TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Cognition in family members

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 cognitive deficits. If cognitive deficits found in people with schizophrenia are also found in their relatives, this may be suggestive of an underlying genetic basis. This is particularly informative in disorders that display complex inheritance patterns such as schizophrenia.

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. Reviews 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. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis.[1] Reviews with less than 50% of items checked have been excluded from the library. 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 (RCTs) may be downgraded to moderate or 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).[2] The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 12 reviews that met inclusion criteria[3-14].

- High quality evidence shows small to medium-sized effects of poor executive functioning (including tasks of attention and language), poor visual memory, verbal memory, short-term and long-term episodic memory, and social cognition (Theory of

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Mind and negative facial expression recognition) in relatives compared with controls.

- Moderate to high quality evidence suggests small to medium-sized effects of lower IQ, working memory, prospective memory, and slower processing speed, and moderate quality evidence suggests poorer psychomotor and visuospatial ability in relatives compared with controls.
- Compared to relatives of people with bipolar disorder, moderate to high quality evidence suggests relatives of people with schizophrenia show small to medium-sized effects of poorer performance on IQ, verbal memory, working memory, processing speed, verbal fluency, and accuracy on executive functioning tasks.

Cognition in family members

Bora E, Pantelis C

Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: Systematic review and meta-analysis

Schizophrenia Research 2013; 144(1-3): 31-36

View review abstract online

Comparison	**Assessing performance on Theory of Mind tasks in relatives of patients with a diagnosis of schizophrenia spectrum disorder vs. healthy controls.**
Summary of evidence	**High quality evidence (medium to large samples, precise, consistent, direct) suggests a small to medium-sized Theory of Mind impairment in relatives of people with schizophrenia. Lower education in patients contributed to lower Theory of Mind scores.**

Combined Theory of Mind score

Small to medium effect showing impaired performance in relatives vs. controls;

12 studies, N = 3,117, d = 0.37, 95%CI 0.19 to 0.54, $p < 0.001$, I^2 = 0%

Longer duration of education in the control groups vs. relatives explained some of the between-group differences (B = 0.41, p = 0.002).

Theory of Mind verbal

Small effect showing impaired performance in relatives vs. controls;

8 studies, N = 2,946, d = 0.24, 95%CI 0.13 to 0.33, $p < 0.001$, I^2 = 0%

Theory of Mind visual

Small to medium effect showing impaired performance in relatives vs. controls;

9 studies, N = 555, d = 0.36, 95%CI 0.10 to 0.63, $p < 0.001$, I^2 = 0%

Eyes task

No differences between groups;

5 studies, N = 261, d = 0.19, 95%CI -0.10 to 0.48, p = 0.19, I^2 = 0%

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Consistency‡	Consistent
Precision§	Precise
Directness‖	Direct

Bora E

A comparative meta-analysis of neurocognition in first-degree relatives of patients with schizophrenia and bipolar disorder

European Psychiatry: the Journal of the Association of European Psychiatrists 2017; 45: 121-8

View review abstract online

Comparison 1	**Cognition in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly precise, some inconsistency, direct) suggests small to medium-sized effects of poorer performance on IQ, verbal, working and visual memory, processing speed, sustained attention, executive functioning and verbal fluency in relatives of people with schizophrenia.**
IQ	
Significant, medium-sized effect of lower IQ in relatives of schizophrenia patients; 13 studies, N = 1,618, d = 0.48, 95CI% 0.29 to 0.67, $p < 0.001$, I^2 = 67%, $p < 0.001$	
Memory	
Significant, medium-sized effects of poorer memory in relatives of schizophrenia patients; Verbal memory: 7 studies, N = 965, d = 0.46, 95CI% 0.23 to 0.69, $p < 0.001$, I^2 = 61%, p = 0.02 Working memory: 9 studies, N = 793, d = 0.57, 95CI% 0.41 to 0.77, $p < 0.001$, I^2 = 21%, p = 0.25 Visual memory (trend): 4 studies, N = 464, d = 0.71, 95CI% -0.02 to 1.44, p = 0.06, I^2 = 94%, $p < 0.001$	
Processing speed	

