TECHNICAL COMMENTARY

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Functional laterality

Introduction

Laterality refers to natural asymmetry in left or right-side dominance, for example in terms of handedness, or brain function. Handedness refers to the preference for using one hand over the other for certain tasks. People may also be 'mixed' handed and show differing hand preference for different tasks. 'Non-right' handedness refers to a combination of left and mixed handedness. Handedness reflects aspects of brain lateralisation, which refers to the localisation of a function to the left or right brain hemisphere. Several tests have been devised to assess handedness. The Annett's Handedness Questionnaire and the Edinburgh Handedness Inventory ask participants' their hand preference for particular tasks (eg. writing, throwing a ball etc.). Participants may answer "right", "left" or "no preference".

As well as showing asymmetry in handedness, people with schizophrenia may also show asymmetry in their footedness, eye dominance, auditory preference and anatomical hemispheric dominance. Dichotic listening tasks (such as the triad task, the fused-word task, consonant-vowel task and the word-monitoring task) can be used to assess language lateralisation. Participants are presented two different stimuli. Verbal stimuli are usually perceived better in the right ear. Future research would benefit from assessing the clinical implications associated with such asymmetries that may reflect abnormalities in cerebral laterality and dominance.

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. We have prioritised reviews with pooled data 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,

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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 four systematic reviews that met our inclusion criteria.[3-6]

- High quality evidence finds people with schizophrenia are more likely to be non-right-handed than controls or people with other psychiatric disorders. Moderate to high quality evidence suggests this finding is similar for males and females.
- Moderate to high quality evidence suggests people with schizophrenia had less right-ear dominance compared with controls, which may be most apparent in patients who experience auditory hallucinations.
- Moderate to low quality evidence suggests people with schizophrenia showed an absence of normal leftward asymmetry in the planum temporale and Sylvian fissure, and an excess rightward asymmetry in the superior temporal gyrus (particularly posterior). There was also a higher frequency of abnormal (reversed) asymmetry in the frontal and occipital lobes in people with schizophrenia compared to controls.

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Dragovic M, Hammond G

Handedness in schizophrenia: a quantitative review of evidence

Acta Psychiatrica Scandinavica 2005; 111: 410-419

View review abstract online

Comparison	**Handedness (left, right and mixed) in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, mostly inconsistent, imprecise, direct) finds people with schizophrenia are more likely to be non-right-handed or mixed handed compared to controls.**

Left handedness

Small effect suggests people with schizophrenia are significantly more likely to be left-handed than controls;

16 studies, N = 68,518, OR = 1.85, 95%CI 1.5 to 2.2, $p < 0.05$, $Q_W = 18.5$, $p = 0.24$

Non-right handedness

Small effect suggests people with schizophrenia are significantly more likely to be non-right-handed than controls;

23 studies, N = 20,183, OR = 1.58, 95%CI 1.22 to 2.04, $Q_W = 133.6$, $p < 0.0001$

Significant publication bias, $p = 0.05$

Subgroup analysis assessed relationship between non-right and various assessment methods:

Annett's Handedness Questionnaire: 8 studies, OR = 1.00, $Q_W = 25.85$, $p < 0.01$

Edinburgh Handedness Inventory: 4 studies, OR = 2.86, $Q_W = 4.09$, $p = 0.25$

Other assessments: 11 studies, OR = 1.89, $Q_W = 57.74$, $p < 0.01$

Mixed handedness

Small effect suggests people with schizophrenia are significantly more likely to be mixed handed than controls;

23 studies, N = 13,080, OR = 1.77, 95%CI 1.29 to 2.45, $Q_W = 137.3$, $p < 0.0001$

Subgroup analysis assessed relationship between mixed handedness and various assessment methods:

Annett's Handedness Questionnaire: 8 studies, OR = 1.19, Q_W = 37.61, p < 0.01 *Edinburgh Handedness Inventory:* 6 studies, OR = 2.82, Q_W = 6.35, *p* = 0.274 *Other assessments:* 9 studies, OR = 1.87, Q_W = 51.46, *p* < 0.01	
Consistency in results‡	Inconsistent for all measures except left handedness and the Edinburgh Handedness Inventory
Precision in results§	Imprecise
Directness of results‖	Direct

Hirnstein M, Hugdahl K

Excess of non-right-handedness in schizophrenia: meta-analysis of gender effects and potential biases in handedness assessment

