TECHNICAL COMMENTARY

Learning

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Introduction

Learning is the ability to acquire, or change, existing knowledge, behaviours or skills. There are two distinct forms of learning: explicit (or declarative) learning occurs during a high level of consciousness regarding specific learnt content, for example, memorising information for an exam. Implicit (or procedural) learning is less conscious and refers to learning that is gained from task performance, for example, juggling. Explicit verbal learning can be measured with the Hopkins Verbal Learning test, the California Verbal Learning test and verbal list-learning, for example. The Brief Visuospatial memory test, the Rey design learning test, the Rey complex figure test, and visual reproduction all measure explicit visual learning. Implicit learning can be measured using the Serial Reaction Time task where learning is inferred from reduced reaction time to stimuli.

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 15 systematic reviews that met our inclusion criteria[3-17].

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Learning

- Compared to controls, moderate to high quality evidence suggests a medium to large effect of poorer performance in verbal learning cued and free recall, verbal span, verbal paired associate learning, verbal recognition, and Serial Reaction Time in people with schizophrenia.
- Compared to people with affective psychoses, moderate to high quality evidence shows a small effect of poorer performance on the California Verbal Learning Test total free recall subscale in people with schizophrenia, but not on the long delayed free recall or recognition hits subscales.
- Moderate to high quality evidence suggests a small to medium size association between increased negative or disorganised symptoms and poorer visual and verbal learning.
- Overall, moderate to high quality evidence finds greater improvements in explicit, but not implicit learning in people with schizophrenia taking second-generation antipsychotics than first-generation antipsychotics. Patients receiving second-generation olanzapine, clozapine or risperidone, or first-generation haloperidol, showed improvements, but patients receiving second-generation quetiapine show no improvement.
- Moderate to high quality evidence showed small associations between better verbal learning and better community functioning, social behavior, problem-solving and social skills. Moderate to low quality evidence finds better work capacity is associated with better verbal learning.
- Moderate to high quality evidence suggests medium to strong associations between increased verbal and visual learning and increased memory, executive functioning, attention, processing speed, reasoning, abstraction and flexibility.
- Moderate to high quality evidence suggests a small effect of better verbal learning and memory in people with a psychotic disorder and a substance use disorder than people with a psychotic disorder without a substance use disorder.
- In people at clinical high risk for psychosis, moderate to high quality evidence finds medium-sized effects of poorer verbal and visual learning compared to controls. There were large effects in those who converted to psychosis, and small to medium-sized effects in non-converters. When compared to people with first-episode psychosis, people at clinical high-risk showed better verbal and visual learning.

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Bogaty SER, Lee RSC, Hickie IB, Hermens DF

Meta-analysis of neurocognition in young psychosis patients with current cannabis use

Journal of Psychiatric Research 2018; 99: 22-32

View review abstract online

Comparison	**Verbal learning in people with psychosis and current cannabis use vs. people with psychosis with no cannabis use.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) no differences in verbal learning.**
Verbal learning	
There were no significant differences in verbal learning; 8 studies, N = 1,153, g = -0.39, 95%CI -0.80 to 0.04, $p < 0.10$, I^2 = 89%	
Consistency in results‡	Consistent for IQ only.
Precision in results§	Precise, apart from working memory, verbal fluency and sustained attention.
Directness of results‖	Direct

Christensen T

The influence of neurocognitive dysfunctions on work capacity in schizophrenia patients: a systematic review of the literature

International Journal of Psychiatry in Clinical Practice 2007; 11(2): 89-101

View review abstract online

Comparison	**Association between work capacity and verbal learning in people with schizophrenia.** **Note: work capacity is the ability to obtain and maintain competitive work and work behaviours and skills.**
Summary of evidence	**Moderate to low quality evidence (medium-sized sample, direct,**

	unable to assess consistency or precision) suggests that lower levels of work capacity are associated with poor verbal learning and language.
Verbal learning	
5 studies (N = 348) reported that poor *verbal learning and language* was associated with worse work behaviour improvements, work performance, less hours worked, wages earned and contact with employment specialist.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