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Significant, medium-sized effects of slower processing speed in relatives of schizophrenia patients; 8 studies, N = 764, *d* = 0.59, 95CI% 0.29 to 0.88, *p* < 0.01, I^2 = 76%, *p* < 0.001	
Attention	
Significant, small effect of poorer sustained attention in relatives of schizophrenia patients; 8 studies, N = 1,835, *d* = 0.20, 95CI% 0.11 to 0.29, *p* < 0.001, I^2 = 0%, *p* = 0.86	
Executive functioning	
Significant, medium-sized effects of poorer executive functioning in relatives of schizophrenia patients; Executive functioning: 11 studies, N = 964, *d* = 0.58, 95CI% 0.32 to 0.85, *p* < 0.001, I^2 = 76% *p* < 0.001 Accuracy: 9 studies, N = 706, *d* = 0.43, 95CI% 0.25 to 0.60, *p* < 0.001, I^2 = 24% *p* = 0.24 Speed: 6 studies, N = 545, *d* = 0.58, 95CI% 0.20 to 0.96, *p* = 0.003, I^2 = 76% *p* < 0.001	
Language	
Significant, medium-sized effect of poorer verbal fluency in relatives of schizophrenia patients; 7 studies, N = 536, *d* = 0.56, 95CI% 0.36 to 0.76, *p* < 0.001, I^2 = 24%, *p* = 0.24	
Consistency	Inconsistent for IQ, visual memory, processing speed, and executive functioning.
Precision	Precise, apart from visual memory.
Directness	Direct
Comparison 2	**Cognition in first-degree relatives of people with schizophrenia vs. first-degree relatives of people with bipolar disorder.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, some inconsistency, direct) suggests small to medium-sized effects of poorer performance on IQ, verbal memory, working memory, processing speed, verbal fluency, and accuracy of executive functioning tasks in relatives of people with schizophrenia. There were no significant differences in speeded executive functioning tasks, IQ, visual memory, and sustained attention.**
IQ	

Cognition in family members

Significant, small to medium-sized effect of lower IQ in relatives of schizophrenia patients; 13 studies, N = 1,263, *d* = 0.38, 95%CI 0.14 to 0.62, *p* < 0.001, I^2 = 72%, *p* < 0.01 Shorter duration of education in the relatives of people with schizophrenia was associated with greater between-group differences in global cognition.	
Memory	
Significant, small to medium-sized effects of poorer memory in relatives of schizophrenia patients; Verbal memory: 8 studies, N = 815, *d* = 0.28, 95%CI 0.04 to 0.53, *p* = 0.02, I^2 = 49%, *p* = 0.06 Working memory: 10 studies, N = 589, *d* = 0.42, 95%CI 0.18 to 0.66, *p* < 0.001, I^2 = 59%, *p* = 0.009 There were no differences in visual memory.	
Processing speed	
Significant, small effect of slower processing speed in relatives of schizophrenia patients; 9 studies, N = 699, *d* = 0.30, 95%CI 0.06 to 0.53, *p* = 0.01, I^2 = 56%, *p* = 0.02	
Executive functioning	
Significant, small effect of poorer executive functioning in relatives of schizophrenia patients; Accuracy: 10 studies, N = 753, *d* = 0.27, 95%CI 0.12 to 0.42, *p* < 0.001, I^2 = 4%, *p* = 0.40 There were no significant differences on speeded tasks.	
Language	
Significant, small effect of poorer verbal fluency in relatives of schizophrenia patients; 7 studies, N = 431, *d* = 0.24, 95%CI 0 to 0.47, *p* = 0.05, I^2 = 33%, *p* = 0.18	
Consistency	Inconsistent for IQ, verbal memory, working memory and processing speed.
Precision	Precise
Directness	Direct

Cohen AS, Brown LA, Auster TL

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

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Schizophrenia Research 2012; 135: 152-157 View review abstract online	
Comparison	**Olfactory identification and acuity in people with a family history of schizophrenia.**
Summary of evidence	**Moderate quality evidence (precise, direct, unable to assess consistency) suggests no impairment in olfactory performance.**
Olfactory performance	
No significant differences were reported; 9 studies, N = 517, *d* = -0.21, 95%CI -0.53 to 0.12, *p* > 0.05	
Consistency	Unable to assess
Precision	Precise
Directness	Direct

Dickinson D, Ramsey ME, Gold JM

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	
Comparison	**Cognitive functioning in relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized samples, unable to assess consistency, precise, direct) 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 with controls. There were no differences in IQ, working memory, or letter fluency.**
Attention	
A small effect suggests relatives showed poorer sustained attention on the degraded stimulus CPT	

compared to controls; 3 studies, N = 171, *g* = -0.39, 95%CI -0.70 to -0.08, *p* < 0.05, Q *p* not reported	
IQ	
No difference IQ; 4 studies, N = 315, *g* = -0.20, 95%CI -0.43 to 0.04, *p* > 0.05, Q *p* not reported	
Memory	
A small to medium effect 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* > 0.05, Q *p* not reported	
Language	
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* > 0.05, Q *p* not reported	
Processing speed	
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	
Executive functioning	
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* < 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* < 0.05, Q *p* not reported	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Precise
Directness of results	Direct