The British Journal of Psychiatry 2014; 205: 260-267

View review abstract online

Comparison	**Non-right-handedness in people with schizophrenia vs. controls according to gender and assessment type.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests people with schizophrenia are more likely to be non-right-handed compared to controls regardless of gender, and this may be more apparent when behavioural assessments are used.**
Non-right handedness according to gender	
Significant, small effects show males and females are both more likely to be non-right-handed than controls; Females: 16 effect sizes, N = 4,368, OR = 1.63, 95%CI 1.16 to 2.30, *p* = 0.005 Males: 17 effect sizes, N = 5,013, OR = 1.50, 95%CI 1.14 to 1.99, *p* = 0.004 The difference between females and males was not significant (Q_B = 0.13, *p* = 0.722) I^2 pooled across subgroups was 1.78% No evidence of publication bias	
Non-right handedness according to behavioural assessments	

Significant, small effect suggests effect sizes are slightly larger in studies with behavioural assessments; Behavioural assessments: 11 effect sizes, N = 7,588, OR = 1.90, 95%CI 1.42 to 2.53, $p < 0.001$ Other forms of assessment: 30 effect sizes, N = 8,425, OR = 1.39, 95%CI 1.15 to 1.69, $p = 0.001$ There was a trend towards greater non-right-handedness when handedness was assessed behaviourally ($Q_B = 3.05$, $p = 0.081$) I^2 pooled across subgroups was < 0.01% No evidence of publication bias

Consistency in results	Consistent over pooled analyses
Precision in results	Imprecise
Directness of results	Direct

Ocklenburg S, Westerhausen R, Hirnstein M, Hugdahl K

Auditory hallucinations and reduced language lateralization in schizophrenia: a meta-analysis of dichotic listening studies

Journal of the International Neuropsychological Society 2013; 19(4): 410-8

View review abstract online

Comparison	**Language lateralisation in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) suggests that people with schizophrenia have lower language laterality than controls (small effect), particularly patients who experience auditory hallucinations (medium-sized effect).**

Language lateralisation

A small, significant effect shows people with schizophrenia had lower mean language laterality (less right-ear dominance) than controls;

21 studies, N = 1,407, $g = -0.26$, 95%CI -0.36 to -0.15, $p < 0.00001$, $I^2 = 53.3\%$, $p < 0.01$

Subgroup analysis of hallucinating patients vs. non-hallucinating controls (2/8 studies included non-hallucinating patients) reported a medium-sized effect of lower mean language laterality in

hallucinating patients; 8 studies, N = 407, *g* = -0.45, 95%CI -0.65 to -0.25, *p* < 0.00001, Q_w = 11.17, *p* = 0.13, I^2 = 37.3% No evidence of publication bias	
Consistency in results	Consistent for hallucinating patients only
Precision in results	Precise
Directness of results	Direct

Sommer I, Aleman A, Ramsey N, Bouma A

Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis

British Journal of Psychiatry 2001; 178: 344-351

View review abstract online

Comparison	**Differences in handedness, language lateralisation and anatomical asymmetry in people with schizophrenia vs. controls.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) suggests that people with schizophrenia are more likely to be non-right-handed than controls or people with other psychiatric disorders.** **Moderate quality evidence (medium-sized samples, consistent, imprecise, direct) suggests people with schizophrenia had a less right-ear dominance compared to controls on fused-word and consonant-vowel listening tasks.** **Moderate to low quality evidence (small to medium-sized samples, mostly inconsistent, imprecise, direct) suggest people with schizophrenia showed an absence of normal leftward asymmetry in the planum temporale and Sylvian fissure, and an excess rightward asymmetry in the STG (particularly posterior). There was also a higher frequency of abnormal (reversed) asymmetry in the frontal and occipital lobes in people with schizophrenia compared with controls.**
Handedness	

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A small effect size suggests people with schizophrenia are significantly more likely to be non-right-handed;

Compared to healthy controls: 16 studies, N = 5,467, OR = 1.61, 95%CI 1.41 to 1.81, $p = 0.0002$, $Q_W = 23.6$, $p = 0.13$

Compared to psychiatric controls: 9 studies, N = 1,492, OR = 1.54, 95%CI 1.28 to 1.84, $p = 0.009$, $Q_W = 11.46$, $p = 0.20$

Prospective assessment suggests that children who went on to develop schizophrenia were significantly more likely to be non-right-handed compared to the general population;

3 studies, N = 55,579, OR = 1.48, 95%CI 1.23 to 1.79, $p = 0.02$, $Q_W = 2.24$, $p = 0.31$

Dichotic listening

Measured by the triad task, the fused-word task, consonant-vowel task and the word-monitoring task

Right-ear advantage was significantly different for consonant-vowel and fused-word tasks, but not for all verbal tasks in people with schizophrenia compared to controls;

All verbal tasks: 10 studies, N = 434, $d = -0.19$, 95%CI -0.6 to 0.2, $p = 0.18$, $Q_W = 29.2$, $p < 0.01$

Consonant-vowel and fused-words: 6 studies, N = 267, $d = -0.48$, 95%CI -0.83 to -0.14, $p < 0.01$, $Q_W = 8.9$, $p = 0.11$

