TECHNICAL COMMENTARY

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Olfactory functioning

Introduction

The olfactory system is the sensory system used to interpret and perceive smell. Olfactory functioning is hierarchical and involves lower-order processing (detection of the stimulus) and higher-order processing (discrimination and identification of the stimulus). Odour detection occurs at the lowest chemical concentration needed to register an odourant. Odour discrimination involves comparing the differences between multiple stimuli, judging odours as pleasant or unpleasant, or comparing the relative concentration of odours. Odour identification draws on a person's knowledge and memory to correctly label the smell[1, 2].

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 given priority 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[3]. 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%. Reviews rated as having less than 50% of items checked have now 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)[4]. 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 three systematic reviews that met our inclusion criteria[5-7].

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- Moderate to high quality evidence suggests a medium to large effect of impaired olfactory processing in people with schizophrenia compared with controls. High heterogeneity between study results may be explained by differences in the tasks used. Memory tasks showed greatest impairment, followed by identification tasks, birhinal presentation, pleasant odour tasks, discrimination tasks, left nostril presentation, unirhinal presentation, right nostril presentation, detection threshold, and then unpleasant odour tasks. A longer duration of illness, first-generation antipsychotics, and increased age were associated with larger effect sizes. Higher percentage of males and higher levels of smoking in patients were associated with smaller effect sizes. No differences were reported for diagnoses, study setting, age of onset, negative symptomatology, medication status or dose, education, handedness.
- Moderate to high quality evidence suggests impaired olfactory identification, but not acuity, in people at high-risk of schizophrenia.
- Moderate to high quality evidence suggests impaired olfactory identification in youths at clinical high-risk of schizophrenia and first-degree relatives, but not in people with schizotypy compared with controls.

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Cohen A, Saperstein A, Gold J, Kirkpatrick B, Carpenter W, Buchanan R

Neuropsychology of the deficit syndrome: New data and meta-analysis of findings to date

Schizophrenia Bulletin 2007; 33(5): 1201-1212

View review abstract online

Comparison	**Olfactory identification in people with deficit schizophrenia (predominantly negative symptoms) vs. people with non-deficit schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) is unable to determine differences in olfactory identification skills.**
Odour identification	
Large effect size suggests greater olfactory identification impairment in people with deficit schizophrenia compared to non-deficit schizophrenia; Number of studies, sample sizes, Q and *p*-values are not reported ES (unspecified) = 1.11, 95%CI not reported	
Consistency in results‡	Unable to assess, consistency measures are not reported.
Precision in results§	Unable to assess, precision measures are not reported.
Directness of results‖	Direct

Cohen AS, Brown LA, Auster TL

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

Schizophrenia Research 2012; 135: 152-157

View review abstract online

Comparison	**Olfactory identification and acuity in people with schizophrenia vs. controls.**

Olfactory functioning

Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) suggests a large effect of impaired olfactory identification and a medium effect of impaired olfactory acuity in people with schizophrenia compared to controls.**
Olfactory performance	
A large effect of impaired identification and a medium effect of impaired acuity in schizophrenia; Olfactory identification: 39 studies, N = 2,598 (1342 schizophrenia, 1256 controls) *d* = -0.99, 95%CI -1.18 to -0.80, *p* value not reported Olfactory acuity: 14 studies, N = 778 (391 schizophrenia, 387 controls) *d* = -0.45, 95%CI -0.61 to -0.29, *p* value not reported	
Consistency	Unable to assess
Precision	Precise
Directness	Direct
Comparison 2	**Olfactory identification and acuity in people at risk of schizophrenia – including people with self-reported schizotypal traits, people at high genetic risk, and people displaying subclinical psychotic symptoms.**
Summary of evidence	**Moderate to high quality evidence (large sample, unable to assess consistency, precise, direct) suggests impaired olfactory identification in people at high risk of schizophrenia.**
Olfactory performance	
Overall, a small significant effect size of impaired identification, but not acuity, in people at high risk; Olfactory identification: 16 studies, N = 1,186 (605 at risk, 581 controls), *d* = -0.25, 95%CI -0.47 to -0.03, *p* value not reported Olfactory acuity: 6 studies, N = (100 at risk, 138 controls), *d* = -0.38, 95%CI -0.70 to 0.07, *p* value not reported *No significant differences reported in subgroup of ultra-high risk studies (family history of psychosis, functional decline or subclinical psychosis);* Identification: 2 studies, N = 219 (154 at risk, 65 controls), *d* = -0.67, 95%CI -4.08 to 2.75 *No significant differences reported in subgroup of psychometrically determined studies (schizotypy self-report);*	

Identification: 5 studies, N = 450 (218 at risk, 232 controls), *d* = -0.14, 95%CI -0.64 to 0.36 *No significant differences reported in familial high-risk studies (relatives of people with schizophrenia);* Identification: 9 studies, N = 517 (233 at risk, 284 controls), *d* = -0.21, 95%CI -0.53 to 0.12	
Consistency	Unable to assess, consistency measures are not reported
Precision	Precise, apart from ultra-high risk studies.
Directness	Direct

Moberg PJ, Kamath V, Marchetto DM, Calkins ME, Doty RL, Hahn C, Borgmann-Winter KE, Kohler CG, Gur RE, Turetsky BI

Meta-Analysis of Olfactory Function in Schizophrenia, First-Degree Family Members, and Youths At-Risk for Psychosis

