

Review article

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

Marco Hirnstein and Kenneth Hugdahl

Background

The notion that schizophrenia is characterised by increased non-right-handedness is a cornerstone of the theory that schizophrenia arises from, and is genetically linked to, abnormal brain lateralisation. Reviews and meta-analyses have reported higher rates of non-right-handers in patients with schizophrenia. However, this was suggested to be the result of a gender artefact or a hidden bias in self-report handedness questionnaires.

Aims

To investigate using a meta-analytical approach whether the excess of non-right-handedness is seen in both females and males, and also when handedness is assessed behaviourally.

Method

Electronic databases were searched for studies that reported (a) the rate of female and male non-right-handers in schizophrenia compared with controls and (b) the rate of non-right-handers in schizophrenia (regardless of gender) based on behavioural handedness assessment.

Results

The odds ratios (ORs) for females (OR = 1.63; based on 621 patients, 3747 controls) and males (OR = 1.50; based on 1213 patients, 3800 controls) differed significantly from 1.0, indicating both female and male patients were more often non-right-handed than controls. Moreover, there was an excess of non-right-handedness in patients with schizophrenia when handedness was assessed behaviourally: OR = 1.84 (1255 patients, 6260 controls). Even when both gender and behavioural handedness assessment were controlled for simultaneously, the excess of non-right-handedness persisted.

Conclusions

The findings clearly demonstrate that the excess of non-right-handedness in schizophrenia does not result from a gender artefact or from biased handedness questionnaires. It is a true empirical effect and may indeed reflect a genetic link between schizophrenia and brain lateralisation.

Declaration of interest

None.

'Sinister psychotics' is the title of an article by Taylor & Amir¹ and it refers to the idea that there is a relatively higher percentage of non-right-handers in schizophrenia compared with healthy individuals. This excess of non-right-handedness is a cornerstone for the assumption that schizophrenia is characterised by – some argue even caused by² – a lack of lateralisation. Indeed, a number of studies have found non-right-handers to be overrepresented in schizophrenia.^{3,4–6} However, there are also null findings^{7,8} and even reports of fewer non-right-handers in schizophrenia samples.^{9,10} A meta-analysis by Sommer *et al*¹¹ revealed significant odds ratios (ORs) in the range of OR = 1.48–1.61, indicating that the odds of being non-right-handed were approximately 1.5 times higher in schizophrenia than in healthy individuals or other psychiatric control patients. This was confirmed in another meta-analysis by Dragovic & Hammond,¹² in which left- and mixed-handers (i.e. individuals with no consistent hand preference) were overrepresented in schizophrenia (OR = 1.5–1.8). These systematic reviews suggest that patients with schizophrenia are indeed more 'sinister' than controls, corroborating Crow's theory.^{2,13} However, critics have argued that the higher prevalence of non-right-handedness would disappear if gender and/or biases in self-report handedness questionnaires are controlled for.

A gender artefact?

Schizophrenia research samples typically consist of more male than female patients and in the general population there are more non-right-handed males (about 12%) than females (about 10%) (for review see Papadatou-Pastou *et al*¹⁴). Thus, unless control groups are matched for gender (or gender is taken into account statistically), most likely one will find a higher proportion of

non-right-handers in the schizophrenia compared with the control sample. Indeed, Buijsrogge *et al*¹⁵ reported that the excess of non-right-handedness in schizophrenia disappeared when gender was taken into account, but the sample was relatively small (73 patients and 81 controls). More recently, Deep-Soboslay *et al*¹⁶ replicated this finding with a total of 1445 participants (375 patients with schizophrenia) and concluded that 'theories of schizophrenia based on anomalous lateralization related to handedness are unsupported by our data' (p. 3120). On the other hand, Cannon *et al*⁴ found increased rates of non-right-handedness, although gender was statistically controlled for, and other studies with gender-matched control groups also reported an excess of non-right-handers.^{3,5,6} However, there are also examples of studies with gender-matched samples which did not find an increased rate of non-right-handers.^{17,18} To add further confusion, some studies report an excess of non-right-handedness in either only female^{19,20} or male patients with schizophrenia.^{21,22} To summarise, the literature is highly inconsistent and it cannot be ruled out that the excess of non-right-handers in schizophrenia is a gender artefact. Moreover, it is unclear whether there is, in fact, a gender difference with respect to non-right-handedness. That is, whether both males and females with schizophrenia are more likely to be non-right-handed. The two meta-analyses^{11,12} did not resolve this matter, because they did not control for gender as a mediating factor.

