TECHNICAL COMMENTARY

Olfactory functioning

Introduction

Olfactory functioning is hierarchical and involves lower-order processing (detection of the stimulus) and higher-order processing (discrimination and identification of the stimulus). Measures of olfactory acuity include odor detection, identification, discrimination, intensity, and quality. Odour detection occurs at the lowest chemical concentration needed to register an odourant. Odour identification draws on a person's knowledge and memory to correctly label the smell. Odour discrimination involves comparing the differences between multiple stimuli, judging odours as pleasant or unpleasant, or comparing the relative concentration of odours.

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 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and comprehensive 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[1]. 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)[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 one systematic review that met our inclusion criteria[3].

- Moderate to low quality evidence suggests poorer olfactory identification in people with bipolar disorder than controls, but better olfactory identification compared to people with psychosis. Olfactory hallucinations were associated particularly with depressive episodes.

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Kazour F, Richa S, Desmidt T, Lemaire M, Atanasova B, El Hage W

Olfactory and gustatory functions in bipolar disorders: A systematic review

Neuroscience and Biobehavioral Reviews 2017; 80: 69-79

View review abstract online

Comparison 1	**Olfactory functioning in people with bipolar disorder vs. controls.**
Summary of evidence	**Moderate to low quality evidence (direct, some inconsistency, unable to assess precision, medium-sized sample) suggests poorer olfactory identification in people with bipolar disorder than controls.** **Low quality evidence (few, small studies) is unable to determine any olfactory physical changes associated with bipolar disorder.**
Odour acuity	
3 of 4 studies (N = 268) found poorer olfactory identification in people with bipolar disorder; 1 study (N = 42) found olfactory identification was poorer in people with bipolar disorder than controls. People with bipolar disorder rated odours as more pleasant than controls. 1 study (N = 79) found olfactory identification and social cognition was poorer in people with bipolar disorder than controls. 1 study (N = 71) found olfactory identification was poorer in people with bipolar disorder than controls. 1 study (N = 76) found no differences in olfactory threshold, identification, or hedonic rating between people with bipolar disorder and controls.	
Physical features	
1 small study found structural changes; 1 study (N = 50) found shallower sulcus and deeper sulcus in the right vs. left hemisphere in people with bipolar disorder than controls. People with bipolar disorder on valproate had longer sulcus bilaterally. There were no sulcus differences on the basis of psychotic vs. no psychotic symptoms, family history vs. no family history, and lithium vs. no lithium treatment. *1 very small study found chemical changes in people with bipolar disorder* 1 study (N = 7) found stimulated and basal intracellular calcium was lower in people with bipolar disorder than controls, but unmedicated patients with bipolar disorder had higher intracellular calcium.	
Consistency in results‡	Some inconsistency for acuity, N/A for physical features.

Precision in results[§]	Unable to assess, confidence intervals are not reported.
Directness of results[‖]	Direct
Comparison 2	**Olfactory functioning in people with bipolar disorder vs. other psychiatric disorders.**
Summary of evidence	**Moderate to low quality evidence (direct, some inconsistency, unable to assess precision, medium-sized sample) suggests better olfactory identification in people with bipolar disorder than people with psychosis. There were no differences in the number of olfactory hallucinations between hallucinating bipolar patients, hallucinating manic bipolar patients, hallucinating depressed bipolar patients, hallucinating schizophrenia patients, and hallucinating patients with major depression.**
Odour acuity	
2 of 3 small studies (N = 156) found better olfactory identification in people with bipolar disorder than people with psychotic disorders; 1 study (N = 71) found better olfactory identification in people with bipolar disorder without psychosis than in people with bipolar disorder with psychosis or in people with schizophrenia. 1 study (N = 26) found better odour identification in people with bipolar disorder than people with schizophrenia, schizoaffective disorder, or psychotic depression. 1 study (N = 59) found no differences in olfactory identification between people with bipolar disorder and people with non-affective psychoses. *1 small study found impaired sense of smell in some, but not all, people with bipolar disorder;* 1 study (N = 82) found impaired sense of smell in 14% of people with bipolar disorder, in 14% of people with recurrent brief depression without hypomania, and in 21% of people with recurrent brief depression with hypomania. *1 small study found more hedonic sense of smell in people with bipolar disorder;* 1 study (N = 76) found more olfactory stimuli rated as pleasant in people with bipolar disorder than in people with recurrent depressive disorder.	
Olfactory hallucinations	
1 large study found no differences in olfactory hallucinations; 1 study (N = 329) found no differences in the number of olfactory hallucinations between hallucinating bipolar patients, hallucinating manic bipolar patients, hallucinating depressed bipolar patients, hallucinating schizophrenia patients, and hallucinating patients with major depression.	
Consistency in results	Some inconsistency for acuity, N/A for hallucinations.
Precision in results	Unable to assess, confidence intervals are not reported.

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Directness of results	Direct
Comparison 3	**Factors associated with olfactory functioning in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (direct, unable to assess consistency or precision, medium-sized sample) suggests tactile, olfactory, and gustative hallucinations were associated with a lifetime history of depressive episodes.** **Low quality evidence (direct, unable to assess consistency or precision, small samples) is unable to determine relationships between olfactory acuity and other outcomes.**
Odour acuity	
1 small study found better odour acuity and sensitivity were associated with more depression; 1 study (N = 64) found increased odour acuity was associated with increased dysthymia symptoms, lower levels of fear and avoidance, and higher independent performance in people with bipolar disorder. Increased odour sensitivity was associated with depressive symptoms and higher social functioning. *1 small study found better odour identification was associated with better social cognition;* 1 study (N = 79) found better olfactory identification was related to better facial emotion recognition, theory of mind, and general cognition. *1 very small study found better odour sensitivity was associated with an event-triggered mood episode;* 1 study (N = 16) found olfactory sensitivity was higher in people with bipolar disorder with an event-triggered mood episode than in people with bipolar disorder without an event-triggered mood episode. There were no differences in olfactory identification or discrimination.	
Olfactory hallucinations	
1 large study found olfactory and related hallucinations were associated with depressive episodes; 1 study (N = 287) found tactile, olfactory and gustative hallucinations were associated with a lifetime history of depressive episodes in people with bipolar disorder. *1 very small study found half of the patients had olfactory hallucinations with epileptic symptoms;* 1 study (N = 12) found 50% of the patients with bipolar disorder had olfactory hallucinations along with psychomotor epileptic symptoms.	
Consistency in results	N/A, no common associations.
Precision in results	Unable to assess, confidence intervals are not reported.
Directness of results	Direct

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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[4].

† 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[4].

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[5]. 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[4];

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

§ 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[6].

‖ 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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