX/IP hits/omission errors</td>
<td>5</td>
<td>450</td>
<td>0.21</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>CPT-X false alarms</td>
<td>3</td>
<td>240</td>
<td>0.25</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

**IQ**

A small effect size suggests first-degree relatives performed significantly worse than controls on full scale IQ.

WAIS: 9 studies, N = 717, g = 0.31, p < 0.05

**Language**

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

- NART/ Wide Range Achievement Test (revised): 6 studies, N = 477, g = 0.50, p < 0.05
- Category fluency tasks: 6 studies, N = 383, g = 0.68, p < 0.05
- Wechsler Adult Intelligence Scale (revised) Vocabulary: 6 studies, N = 604, g = 0.21, p < 0.05
- Letter fluency tasks: 7 studies, N = 533, g = 0.48, p < 0.05

However, there was no significant difference between groups in:

WAIS (revised) Information: 3 studies, N = 194 (82 relatives, 112 controls), g = 0.27, p > 0.05

**Memory**

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

- Auditory verbal learning task: 3 studies, N = 303, g = 0.56, p < 0.05
- Wechsler Memory Scale – logical memory I: 8 studies, N = 727, g = 0.49, p < 0.05
- Wechsler Memory Scale – logical memory II: 8 studies, N = 848, g = 0.32, p < 0.05
- Wechsler Memory Scale – verbal paired associations: 4 studies, N = 412, g = 0.42, p < 0.05
- Wechsler Memory Scale – visual reproduction I: 7 studies, N = 680, g = 0.38, p < 0.05
- Wechsler Memory Scale – visual reproduction II: 8 studies, N = 998, g = 0.34, p < 0.05

**Psychomotor**

- Digit span forward: 11 studies, N = 983, g = 0.29, p < 0.05
- Digit span backwards: 9 studies, N = 822, g = 0.27, p < 0.05
**Small effect sizes suggest first-degree relatives performed significantly worse than controls on:**

- **Pegboard task – non-dominant hand:** 4 studies, N = 555, $g = 0.26$, $p < 0.05$
- **Finger tapping – dominant hand:** 3 studies, N = 321, $g = 0.33$, $p < 0.05$
- **Finger tapping – non-dominant hand:** 3 studies, N = 321, $g = 0.25$, $p < 0.05$
- **Pegboard tasks – dominant hand:** 4 studies, N = 555, $g = 0.18$, $p < 0.05$

**Visuospatial**

**Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:**

- **Design and copy task:** 4 studies, N = 329, $g = 0.63$, $p < 0.05$
- **WAIS-R block design:** 7 studies, N = 736, $g = 0.34$, $p < 0.05$

**No significant difference in line orientation:** 3 studies, N = 353, $g = 0.09$, $p > 0.05$

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Unable to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precision</td>
<td>Unable to assess</td>
</tr>
<tr>
<td>Directness</td>
<td>Direct</td>
</tr>
</tbody>
</table>

**Szöke A., Schurhoff F., Mathieu F., Meary A., Ionescu S., Leboyer M.**

**Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis**

*Psychological Medicine, 2005, 35: 771–782*

[View review abstract online](#)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Executive functioning in first-degree relatives of people with schizophrenia vs. healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (direct, precise, consistent) shows a small to medium effect of poorer executive functioning in general (also including measures of attention and language), and a large effect of poorer semantic fluency in relatives compared to controls</td>
</tr>
</tbody>
</table>
Executive functioning (includes attention and language tasks)

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Studies</th>
<th>N</th>
<th>Effect Size (g)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCST (categories)</td>
<td>13</td>
<td>1619</td>
<td>0.31</td>
<td>0.21 to 0.42</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>WCST (perseverative)</td>
<td>12</td>
<td>1261</td>
<td>0.26</td>
<td>0.14 to 0.38</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>TMT-B</td>
<td>11</td>
<td>1179</td>
<td>0.49</td>
<td>0.37 to 0.62</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Stroop</td>
<td>6</td>
<td>563</td>
<td>0.38</td>
<td>0.21 to 0.55</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Phonological fluency</td>
<td>8</td>
<td>664</td>
<td>0.65</td>
<td>0.48 to 0.82</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>5</td>
<td>336</td>
<td>0.87</td>
<td>0.64 to 1.10</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

With a large effect on:

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Studies</th>
<th>N</th>
<th>Effect Size (g)</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
</table>
| Memory tests in adult relatives of schizophrenic patients: a meta-analysis

Trandafir A, Meary A., Schurhoff F., Leboyer M., Szoke A.

Schizophrenia Research, 2006, 81: 217–226

Comparison

Memory in first-degree relatives of people with schizophrenia vs. healthy controls

Summary of evidence

High quality evidence (direct, precise, consistent) shows a small to medium effect of poorer visual and verbal memory in relatives compared to controls

Memory

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

Verbal paired Associates: 4 studies, N = 369, g = 0.54, 95%CI 0.33 to 0.75, p < 0.05, (Q: p = 0.85)
Families – Cognition in First-Degree Relatives