Schizophrenia Bulletin 2014; 40(1): 50-59

View review abstract online

Comparison	**Olfactory functioning in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium to large effect of impaired olfactory processing in people with schizophrenia compared to controls. High heterogeneity between study results may be explained by differences in the tasks used. Memory tasks showed greatest impairment, followed by identification, birhinal presentation, pleasant odour tasks, discrimination, left nostril presentation, unirhinal presentation, right nostril presentation, detection threshold and unpleasant odour tasks. A longer duration of illness, typical antipsychotics and increased age were associated with larger effect sizes. Higher percentage of males, and higher levels of smoking in patients were associated with smaller effect sizes. No differences were reported for diagnoses, study setting, age of onset, negative symptomatology, medication status or dose, education, handedness.**
Olfactory processing	

Olfactory functioning

A significant, medium to large effect was reported for reduced olfactory processing in patients with schizophrenia compared to controls;

161 studies, N = 8,899 (4491 schizophrenia, 4408 controls), d = -0.74, 95%CI -0.83 to -0.65, p < 0.05, Q_w = 630.0, p < 0.001

Subgroup analyses to investigate the significant heterogeneity in results found that there were significant differences in effect sizes on olfactory tasks, although all tasks showed significant impairment in patients compared to controls. Odour memory tasks yielded a larger effect size than all other tasks, odour identification tasks yielded a larger effect size than odour detection and odour hedonics tasks, and pleasant odour tasks yielded a larger effect size than unpleasant odour tasks. There were no other significant differences between tasks;

Odour memory: 2 studies, d = -1.62, 95%CI -2.23 to -1.01, p < 0.05

Odour identification: 76 studies, d = -0.93, 95%CI -1.06 to -0.79, p < 0.05

Birhinally (both nostrils at once): 90 studies, d = -0.86, 95%CI -0.97 to -0.75, p < 0.05

Unirhinal (each nostril separately): 71 studies, d = -0.59, 95%CI -0.73 to -0.45, p < 0.05

Odour discrimination: 13 studies, d = -0.69, 95%CI -0.93 to -0.44, p < 0.05

Odour hedonics: 30 studies, d = -0.55, 95%CI -0.68 to -0.42, p < 0.05

Pleasant odours: 12 studies, d = -0.78, 95%CI -0.97 to -0.58, p < 0.05

Unpleasant odours: 11 studies, d = -0.33, 95%CI -0.50 to -0.16, p < 0.05

Odour detection threshold: 40 studies, d = -0.51, 95%CI -0.69 to -0.33, p < 0.05

Left nostril: 32 studies, d = -0.61, 95%CI -0.83 to -0.39, p < 0.05

Right nostril: 33 studies, d = -0.57, 95%CI -0.78 to -0.36, p < 0.05

Memory vs. detection: Q_B = 11.77, p = 0.001

Memory vs. hedonics: Q_B = 11.44, p = 0.001

Memory vs. discrimination: Q_B = 7.83, p = 0.005

Memory vs. identification: Q_B = 4.79, p = 0.03

Identification vs. detection: Q_B = 12.93, p < 0.001

Identification vs. hedonics: Q_B = 15.67, p < 0.001

Pleasant odours vs. unpleasant odours: Q_B = 22.21, p = 0.001

Birhinally vs. unirhinally: Q_B = 8.98, p = 0.003

Further subgroup analyses revealed larger effect sizes were significantly associated with; a longer duration of illness, positive symptoms as measured on the PANSS-Pos, typical antipsychotics, and increased age. Smaller effect sizes were associated with; increased positive symptoms as measured on the SAPS, samples with a higher percentage of males, and higher levels of smoking in patients. No differences were reported for diagnoses, study setting, age of onset, negative symptomatology, medication status or dose, education, handedness.

Olfactory functioning

Consistency	Inconsistent for overall analysis, within subgroup heterogeneity measures were not reported.
Precision	Precise, apart from odour memory tasks.
Directness	Direct
Comparison 2	**Olfactory functioning in people at high-risk of schizophrenia, those with schizotypy and first-degree relatives vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small to medium effect of impaired olfactory identification in youths at clinical high-risk of schizophrenia and first-degree relatives, but not people with schizotypy compared with controls.**
Olfactory performance	
A significant, small to medium effect was reported for reduced olfactory processing in those at risk, first-degree relatives, and people with schizotypy compared to controls; 37 studies, N = 2, 065 (875 subjects, 1190 controls), d = -0.33, 95%CI -0.42 to -0.23, $p < 0.05$, Q_w = 59.66, $p < 0.01$ *Subgroup analysis found that only high-risk youths and first-degree relatives showed olfactory impairment compared with controls, and the effect size for high-risk youths was significantly greater than first-degree relatives or people with schizotypy. The effect sizes in the latter two groups were not significantly different;* Clinical high-risk youths: 6 studies, d = -0.71, 95%CI -0.93 to -0.49, $p < 0.05$ First-degree relatives: 23 studies, d = -0.25, 95%CI -0.36 to -0.13, $p < 0.05$ People with schizotypy: 8 studies, d = -0.19, 95%CI -0.43 to 0.05, $p > 0.05$ Clinical high-risk youths vs. first-degree relatives: Q_B = 13.64, $p < 0.001$ Clinical high-risk youths vs. schizotypy: Q_B = 9.92, $p < 0.01$	
Consistency	Inconsistent for overall analysis, within subgroup heterogeneity measures were not reported
Precision	Precise
Directness	Direct

Explanation of acronyms

CI = Confidence Interval, ES = effect size, N = number of participants, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences (see below for interpretation of effect size), Q = Q statistic for the test of heterogeneity, Q_B = test for between group differences (heterogeneity in results between subgroups of studies), Q_w = test for within group differences (heterogeneity in results of studies within a group), *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS-POS = positive and negative syndrome scale, positive symptoms, SAPS = scale for the assessment of positive symptoms, vs. = versus

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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[8].

† 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[8].

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[9]. 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[8];

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

§ 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[10].

‖ 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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