Anatomical asymmetry

Significantly higher frequency of absent or reversed frontal lobe asymmetry in people with schizophrenia compared to controls;

3 studies, N = 383, weighted difference rate = 0.24, 95%CI 0.15 to 0.34, $p = 0.05$, $Q_W = 8.4$, $p = 0.05$

Significantly higher frequency of absent or reversed occipital lobe asymmetry in people with schizophrenia compared to controls;

5 studies, N = 579, weighted difference rate = 0.22, 95%CI 0.12 to 0.28, $p = 0.01$, $Q_W = 87.55$, $p = 0.003$

Planum temporale

Significant left asymmetry in controls but not in people with schizophrenia;

Controls: 11 studies, N = 187, $d = 0.7$, 95%CI 0.49 to 0.91, $p < 0.01$, $Q_W = 4.3$, $p = 0.89$

Schizophrenia: 11 studies, N = 191, $d = 0.18$, 95%CI -0.33 to 0.69, $p = 0.24$, $Q_W = 48.7$, $p < 0.01$

Significantly less asymmetry of the planum temporale in people with schizophrenia compared to controls;

11 studies, N = 368, $d = -0.51$, 95%CI -1.04 to 0.02, $p = 0.03$, $Q_W = 54.5$, $p = 0.0005$

Sylvian Fissure

Significant left asymmetry in both controls and people with schizophrenia; *Controls:* 3 studies, N = 100, *d* = 0.87, 95%CI 0.43 to 1.32, *p* < 0.01, Q_W = 9.85, *p* = 0.04 *Schizophrenia:* 3 studies, N = 97, *d* = 0.31, 95%CI -1.04 to 0.2, *p* < 0.01, Q_W = 4.72, *p* = 0.32 *Significantly less asymmetry of the Sylvian fissure in people with schizophrenia compared to controls;* 3 studies, N = 185, *d* = -0.62, 95%CI -1.04 to 0.2, *p* < 0.01, Q_W = 11.1, *p* = 0.03 <u>Temporal horn of the lateral ventricle</u> *Significant right asymmetry in both controls and people with schizophrenia;* *Controls:* 12 studies, N = 303, *d* = -0.25, 95%CI -0.41 to -0.09, *p* < 0.01, Q_W = 9.32, *p* = 0.59 *Schizophrenia:* 12 studies, N = 324, *d* = -0.42, 95%CI -0.88 to -0.04, *p* = 0.04, Q_W = 92.5, *p* < 0.01 *No significant difference in degree of asymmetry of the temporal horn between people with schizophrenia and controls;* 12 studies, N = 629, *d* = -0.11, 95%CI -0.61 to 0.4, *p* = 0.34, Q_W = 106.83, *p* < 0.01 <u>Superior temporal gyrus (STG)</u> *Significant right asymmetry reported in schizophrenia only (trend level in controls);* *Controls:* 17 studies, N = 399, *d* = -0.47, 95%CI -1.1 to 0.14, *p* = 0.07, Q_W = 140.23, *p* < 0.01 *Schizophrenia:* 17 studies, N = 469, *d* = -0.73, 95%CI -1.2 to -0.25, *p* < 0.01, Q_W = 151.7, *p* < 0.01 *No significant difference in degree of asymmetry of STG between people with schizophrenia and controls;* 17 studies, N = 1020, *d* = 0.21, 95%CI -0.08 to 0.51, *p* = 0.08, Q_W = 93.3, *p* < 0.01 <u>Posterior segment of the superior temporal gyrus</u> *Significant right asymmetry reported in schizophrenia only (trend level in controls);* *Controls:* 5 studies, N = 130, *d* = -0.2, 95%CI -0.44 to 0.05, *p* = 0.06, Q_W = 1.5, *p* = 0.9 *Schizophrenia:* 5 studies, N = 108, *d* = -0.9, 95%CI-0.17 to -0.62, *p* < 0.01, Q_W = 4.85, *p* = 0.43 *Significantly more right asymmetry of posterior STG in people with schizophrenia compared to controls;* 5 studies, N = 238, *d* = 0.7, 95%CI 0.4 to 1, *p* < 0.01, Q_W = 5.42, *p* = 0.37	
Consistency	Inconsistent for all measures except handedness, dichotic listening, and posterior STG
Precision	Imprecise
Directness	Direct

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Explanation of acronyms

CI = confidence interval, *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), N = number of participants, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, Q_B = statistic for test of heterogeneity between groups of studies, Q_W = statistic for test of heterogeneity within groups of studies, STG = Superior Temporal Gyrus, 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.[7]

† 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.[7]

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[8]. 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;[7]

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

§ 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 0.50 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.[9]

‖ 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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