de Gracia Domingues M, Viechtbauer W, Simons C, van Os J

Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations

Psychological Bulletin 2009; 135(1): 157-171

View review abstract online

Comparison	**Association between learning and symptom dimensions in people with non-affective psychosis.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, direct, precise, consistent) suggests small to medium-sized associations between increased negative or disorganised symptoms and poorer visual and verbal learning.**
Memory	
A significant small to medium association between increased negative symptoms and lower; Verbal learning and memory: 20 studies, $\mu_p^{\dagger} = -0.214$, 95%CI -0.279 to -0.146, $p = 0.00$, $I^2 = 54\%$ Visual learning and memory: 13 studies, $\mu_p = -0.126$, 95%CI -0.202 to -0.047, $p = 0.001$, $I^2 = 29\%$ *A significant small to medium association between increased disorganised symptoms and lower;* Visual learning and memory: 6 studies, $\mu_p = -0.206$, 95%CI -0.331 to -0.074, $p = 0.002$, $I^2 = 42\%$ Verbal learning and memory: 13 studies, $\mu_p = -0.169$, 95%CI -0.27 to -0.064, $p = 0.001$, $I^2 = 59\%$	

No association with positive symptoms; Verbal learning and memory: 17 studies, μ_p = -0.021, 95%CI -0.096 to 0.054, p = 0.578, I^2 = 47% Visual learning and memory: 9 studies, μ_p = -0.005, 95%CI -0.089 to 0.079, p = 0.91, I^2 = 0%	
Consistency	Consistent
Precision	Precise
Directness	Direct

De Herdt A, Wampers M, Vancampfort D, De Hert M, Vanhees L, Demunter H, Van Bouwel L, Brunner E, Probst M

Neurocognition in clinical high risk young adults who did or did not convert to a first schizophrenic psychosis: a meta-analysis

Schizophrenia Research 2013; 149(1-2): 48-55

View review abstract online

Comparison	**Baseline cognitive functioning in people at clinical high risk for psychosis who transitioned to psychosis at follow-up compared with those who did not transition to psychosis at follow-up.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, consistent, precise, direct) suggests small to medium-sized effects of poor visual learning in people at clinical high risk for psychosis who transitioned to psychosis compared with people at clinical high risk for psychosis who did not transition to psychosis.**
Verbal and visual learning	
Significant, medium effect of poor visual learning in people at clinical high risk for psychosis who transitioned to psychosis compared with those who did not transition to psychosis; 5 studies, g = -0.40, 95%CI -0.68 to -0.13, p = 0.004, Q-test p = 0.733 *No significant differences between groups in verbal learning;* 8 studies, g = -0.79, 95%CI -1.82 to 0.25, p = 0.137, Q-test p < 0.0001	
Consistency	Consistent for visual learning only
Precision	Precise for visual learning only

Directness	Direct

Dickinson D, Gold JM

Less unique variance than meets the eye: Overlap among traditional neuropsychological dimensions in schizophrenia

Schizophrenia Bulletin 2008; 34(3): 423-434

View review abstract online

Comparison	**Association between individual and composite measures of learning and other neuropsychological tests in people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample, direct, unable to assess consistency, precise) showed medium to strong associations between increased scores on verbal and visual learning and increased scores on other Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) domains including memory, executive functioning, attention, processing speed, reasoning, abstraction and flexibility.**

Verbal and visual learning

9 studies (N = 1,860)

Meta-analysis combined multiple correlations within each study into a single study-level effect size, and then calculated an overall weighted effect size between studies.

Weighted effect size of these 9 studies indicated a significant correlation across composite MATRICS cognitive scores; such that increased performance on reasoning tasks was associated with increased performance on other cognitive tests, $r = 0.45$, 95%CI 0.35 to 0.54, $p < 0.001$.

1 study (N = 40) reported a medium association between increased verbal learning (logical memory, paired associates, CVLT variables) and visual learning (visual reproduction variables) and increased working memory and processing speed; $r = 0.35$, 95%CI 0.21 to 0.47.

1 study (N = 148) reported a strong association between increased verbal learning (CVLT and logical memory variables) and visual learning (visual reproduction variables) and increased processing speed and executive functioning; $r = 0.61$, 95%CI 0.56 to 0.66.

1 study (N = 219) reported a medium association between increased verbal learning (CVLT variables) and increased working memory and executive functioning; $r = 0.34$, 95%CI 0.27 to 0.40.