Biases in handedness questionnaires?

Dragovic & Hammond¹² did not find an excess of non-right-handedness when Annett's hand preference questionnaire²³ was used (OR = 1.0–1.2). Conversely, studies using the Edinburgh

Handedness Inventory (EHI)²⁴ revealed that the odds of being non-right-handed were about three times higher in patients with schizophrenia than in controls. Although both questionnaires consist of similar items, it has been demonstrated in healthy controls that the EHI produces significantly more ‘either hand’ responses than Annett’s questionnaire.^{25,26} This discrepancy might be rooted in the instructions of the EHI,²⁶ which encourage participants to indicate ‘either hand’ responses, whereas such a statement is missing in the instructions for Annett’s questionnaire. If patients with schizophrenia have a higher propensity to follow this instruction, this would lead to an excess of non-right-handedness, especially mixed-handedness. We could only find one study that assessed handedness with both Annett’s questionnaire and the EHI.²⁷ Here, however, participants did not fill in the questionnaires. They either demonstrated the questionnaire items (i.e. performing the actions as described in the items) or they gave verbal responses, which makes comparison with self-report questionnaires difficult. Moreover, verbal responses on Annett’s questionnaire items were not consistently recorded and data were missing for a few participants. Byrne *et al*²⁷ found that there were more mixed-handed controls when handedness was based on verbal reports than when it was based on demonstration. In other words, controls rated themselves less left- or right-handed than the behavioural assessment implied. No such effect was found in schizophrenia, but there were only 17 patients, as the main focus was on participants with a high risk of developing schizophrenia ($n = 115$). Interestingly, the high-risk participants also rated themselves more mixed-handed than the behavioural assessment implied.

The findings of Byrne *et al*²⁷ do not resolve the discrepancy between the EHI and Annett’s questionnaire,¹² but they point to yet another problem: participants may not always report their handedness accurately. This applies especially to patients with schizophrenia, whose completion of handedness questionnaires might be affected by cognitive deficits and, perhaps, a higher propensity for mixing up ‘left’ with ‘right’.²⁸ There are, in fact, reports in the literature that support such a notion. For example, Wahl⁷ found that the significant excess of non-right-handedness disappeared on exclusion of all participants who showed a mismatch between handedness based on self-report and based on observation. In another article, the authors⁹ noted: ‘Two females and eight males, all right-handed writers, had right-left confusion and consistently referred to their right hand as their left hand’ (p. 376). We do not go so far as arguing that the majority of patients cannot correctly self-report their handedness. The two examples, however, highlight that handedness determined with self-report questionnaires, particularly in patients with schizophrenia, might indeed lack validity.

In summary, there are indications that the higher prevalence of non-right-handedness in schizophrenia might be the result of biases and/or invalid responses in self-report handedness questionnaires. It would be interesting to further investigate why the excess of non-right-handedness in schizophrenia only emerges for the EHI and not Annett’s questionnaire.¹² However, given the findings of Byrne *et al*,²⁷ behavioural assessment seems a far more reliable method to determine handedness. So far it has not been investigated in a systematic, quantitative way whether studies that assessed handedness behaviourally also show an excess of non-right-handedness in schizophrenia.

New meta-analyses

There are reasons to question the excess of non-right-handedness in schizophrenia. Reviews^{13,29} and meta-analyses^{11,12} propagating this excess might be subject to a gender artefact and/or biases and validity problems related to self-reported handedness. This would

have far-reaching consequences, since the excess of non-right-handedness is a key argument for the theory that schizophrenia is characterised or even caused by anomalous lateralisation. As a consequence, we carried out three separate meta-analyses. These analyses addressed whether the excess of non-right-handedness in schizophrenia persists when (a) gender is taken into account, (b) handedness is assessed behaviourally, and (c) both factors are taken into account simultaneously. In addition, the present study provides an update of previous meta-analyses^{11,12} by including more recent studies.