Jameson KG, Nasrallah HA, Northern TG, Welge JA

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 (large samples, inconsistent or imprecise, direct, potential publication bias) suggests poorer executive functioning in first-degree relatives of people with schizophrenia.**
Executive functioning	
A small to medium effect suggests significantly fewer categories achieved and significantly more perseverative errors on the WCST in relatives of people with schizophrenia compared to controls; Categories achieved: 17 studies, N = 1,602, *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 = 2,173, *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)	
Consistency	Consistent for categories, inconsistent for perseverative errors.
Precision	Precise for perseverative errors, imprecise for categories.
Directness	Direct

Lin SZ, Wu YK, Su YA, Si TM

Prospective memory in non-psychotic first-degree relatives of patients with schizophrenia: A meta-analysis

Neuropsychiatric Disease and Treatment 2019; 15: 1563-71

View review abstract online

Comparison	**Prospective memory in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (small to medium-sized sample, consistent, precise, direct) suggests poorer facial emotion recognition, particularly negative expressions, in first-degree relatives of people with schizophrenia.**
Prospective memory	
First-degree relatives of patients with schizophrenia showed impairments in; Overall prospective memory: 2 studies, N = 127, SMD = -0.46, 95%CI -0.82 to -0.11, p = 0.01, I^2 = 0% Event-based prospective memory: 4 studies, N = 268, SMD = -0.56, 95%CI -0.80 to -0.31, p < 0.00001, I^2 = 0% Time-based prospective memory: 4 studies, N = 268, SMD = -0.66, 95%CI -0.90 to -0.41, p < 0.00001, I^2 = 0%	
Consistency	Consistent
Precision	Precise
Directness	Direct

Martin D, Croft J, Pitt A, Strelchuk D, Sullivan S, Zammit S

Systematic review and meta-analysis of the relationship between genetic risk for schizophrenia and facial emotion recognition

Schizophrenia Research 2020; 218: 7-13

View review abstract online

Comparison	**Facial emotion recognition in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests poorer facial emotion recognition, particularly negative expressions, in first-degree relatives of people with schizophrenia.**
Facial expression recognition	

A medium-sized effect of poorer facial emotion recognition in first-degree relatives of people with schizophrenia; 23 studies, N = 2,237, SMD = 0.38 95%CI 0.25 to 0.51, $p < 0.001$, $I^2 = 47\%$, $p < 0.007$ There was a small, significant effect of poorer recognition of negative valence facial expressions but not positive valance facial expressions.	
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

Schizophrenia Research 2004; 17: 285-295

View review abstract online

Comparison	**Cognitive functioning in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) finds 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) suggests poorer performance on executive functioning as measured by WCST, attention as measured by CPT, and verbal fluency.**
Executive functioning	
Small to medium effect sizes suggest first-degree relatives performed significantly worse on; TMT-B: 12 studies, N = 1,424, $d = 0.51$, 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 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 Stroop: 8 studies, N = 1,689, *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
A small effect size suggest first degree relatives performed significantly worse 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 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 = 1,148, *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

Consistency	Consistent, apart from language, CPT and WCST.
Precision	Precise
Directness	Direct

Snitz B, MacDonald III A, 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 (large sample, unable to assess consistency or precision, direct) 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 in relatives.**

Cognition in family members

Executive functioning
Small to medium effect sizes suggest first-degree relatives performed significantly worse on;
Wisconsin Card Sorting Task (categories): 17 studies, N = 1,114, *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 = 1,572, *g* = 0.40, *p* < 0.05
Attention
Small to medium effects sizes suggest first degree relatives performed significantly worse 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 = 1,364, *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*
There were no significant differences between groups on:
Prosaccade (reaction time): 6 studies, N = 599, *g* = -0.00, *p* > 0.05
Stroop test- word reading: 4 studies, N = 284, *g* = 0.07, *p* > 0.05
Spatial delayed response task (reaction time): 4 studies, N = 236, *g* = 0.24, *p* > 0.05
Spatial span forward: 3 studies, N = 251, *g* = 0.25, *p* > 0.05
CPT-AX/-IP hits/omission errors: 5 studies, N = 450, *g* = 0.21, *p* > 0.05
CPT-X false alarms: 3 studies, N = 240, g = 0.25, *p* > 0.05
IQ
A small effect size suggests first-degree relatives performed significantly worse on;
IQ: 9 studies, N = 717, *g* = 0.31, *p* < 0.05