1 study (N = 53) reported a strong association between increased verbal learning (logical memory, CVLT and Penn word memory test) and increased executive functioning; *r* = 0.54, 95%CI 0.40 to 0.66. 1 study (N = 45) reported a strong association between increased verbal learning (CVLT) and visual learning (visual reproduction variables) and increased executive functioning and attention; *r* = 0.52, 95%CI 0.38 to 0.64. 1 study (N = 1,123) reported a strong association between increased verbal learning (HVLT variables) and increased processing speed, reasoning, working memory, vigilance; *r* = 0.50; 95%CI 0.47 to 0.53. 1 study (N = 113) reported a strong association between increased verbal learning (Spanish verbal learning test, verbal fluency variables, Trails B) and increased attention and abstraction and flexibility; *r* = 0.45, 95%CI 0.35 to 0.54. 1 study (N = 118) reported a medium association between increased scores on individual measures of learning (CVLT) and increased scores on Rey complex figure memory, category fluency, Stroop (colour and word) and Gordon's CPT; *r* = 0.30, 95%CI 0.24 to 0.36. 1 study (N = 1,123 to 1,332) reported a strong association between increased scores on individual measures of learning (HVLT) and increased scores on category and letter fluency, digit symbol, WCST, WISC mazes, visuospatial working memory, letter-number sequencing and identical pairs CPT variables; *r* = 0.40, 95%CI 0.37 to 0.44. 1 study (N = 140) reported a medium association between increased scores on individual measures of learning (verbal list learning) and increased scores on digit sequencing, category and letter fluency, symbol digit coding and Tower of London; *r* = 0.33, 95%CI 0.24 to 0.41. 1 study (N = 32) reported a strong association between increased scores on individual measures of learning (HVLT) and increased scores on WCST (perseverative errors), Penn conditional exclusion test with letter fluency, trails A and B and digit symbol; *r* = 0.40, 95%CI 0.28 to 0.50. 1 study (N = 30) reported a medium association between increased scores on individual measures of learning (Rey AVLT) and increased scores on symbol digit, WCST, identical pairs CPT, letter number sequencing, trials A and B; *r* = 0.30, 95%CI 0.18 to 0.41. 1 study (N = 27) reported a medium association between increased scores on individual measures of learning (visual object learning test) and increased scores on working memory tasks, digit span, Dot working memory test with Penn CPT, Benton visual retention test, Penn face memory, Penn abstraction, inhibition and working memory test; *r* = 0.46, 95%CI 0.29 to 0.61.	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Precise
Directness	Direct

Donoghue K, Doody GA

Effect of Illegal Substance Use on Cognitive Function in Individuals With a Psychotic Disorder, A Review and Meta-Analysis

Neuropsychology 2012; 26 (6): 785-801

View review abstract online

Comparison	**Cognitive functioning in people with a psychotic disorder and a substance use disorder vs. people with a psychotic disorder without a substance use disorder.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, precise, direct) suggests a small effect of better verbal learning and memory in people with a psychotic disorder and a substance use disorder than people with a psychotic disorder without a substance use disorder.**
Cognitive functioning in people with a polysubstance use disorder	
A significant small effect suggests people with a psychotic disorder and a polysubstance use disorder showed better verbal learning and memory than people with a psychotic disorder without a substance use disorder; 5 studies, N = 296, g = 0.257, 95%CI 0.011 to 0.503, p = 0.040, I^2 = 0%, p = 0.780	
Cognitive functioning in people with a cannabis use disorder	
A significant small effect suggests people with a psychotic disorder and a cannabis use disorder showed better verbal learning and memory than people with a psychotic disorder without a substance use disorder; 3 studies, N = 551, g = 0.351, 95%CI 0.179 to 0.523, p < 0.001, I^2 = 0%, p = 0.910	
Consistency in results	Consistent
Precision in results	Precise
Directness of results	Direct