Method

Literature search and study selection

The platforms PubMed, ISI Web of Knowledge and PsycINFO were searched with the key words “schizophrenia”, “handedness”, “sex” and “gender” between January and March 2013 (for the full electronic search strategy, see the online supplement to this paper). Moreover, we examined the studies included in Dragovic & Hammond¹² and Sommer *et al*¹¹ and contacted authors of recent articles with substantial sample sizes to obtain additional information on the handedness of their female and male participants. In principle, we had no restrictions regarding study language but the meta-analysis contains only English articles, presumably as a result of conducting most of the literature search via English platforms. We applied the following inclusion criteria.

Diagnosis of schizophrenia

We did not restrict the meta-analysis to studies that used DSM or ICD criteria, because this would exclude older studies that investigated handedness in schizophrenia before DSM was introduced and because the core symptoms of schizophrenia (hallucinations, delusions, negative symptoms) have changed relatively little over the last decades. We did not include psychiatric disorders other than schizophrenia and, if possible, only included ‘pure’ schizophrenia cases and not schizophreniform or schizoaffective cases. However, if handedness was only available for patients with schizophrenia, schizophreniform and schizoaffective disorder combined, then the combined handedness data were included.

Number of patients and controls that were right- and non-right-handed

In cases where percentages were reported (e.g. 5% non-right-handers), these were transformed into integers. For the meta-analysis that specifically examined gender effects, only studies that reported the exact number (or percentages) of female and male participants were included.

Control group

Dragovic & Hammond¹² included studies in which the schizophrenia sample was matched with a control sample obtained from other studies to increase the number of available studies. We took a more restrictive approach (see also Sommer *et al*¹¹), because we wanted to make sure not only that the same handedness test was used, but that it was also applied under similar circumstances by the same experimenters. If there were two control groups, one comprising healthy siblings and the other random healthy controls, the two groups were combined. Studies including patients with psychiatric disorders as controls were excluded.

Patient and control samples were not matched for handedness. Studies were excluded if control samples were described as 'handedness-matched' or 'matched for handedness', because this does not represent a natural proportion of right- and non-right-handers. We did not exclude studies that specifically stated they were gender-, age-, education- or ethnicity-matched but did not include handedness in the list of matching factors. We also included four studies that described their controls as 'similar' or 'comparable' to patients with schizophrenia in handedness,^{30–33} as participants were apparently not actively matched for handedness.

Patient and control samples did not solely consist of right-handers

Several studies, particularly neuroimaging studies, tested only right-handed participants. We excluded those studies because it is unclear whether only right-handed participants were recruited or whether participants were randomly selected and just happened to be all right-handed.

Reporting bias

The final two criteria were implemented to reduce the risk of selection bias (i.e. systematic differences between baseline characteristics of participants) and were checked in every eligible study. Moreover, we checked every eligible study for duplicates and sample overlaps to reduce the risk of reporting bias. Handedness assessment is very basic and the questionnaires and behavioural tasks used to assess it leave examiners very little room for subjective decisions. Therefore 'masking' participants or examiners to prevent a detection or performance bias did not seem vital. Finally, to investigate the robustness of effects and to address the reporting bias *across* all studies we computed Rosenthal's fail-safe n .³⁴ The data extraction and statistical analysis were carried out by M.H.

Handedness

In the literature, the by far most common and prolific comparison is between right- and non-right-handers (i.e. left- plus mixed-handers, see also Sommer *et al*¹¹). However, there is disagreement whether schizophrenia is marked by a general excess of non-right-handedness that includes left- and mixed-handedness¹² or a specific excess of only mixed-handedness.^{20,29,35} As a result, we provide separate meta-analyses for left- and mixed-handedness in the online supplement.

Statistical analyses

For each study, ORs were computed so that a value of 1 indicates equal handedness proportions in patients with schizophrenia and controls, OR < 1 indicates an excess of non-right-handedness in controls, and OR > 1 indicates an excess of non-right-handedness in patients.