<table>
<thead>
<tr>
<th>Test Type</th>
<th>N</th>
<th>g</th>
<th>95%CI</th>
<th>p</th>
<th>Q</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digit Span forward</strong>: 10 studies, N = 748</td>
<td>0.45</td>
<td>0.30 to 0.60</td>
<td>&lt; 0.05</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td><strong>Digit Span backward</strong>: 10 studies, N = 773</td>
<td>0.35</td>
<td>0.20 to 0.50</td>
<td>&lt; 0.05</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td><strong>Logical Stories immediate</strong>: 10 studies, N = 994</td>
<td>0.47</td>
<td>0.33 to 0.60</td>
<td>&lt; 0.05</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td><strong>Logical Stories delayed (raw score)</strong>: 6 studies, N = 621</td>
<td>0.38</td>
<td>0.20 to 0.55</td>
<td>&lt; 0.05</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td><strong>Logical Stories delayed (retained)</strong>: 4 studies, N = 351</td>
<td>0.18</td>
<td>0.03 to 0.40</td>
<td>&lt; 0.05</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td><strong>Visual reproduction immediate</strong>: 8 studies, N = 1094</td>
<td>0.17</td>
<td>0.02 to 0.32</td>
<td>&lt; 0.05</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td><strong>Visual reproduction delayed (raw score)</strong>: 4 studies, N = 551</td>
<td>0.24</td>
<td>0.05 to 0.33</td>
<td>&lt; 0.05</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td><strong>Visual reproduction delayed (retained)</strong>: 4 studies, N = 351</td>
<td>0.16</td>
<td>0.05 to 0.37</td>
<td>&lt; 0.05</td>
<td>&gt; 0.05</td>
<td></td>
</tr>
</tbody>
</table>

**CVLT**: 5 studies, N = 548, g = 0.30, 95%CI 0.10 to 0.48, p < 0.05, (Q: p = 0.65)

<table>
<thead>
<tr>
<th>Consistency</th>
<th>Consistent</th>
</tr>
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<tbody>
<tr>
<td>Precision</td>
<td>Precise</td>
</tr>
<tr>
<td>Directness</td>
<td>Direct</td>
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</table>

**Whyte M, McIntosh A, Johnstone E, Lawrie S**

**Declarative memory in unaffected adult relatives of patients with schizophrenia: A systematic review and meta-analysis**

Schizophrenia Research, 2005, 78: 13–26

View review abstract online

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<tr>
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<th>Memory in first-degree relatives of people with schizophrenia vs. healthy controls</th>
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<tbody>
<tr>
<td>Summary of evidence</td>
<td>High quality evidence (direct, precise, consistent) shows a small to medium effect of poorer short and long term episodic memory in relatives compared to controls. Moderate to high quality evidence (inconsistent) also suggests a small to medium effect of poorer IQ</td>
</tr>
</tbody>
</table>
**Declarative memory**

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

**Short-term episodic encoding and retrieval**

- **Trial 1 list recall:** 3 studies, N = 267, $d = 0.65$, 95%CI 0.36 to 0.95, $p < 0.001$, (Q: $p = 0.99$)
- **Immediate story recall:** 10 studies, N = 1248, $d = 0.53$, 95%CI 0.40 to 0.67, $p < 0.001$, (Q: $p = 0.59$)
- **Immediate visual recall:** 7 studies, N = 941, $d = 0.32$, 95%CI 0.08 to 0.56, $p = 0.008$, (Q: $p = 0.038$, $I^2 = 54.9$)

**Long-term episodic encoding and retrieval**

- **Delayed story recall:** 7 studies, N = 955, $d = 0.52$, 95%CI 0.36 to 0.69 $p < 0.001$, (Q: $p = 0.64$)

**CVLT 1–5 total:** 6 studies, N = 683, $d = 0.44$, 95%CI 0.25 to 0.63, $p < 0.001$, (Q: $p = 0.30$)

**Paired associates:** 4 studies, N = 416, $d = 0.41$, 95%CI 0.19 to 0.62, $p < 0.001$, (Q: $p = 0.50$)

**Delayed visual recall:** 6 studies, N = 867, $d = 0.32$, 95%CI 0.12 to 0.52, $p = 0.002$, (Q: $p = 0.22$)

**Semantic retrieval**

- **Verbal letter fluency:** 12 studies, N = 1037, $d = 0.42$, 95%CI 0.24 to 0.60, $p < 0.001$, (Q: $p = 0.40$)

- **Verbal category fluency:** 9 studies, N = 901, $d = 0.39$, 95%CI 0.19 to 0.59, $p < 0.001$, (Q: $p = 0.09$)

**IQ**

Small to medium effect sizes suggest first-degree relatives performed significantly worse than controls on:

- **NART/ Wide Range Achievement Test:** 6 studies, N = 850, $d = 0.53$, 95%CI 0.09 to 0.96, $p = 0.017$, Q: $p < 0.001$, $I^2 = 81.0$

- **WAIS-R IQ:** 10 studies, N = 1141, $d = 0.34$, 95%CI 0.07 to 0.61, $p = 0.014$, Q: $p < 0.001$, $I^2 = 72.6$

**Consistency**

Inconsistent for IQ and visual recall

**Precision**

Precise
Families – Cognition in First-Degree Relatives

### Directness

| Directness | Direct |

### Explanation of acronyms

| CI | Confidence Interval, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, d = Cohen’s d and g = Hedges’ g = standardised mean differences (see below for interpretation of effect size), I² = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), Q = Q statistic for the test of heterogeneity, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), TMT = Trail Making Test, vs = versus, WAIS = Wechsler Adult Intelligence Scale, WCST= Wisconsin Card Sorting Test, WMS = Wechsler Memory Scale |
Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials which are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.11

† Different effect measures are reported by different reviews.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study’s mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect.11

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium to large effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2.12 InOR stands for logarithmic OR where a lnOR of 0...
shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforeseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (b) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

\[ I^2 = \left( \frac{Q - df}{Q} \right) \times 100\% \]

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed.$^12$

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) which is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. \( I^2 \) is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. \( I^2 \) can be calculated from Q (chi-square) for the test of heterogeneity with the following formula$^11$;
TECHNICAL COMMENTARY

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References