Fett AK, Viechtbauer W, Dominguez M, Penn D, van Os J, Krabbendam L

The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis

Neuroscience and Biobehavioural Reviews 2011; 35: 573-588 View review abstract online	
Comparison	**Association between functional outcomes (community function, social behaviour, social problem solving, social skills) and performance on various cognitive domains in patients with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (mixed sample, direct, mostly consistent, precise) showed small associations between better community functioning, social behavior, problem-solving ability and social skills and better verbal and visual learning.**
Community functioning (work performance, social interaction)	
Significant, small association between increased performance on verbal learning tasks and greater community functioning; 17 studies, N = 1,125, r = 0.26, 95%CI 0.15 to 0.37, $p < 0.001$, Q_w = 69.54, I^2 = 71.65%, $p < 0.05$ *Significant weak association between increased performance on visual learning task and greater community functioning;* 6 studies, N = 230, r = 0.20, 95%CI 0.07 to 0.33, p = 0.003, Q_w = 2.90, I^2 = 0%, $p > 0.05$	
Social behaviour	
Significant, small association between increased performance on verbal learning tasks and improved social behavior: 4 studies, N = 253, r = 0.32, 95%CI 0.15 to 0.47, $p < 0.001$, Q_w = 4.84, I^2 = 39.22%, $p > 0.05$ *Significant small association between better performance on visual learning task and improved social behavior;* 4 studies, N = 122, r = 0.30, 95%CI 0.10 to 0.47, p = 0.002, Q_w = 3.47, I^2 = 11.76%, $p > 0.05$	
Social problem solving	
Significant small association between increased performance on verbal learning tasks and greater social problem solving; 4 studies, N = 117, r = 0.26, 95%CI 0.07 to 0.43, p = 0.003, Q_w = 0.44, I^2 = 0%, $p > 0.05$	
Social skills	

Significant small association between increased performance on verbal learning task and better social skills; 7 studies, N = 250, r = 0.18, 95%CI 0.06 to 0.31, p = 0.005, Q_w = 8.54, I^2 = 0%, p > 0.05 *Significant small association between increased performance on visual learning task and better social skills;* 4 studies, N = 149, r = 0.28, 95%CI 0.07 to 0.46, p = 0.008, Q_w = 5.22, I^2 = 30.81%, p > 0.05

Consistency	Consistent, apart from community functioning.
Precision	Precise
Directness	Direct

Forbes NF, Carrick LA, McIntosh AM, Lawrie SM

Working memory in schizophrenia: a meta-analysis

Psychological Medicine 2009; 39: 889-905

View review abstract online

Comparison	**Verbal learning in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (unclear sample size, direct, consistent, precise) suggests medium to large effects of poorer verbal learning List A trial 1, verbal learning List B and verbal span tasks without manipulation in people with schizophrenia. Moderate quality evidence (inconsistent) finds medium to large effects of poorer verbal paired associate learning, verbal learning test list A trail 5, list A trial 6 (cued and free recall), total list A 1-5, verbal recall test, verbal span tasks with manipulation, and verbal recognition test.**

Verbal learning

A significant large effect size suggests poorer performance on the following learning tests in people with schizophrenia compared with controls;

Verbal paired associate learning test: 18 studies, d = -0.88, 95%CI -1.07 to -0.69, p < 0.001, I^2 = 64.0, p < 0.001

Verbal learning test: List A Trial 1: 11 studies, d = -1.01, 95%CI -1.26 to -0.76, p < 0.001, I^2 = 62.1, p = 0.36