In the first analysis we only included studies that provided handedness information for female and male participants (regardless of how handedness was assessed) to investigate whether the excess of non-right-handedness in schizophrenia is a gender artefact. This also enabled us to test whether there is a gender difference with respect to handedness in schizophrenia. In the second analysis, we examined whether behavioural assessment yields an excess of non-right-handedness and whether this excess is greater or smaller than in other forms of handedness assessment (regardless of gender). Finally, we combined gender and behavioural assessment: that is, we examined whether those

studies that assessed handedness behaviourally *and* provided handedness information for male and female participants also revealed an excess of non-right-handedness.

The criteria for handedness categorisation vary substantially across studies. In addition, different diagnostic systems were used, samples were collected in several different countries, and the studies cover a time period of almost 40 years. As a result we chose a random effects model to compute the summary effect *within* a group (e.g. females) assuming the true effect is not the same in each study. By contrast, when we combined the summary effects to compute an overall effect *across* groups we used a fixed-effects model, since effect sizes can only fall in one of two categories (female or male, behavioural or other forms of assessment). This is called a mixed-effects model and follows the recommendations of Borenstein *et al*.³⁶ The variance was assumed to be the same for all subgroups (i.e. Cochran's Q and I^2 as indicators for heterogeneity were computed within subgroups and then pooled across groups). The meta-analysis was carried out with Comprehensive Meta-Analysis software for Windows version 2.0.³⁷

Results

In total, 540 references were screened. The 50 studies that were included in the meta-analysis^{4,7,16,18,19,21,22,27,30,31,35,38–74} are provided in the online supplement (Table DS1) and a comprehensive overview of the study selection process is provided in Fig. 1.

Controlling for gender

There were 33 effect sizes covering data from 1834 patients with schizophrenia and 7547 controls, 16 effect sizes for females (patients: $n = 621$, controls: $n = 3747$) and 17 effect sizes for males (patients: $n = 1213$, controls: $n = 3800$). In females, an OR of 1.63 with a 95% confidence interval (CI) of 1.16–2.30 emerged that deviated significantly from 1 ($Z = 2.80$, $P = 0.005$), suggesting an excess of non-right-handedness in schizophrenia. The same pattern was found in males (OR = 1.50, 95% CI 1.14–1.99, $Z = 2.84$, $P = 0.004$) and the difference between females and males did not become significant ($Q(1) = 0.13$, $P = 0.722$). The combined, overall effect also became significant (OR = 1.55, 95% CI 1.25–1.93, $Z = 3.97$, $P < 0.0001$) demonstrating that, in general, the odds of being non-right-handed are 1.5 times higher in schizophrenia than in the control group when gender is accounted for (Fig. 2). The overall variance across studies I^2 (pooled across subgroups) was 1.78 ($Q(32) = 32.58$). Rosenthal's fail-safe n for the overall effect is 216; thus 216 studies with a null effect (OR = 1) would be required to offset the overall effect.

Behavioural assessment of handedness

Handedness was behaviourally assessed in 1308 patients and 6280 controls (11 effect sizes). Other forms of handedness assessment were available for 2714 patients and 5711 controls (39 effect sizes); thus we had data for 4022 patients and 11 991 controls in total. Both behavioural assessment (OR = 1.90, 95% CI 1.42–2.53, $Z = 4.35$, $P < 0.001$) as well as other forms of handedness assessment (OR = 1.39, 95% CI 1.15–1.69, $Z = 3.39$, $P = 0.001$) revealed significantly greater non-right-handedness in schizophrenia patients than in healthy controls (online Fig. DS1). As expected, the overall effect was also clearly significant (OR = 1.53, 95% CI 1.31–1.80, $Z = 5.23$, $P < 0.001$, $I^2 < 0.01$, $Q(49) = 46.36$) resulting in a fail-safe $n = 481$. There was a trend towards greater non-right-handedness in schizophrenia when handedness was assessed behaviourally ($Q(1) = 3.05$, $P = 0.081$).