Cognition in family members

Language
Small to medium effect sizes suggest first-degree relatives performed significantly worse 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, $g = 0.48$, $p < 0.05$
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 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 = 908, $g = 0.34$, $p < 0.05$
Digit span forward: 11 studies, N = 983, $g = 0.29$, $p < 0.05$
Digit span backwards: 9 studies, N = 822, $g = 0.27$, $p < 0.05$
Psychomotor
Small effect sizes suggest first-degree relatives performed significantly worse 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 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;

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Line orientation: 3 studies, N = 353, *g* = 0.09, *p* > 0.05	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Unable to assess; no measure of precision is reported.
Directness	Direct

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

Comparison	**Executive functioning in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) 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 with controls.**
Executive functioning **Includes attention and language tasks**	
Small to medium effect sizes suggest first-degree relatives performed significantly worse on; WCST (categories): 13 studies, N = 1,619, *g* = 0.31, 95%CI 0.21 to 0.42, *p* < 0.05, Q *p* = 0.10 WCST (perseverative): 12 studies, N = 1,261, *g* = 0.26, 95%CI 0.14 to 0.38, *p* < 0.05, Q *p* > 0.05 TMT-B: 11 studies, N = 1,179, *g* = 0.49, 95%CI 0.37 to 0.62, *p* < 0.05, Q *p* = 0.47 Stroop: 6 studies, N = 563, *g* = 0.38, 95%CI 0.21 to 0.55, *p* < 0.05, Q *p* = 0.15 Phonological fluency: 8 studies, N = 664, *g* = 0.65, 95%CI 0.48 to 0.82, *p* < 0.05, Q *p* = 0.12 *With a large effect on:* Semantic fluency: 5 studies, N = 336, *g* = 0.87, 95%CI 0.64 to 1.10, *p* < 0.05, Q *p* = 0.83	
Consistency	Consistent
Precision	Precise

Directness	Direct

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

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

Schizophrenia Research 2006; 81: 217-226

View review abstract online

Comparison	**Memory in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) shows a small to medium effect of poorer visual and verbal memory in relatives compared with controls.**

Memory

Small to medium effect sizes suggest first-degree relatives performed significantly worse 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

Digit Span forward: 10 studies, N = 748, *g* = 0.45, 95%CI 0.30 to 0.60, *p* < 0.05, Q*p* = 0.42

Digit Span backward: 10 studies, N = 773, *g* = 0.35, 95%CI 0.20 to 0.50, *p* < 0.05, Q*p* = 0.14

Logical Stories immediate: 10 studies, N = 994, *g* = 0.47, 95%CI 0.33 to 0.60, *p* < 0.05, Q*p* = 0.20

Logical Stories delayed (raw): 6 studies, N = 621, *g* = 0.38, 95%CI 0.20 to 0.55, *p* < 0.05, Q*p* = 0.26

Logical Stories delayed (retained): 4 studies, N = 351, *g* = 0.18, 95%CI 0.03 to 0.40, *p* < 0.05, Q*p* = 0.52

Visual reproduction immediate: 8 studies, N = 1,094, *g* = 0.17, 95%CI 0.02 to 0.32, *p* < 0.05, Q*p* = 0.18

Visual reproduction delayed (raw): 4 studies, N = 551, *g* = 0.24, 95%CI 0.05 to 0.33, *p* < 0.05, Q*p* = 0.16

Visual reproduction delayed (retained): 4 studies, N = 351, *g* = 0.16, 95%CI 0.05 to 0.37, *p* < 0.05, Q*p* > 0.05

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

Consistency	Consistent
Precision	Precise

Directness	Direct

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

Comparison	**Memory in first-degree relatives of people with schizophrenia vs. healthy controls.**
Summary of evidence	**High quality evidence (medium to large samples, consistent, precise, direct) shows a small to medium effect of poorer short and long term episodic memory in relatives compared with controls. Moderate to high quality evidence (inconsistent) also suggests a small to medium effect of poorer IQ.**

Memory

Small to medium effect sizes suggest first-degree relatives performed significantly worse 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 = 1,248, *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 = 1,037, *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

Cognition in family members

Small to medium effect sizes suggest first-degree relatives performed significantly worse 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 = 1,141, *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
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), I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IQ = intelligence quotient, 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), SMD = standardised mean difference, TMT = Trail Making Test, vs. = versus, WAIS = Wechsler Adult Intelligence Scale, WCST= Wisconsin Card Sorting Test, WMS = Wechsler Memory Scale

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

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 that 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.[15]

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that 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) that 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.[15]

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 effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[16]. lnOR 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 unforseen 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.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that 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[15];

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

§ 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.[17]

‖ 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 that 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.

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