Verbal learning test: List A Trial 5: 13 studies, *d* = -1.25, 95%CI -1.54 to -0.97, *p* < 0.001, I² = 78.8, *p* < 0.001 Verbal learning test: List A Trial 6, cued: 6 studies, *d* = -0.98, 95%CI -1.32 to -0.65, *p* < 0.001, I² = 59.2, *p* = 0.031 Verbal learning test: List A Trial 6, free recall: 13 studies, *d* = -1.08, 95%CI -1.35 to -0.80, *p* < 0.001, I² = 76.6, *p* < 0.001 Verbal learning test: Total list A, Trials 1-5: 28 studies, *d* = -1.32, 95%CI -1.48 to -1.17, *p* < 0.001, I² = 60.4, *p* < 0.001 Verbal learning test: List B: 6 studies, *d* = -0.92, 95%CI -1.19 to -0.65, *p* < 0.001, I² = 40.4, *p* = 0.136 Verbal recall test: 24 studies, *d* = -1.21, 95%CI -1.39 to -1.03, *p* < 0.001, I² = 53.3, *p* = 0.001 Verbal span tasks involving manipulation: 9 studies, *d* = -1.02, 95%CI -1.32 to -0.71, *p* < 0.001, I² = 67.6, *p* = 0.002 *A significant medium effect size suggests poorer performance on the following verbal learning tests in people with schizophrenia compared with controls;* Verbal span tasks without manipulation: 7 studies, *d* = -0.72, 95%CI -0.91 to -0.51, *p* < 0.001, I² = 0, *p* = 0.433 Verbal recognition test: 19 studies, *d* = -0.63, 95%CI -0.84 to -0.42, *p* < 0.001, I² = 58.9, *p* = 0.001 Meta-regression analysis suggests a significant association between longer duration of illness and poorer performance on verbal learning test cued recall post-distraction (*b* = -0.037, *p* = 0.001) and verbal learning test free recall post-distraction (*b* = -0.0339, *p* = 0.015). Dose of chlorpromazine was associated with performance on verbal list learning list 1 (*b* = -0.0026, *p* < 0.001), verbal list learning list 5 (*b* = -0.0027, *p* < 0.001), total recall on verbal learning tests recall trials (*b* = -0.0013, *p* < 0.001) and verbal learning test, short delay, free recall (*b* = -0.002, *p* = 0.01). Verbal list learning list 1 was associated with increased positive symptoms (*b* = 0.09, *p* = 0.35) and negative symptoms (*b* = 0.13, *p* = 0.019).	
Consistency	Inconsistent for all except verbal learning list A trial 1, List B and verbal span task without manipulation.
Precision	Precise
Directness	Direct

Guilera G, Pino O,Gomez-Benito J, Rojo JE

Antipsychotic effects on cognition in schizophrenia: A meta-analysis of

randomised control trials **The European Journal of Psychiatry 2009; 23(2): 77-89** View review abstract online	
Comparison	**Implicit learning in people with schizophrenia on second generation antipsychotics vs. first generation antipsychotics.**
Summary of evidence	**Moderate to low quality evidence (small sample, direct, precise, unable to assess consistency) finds no difference in automatic or procedural learning in people with schizophrenia receiving second-generation antipsychotics compared with those receiving first-generation antipsychotics.**
Implicit learning	
No significant difference in people with schizophrenia receiving second generation antipsychotics compared with first generation antipsychotics; 2 RCTs, N = 85, g = 0.27, 95%CI -0.13 to 0.64, *p* = 0.23	
Consistency	Unable to assess; no measure of consistency is reported.
Precision	Precise
Directness	Direct

Hauser M, Zhang JP, Sheridan EM, Burdick KE, Mogil R, Kane JM, Auther A, Carrion RE, Cornblatt BA, Correll CU

Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and to Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis

Journal of Clinical Psychiatry 2017; 78: e28-e40

View review abstract online

Comparison 1	**Learning in individuals at clinical high-risk of psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium to large samples,**

	inconsistent or imprecise, direct) shows medium-sized effects of poorer verbal and visual learning in people at clinical high-risk for psychosis.
Verbal and visual learning	
Significant, medium-sized effect of poorer verbal learning in people at clinical high-risk; 11 studies, N = 1,132, *g* = -0.42, 95%CI -0.64 to -0.20, *p* < 0.0002, I^2 = 67% This effect was smaller in longitudinal studies (follow-up 10.4 months, *g* = -0.28). The effect was significant in studies using the California Verbal Learning Test, Logical Memory Test and the Rey Auditory Verbal Learning Test. *Significant, small effect of poorer visual learning in people at clinical high-risk;* 5 studies, N = 520, *g* = -0.27, 95%CI -0.47 to -1.03, *p* = 0.002, I^2 = 6% This effect was significant in studies using the Rey-Osterrieth Complex Figure Test.	
Consistency in results	Inconsistent for verbal learning, consistent for visual learning.
Precision in results	Precise for verbal learning, imprecise for visual learning.
Directness of results	Direct
Comparison 2	**Learning in individuals at clinical high-risk for psychosis vs. people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) shows a medium-sized effect of better verbal learning in people at clinical high-risk of psychosis compared to people with first-episode psychosis.**
Verbal learning	
Significant, medium-sized effect of better verbal learning in people at clinical high-risk; 6 studies, N = 655, *g* = 0.39, 95%CI 0.17 to 0.62, *p* = 0.002, I^2 = 44%	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct
Comparison 3	**Cognitive functioning in individuals at clinical high-risk of psychosis that converted or did not convert to psychosis vs. controls.**

