Introduction

Laterality refers to natural asymmetry in left or right-side dominance, for example in terms of handedness, or brain function. People with schizophrenia show differences in handedness and footedness, as well as altered visual and auditory dominance, which may reflect abnormalities in cerebral laterality and dominance.¹ ²

Handedness refers to the preference for using one hand over the other for certain tasks. Right handed people show increased dexterity in their right hand, left handed people show increased ability the left hand. People may also be ‘mixed’ handed and show differing hand preference for different tasks.³ ‘Non-right’ handedness refers to a combination of left and mixed handedness. Handedness reflects aspects of brain lateralisation,⁴ 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.⁵ Future research would benefit from assessing the clinical implications associated with such asymmetries.

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 for inclusion reviews with pooled data.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis.⁶ 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 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 (RCT) may be downgraded to moderate, low or very 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). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.

Results

See table below for a detailed summary of the available evidence pertaining to handedness and laterality in schizophrenia. We found three systematic reviews that met our inclusion criteria. See PRISMA checklists for assessment of reporting transparency.

Conclusions

- High quality evidence suggests that 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, and may be most apparent when behavioural assessments are used.
- Moderate quality evidence 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 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 STG (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.
Dragovic M, Hammond G

Handedness in schizophrenia: a quantitative review of evidence

Acta Psychiatrica Scandinavica 2005; 111: 410-419

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<td>Moderate to low quality evidence (direct, imprecise, mostly inconsistent, publication bias) suggests that people with schizophrenia are more likely to be non-right handed or mixed handed compared to controls</td>
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### 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, QW = 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, QW = 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, QW = 25.85, p < 0.01
- Edinburgh Handedness Inventory: 4 studies, OR = 2.86, QW = 4.09, p = 0.25
- Other assessments: 11 studies, OR = 1.89, QW = 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, QW = 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

<table>
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<th>Consistency in results‡</th>
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<tr>
<td>Directness of results‖</td>
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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 (direct, imprecise, consistent, large samples) suggests that 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 suggest males and females are similarly more likely to be non-right handed than controls

Females: 16 effect sizes, N = 4368, OR = 1.63, 95%CI 1.16 to 2.30, p = 0.005
Males: 17 effect sizes, N = 5013, 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)

I² 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 = 7588, OR = 1.90, 95%CI 1.42 to 2.53, p < 0.001

Other forms of assessment: 30 effect sizes, N = 8425, 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)

I² 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

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**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

Note: prevalence of mixed- and left-handedness were grouped together as ‘non-right handed’

### Summary of evidence
High quality evidence (direct, consistent, precise, large sample) suggests that people with schizophrenia are more likely to be non-right handed than controls or people with other psychiatric disorders.

Moderate quality evidence (direct, consistent, imprecise) 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 (mostly inconsistent, imprecise, direct) suggest people with schizophrenia showed an absence of normal leftward asymmetry in the planum temporale.
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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 to controls

**Handedness**

_A small effect size suggests people with schizophrenia are significantly more likely to be non-right handed_

*Compared to healthy controls:* 16 studies, N = 5467, 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 = 1492, 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_
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### 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, $p < 0.01$, $Q_W = 11.1$, $p = 0.03$

### Temporal horn of the lateral ventricle

**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, $p = 0.34$, $Q_W = 106.83$, $p < 0.01$

### Superior temporal gyrus (STG)

**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, $p = 0.08$, $Q_W = 93.3$, $p < 0.01$

### Posterior segment of the superior temporal gyrus

**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**

17 studies, N = 1020, $d = 0.21$, 95%CI -0.08 to 0.51, $p = 0.08$, $Q_W = 93.3$, $p < 0.01$
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5 studies, N = 238, $d = 0.7$, 95%CI 0.4 to 1, $p < 0.01$, $Q_W = 5.42$, $p = 0.37$

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<tr>
<th>Consistency</th>
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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
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 which 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.11

† 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 which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which 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) which 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.11

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 to large effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2.12 lnOR stands for logarithmic OR where a InOR 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 unforeseen 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.

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

§ 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.\textsuperscript{12}

|| 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 which 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.

This topic is yet to be reviewed by a content expert
Signs and Symptoms – Functional Laterality

References