Summary of evidence	**Moderate to high quality evidence (medium to large samples, some inconsistency, precise, direct) found large effects of poorer verbal and visual learning in converters. In non-converters, there was a medium-sized effect of poorer verbal learning and no differences in visual learning compared to controls.**
Verbal and visual learning	
Significant, medium-sized effect of poorer verbal learning in non-converters vs. controls; 7 studies, N = 489, g = -0.54, 95%CI -0.90 to -0.19, p = 0.003, I^2 = 66% This effect was significant in studies using the California Verbal Learning Test, the Logical Memory Test and the Rey Auditory Verbal Learning Test. *Significant, large effect of poorer verbal learning in converters vs. controls;* 7 studies, N = 400, g = -0.87, 95%CI -1.22 to -0.52, p < 0.0001, I^2 = 58% This effect was significant in studies using the California Verbal Learning Test, the Rey Auditory Verbal Learning Test, but not the Logical Memory Test. *No significant differences in visual learning in non-converters vs. controls;* 4 studies, N = 285, g = -0.16, 95%CI -0.39 to 0.07, p = 0.18, I^2 = 0% *Significant, medium to large effect of poorer visual learning in converters vs. controls;* 4 studies, N = 240, g = -0.75, 95%CI -1.06 to -0.44, p < 0.0001, I^2 = 22%	
Consistency in results	Consistent for visual learning, inconsistent for verbal learning.
Precision in results	Precise
Directness of results	Direct

Siegert RJ, Weatherall M, Bell EM

Is implicit sequence learning impaired in schizophrenia? A meta-analysis

Brain and Cognition 2008; 67: 351-359

View review abstract online

Comparison	**Implicit learning in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) finds poorer Serial Reaction Time in**

	people with schizophrenia.
Implicit learning	
Significant, medium-sized effect of poorer Serial Reaction Time performance in people with schizophrenia; 9 studies, N = 364, *d* = 0.51, 95%CI 0.30 to 0.73, *p* > 0.05, I^2 = 0, 95%, *p* > 0.05 The authors report a greater change in reaction time from sequences and random blocks for controls than for people with schizophrenia.	
Consistency	Consistent
Precision	Precise
Directness	Direct

Stefanopoulou E, Manoharan A, Landau S, Geddes J, Goodwin G, Frangou S

Cognitive functioning in patients with affective disorders and schizophrenia: A meta-analysis

International Review of Psychiatry 2009; 21(4):336-356

View review abstract online

Comparison	**Verbal learning in people with schizophrenia vs. bipolar disorder.**
Summary of evidence	**Moderate to high quality (unclear sample size, direct, consistent, precise) evidence shows a small effect of lower performance on the California Verbal Learning Test total free recall subscale, but not on the long delayed free recall or recognition hits subscales in patients with schizophrenia vs. bipolar disorder.**
Verbal learning	
A significant, small effect of poorer verbal learning on the California Test total free recall subscale in people with schizophrenia, with no differences on the long delayed free recall and recognition hits subscales; Total free recall: (number of studies not reported), SMD = 0.39, 95%CI 0.06 to 0.72, *p* = 0.02, I^2 = not reported, *p* = 0.71	

Long delayed free recall: SMD = 0.16, 95%CI -0.16 to 0.48, p = 0.33, I^2 = not reported, p = 0.73 Recognition hits: SMD = 0.07, 95%CI -0.31 to 0.47, p = 0.69, I^2 = not reported, p = 0.50	
Consistency	Consistent
Precision	Precise
Directness	Direct

Ventura J, Helleman GS, Thames AD, Koellner V, Nuechterlein KH

Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: a meta-analysis

Schizophrenia Research 2009; 113(2-3): 189-99

View review abstract online

Comparison	**Association between learning, positive symptoms and negative symptoms in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (mixed samples, direct, inconsistent, unable to assess precision) suggests increased negative symptoms but not positive symptoms are significantly associated with poorer working memory, verbal learning and memory, and visual learning and memory. Symptom severity may act as a mediator between memory and functional impairment.**
Positive Symptoms	
No significant association was reported; Verbal learning and memory: 10 studies, N = 531, r = 0.00, p = 0.93 Visual learning and memory: 4 studies, N = 197, r = -0.10, p = 0.20	
Negative Symptoms	
Significant, small association between increased negative symptom severity and poorer; Verbal learning and memory: 23 studies, N = 2,978, r = -0.21, p < 0.01 Visual learning and memory: 8 studies, N = 454, r = -0.16, p < 0.01 *Subgroup analysis examined the potential for negative symptom severity to mediate the effect of*	

neurocognitive performance on functional outcomes; The relationship between verbal learning and memory, and visual learning and memory with community function appears to be at least partially mediated by negative symptom severity, $p < 0.01$. The relationship between verbal learning and memory, and visual learning and memory with skills assessment also appears to be mediated by negative symptom severity, $p < 0.01$.	
Consistency	Authors report all results are inconsistent.
Precision	Unable to assess; no measure of precision is reported.
Directness	Direct for symptom relationships, indirect subgroup analysis.

Woodward ND, Purdon SE, Meltzer HY, Zald DH

A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia

International Journal of Neuropsychopharmacology 2005; 8: 457-472

View review abstract online

Comparison	**Learning in people with schizophrenia receiving second-generation antipsychotics (clozapine, olanzapine, risperidone and quetiapine) vs. first-generation antipsychotics (various) or pre- to post-treatment comparison with second generation antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (mixed samples consistent, precise, direct) shows greater improvements in explicit learning in patients receiving second-generation antipsychotics compared with first-generation antipsychotics.** **Moderate quality evidence (unable to assess precision) suggests patients receiving olanzapine, clozapine or risperidone show improvement pre- to post-treatment, however patients receiving quetiapine show no improvement in learning.**
Learning	
Greater improvements in explicit learning were reported for patients receiving second generation antipsychotics compared with patients receiving first generation antipsychotics;	

14 studies, N= 442, *g* = 0.24, 95%CI 0.10 to 0.38, *p* < 0.001, Q-test *p* > 0.05 *Post-treatment, patients receiving olanzapine, clozapine or risperidone showed improved learning;* Olanzapine: 10 studies, N = 625, *g* = 0.61, CI not reported, *p* < 0.006, Q-test *p* < 0.05 Risperidone: 7 studies, N = 251, *g* = 0.41, CI not reported, *p* < 0.006, Q-test *p* > 0.05 Clozapine: 10 studies, N = 210, *g* = 0.31, CI not reported, *p* < 0.006, Q-test *p* > 0.05 *Patients receiving quetiapine showed no significant improvement post medication;* Quetiapine: 6 studies, N = 108, *g* = 0.24, CI not reported, *p* > 0.05, Q-test *p* > 0.05	
Consistency	Consistent apart from olanzapine.
Precision	Precise for first vs. second generation antipsychotics, unable to assess pre-post comparison.
Directness	Direct

Woodward ND, Purdon SE, Meltzer HY, Zald DH

A meta-analysis of cognitive changes with haloperidol in clinical trials of atypical antipsychotics: Dose effects and comparison to practice effects

Schizophrenia Research 2007; 89: 211-224

View review abstract online

Comparison	**Verbal learning in people with schizophrenia receiving haloperidol to assess pre-post treatment effects.**
Summary of evidence	**Moderate to high quality evidence (mixed samples, consistent, precise, direct) shows improvements on verbal learning after treatment with haloperidol.**
Verbal learning	
Significant, small effect of improved verbal learning post-treatment; All studies: 11 studies, N = 538, *g* = 0.32, 95%CI 0.19 to 0.43, *p* < 0.05 Low dose: 6 studies, N = 371, *g* = 0.37, 95%CI 0.23 to 0.51, *p* < 0.05 High dose: 5 studies, N = 167, *g* = 0.20, 95%CI 0.00 to 0.40, *p* < 0.05	
Consistency	Authors report all results are consistent (using fixed effects model).

Precision	Precise
Directness	Direct

Explanation of acronyms

AVLT = Auditory Verbal Learning Test, 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), ES = effect size, HVLT = Hopkins Verbal Learning Test, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia, 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_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), *r* = correlation coefficient, RCT = randomised control trial, SMD = standard mean difference, SRT = Serial Reaction Time, vs. = versus, WCST = Wisconsin Card Sorting Task, WISC = Wechsler Intelligence Scale for Children

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[18].

† 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[18].

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[19]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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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[18];

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

§ 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[20].

‖ 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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