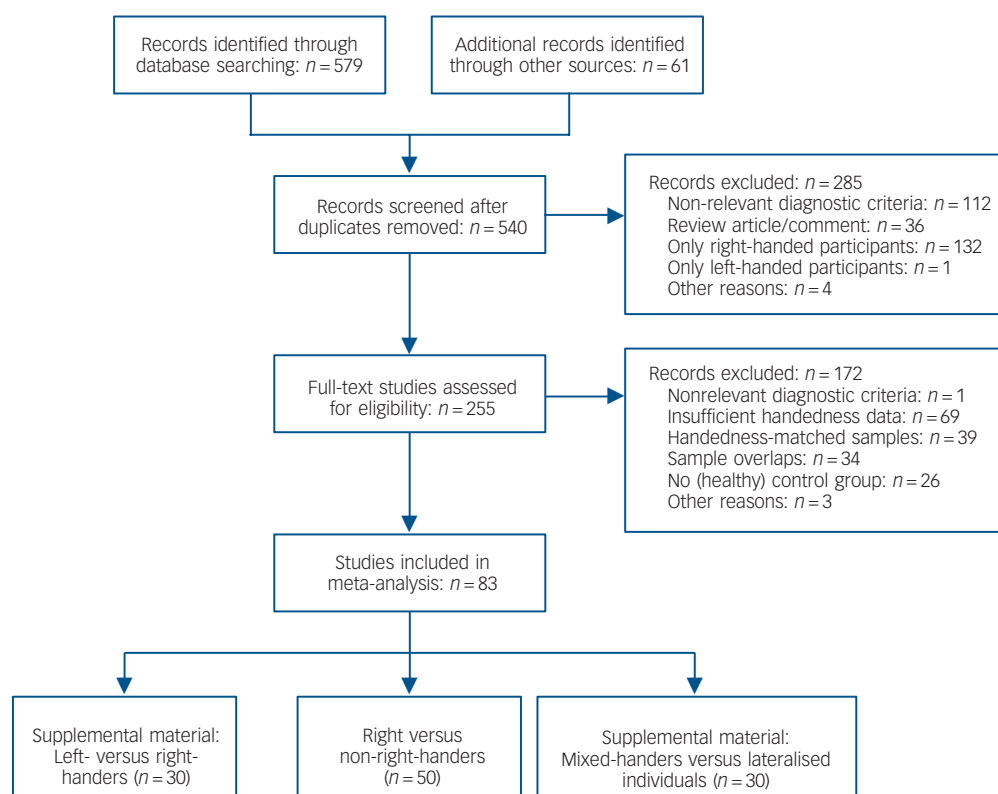


Fig. 1 Selection procedure for the present meta-analysis on handedness in schizophrenia.

Gender effects and behavioural assessment of handedness combined

Eight studies reported the exact number of right- and non-right-handed females (patients: $n = 428$, controls: $n = 3468$) and males (patients: $n = 819$, controls: $n = 3458$) and assessed handedness behaviourally. As shown in Fig. 3, females (OR = 1.98, 95% CI 1.25–3.14) differed significantly from 1 ($Z = 2.89$, $P = 0.004$) and in males a trend towards greater non-right-handedness in schizophrenia emerged (OR = 1.45, 95% CI 0.98–2.15, $Z = 1.85$, $P = 0.065$). The difference between the two was not significant ($Q(1) = 1.01$, $P = 0.315$) and the combined, overall effect confirmed that schizophrenia patients were more likely to be non-right-handed than controls (OR = 1.65, 95% CI 1.22–2.23, $Z = 3.28$, $P = 0.001$, $I^2 < 0.01$, $Q(15) = 14.34$). To offset the overall effect 78 studies with a null effect would be necessary.

Discussion

The present study investigated in a meta-analytical approach whether the excess of non-right-handedness in patients with schizophrenia is confounded by gender^{15,16} and/or biases in self-report handedness²⁷ and the results were unequivocal: patients are indeed more likely to be non-right-handed than controls and this is neither the result of a gender artefact nor of biases in handedness questionnaires.

No gender artefact or handedness assessment bias

It is tempting to assume that the excess of non-right-handedness in schizophrenia is a gender artefact when one considers that males are more often non-right-handed than females in the general population, and that in schizophrenia samples there are often more males than females. Indeed, the present study also found

66% males in the schizophrenia and 50% males in the control sample. However, this imbalance could not account for the excess of non-right-handedness: both female and male patients with schizophrenia had significant ORs of about 1.6. Moreover, we did not find significant gender differences. This argues against claims that the excess of non-right-handedness in schizophrenia only exists in either females^{19,20} or males.^{21,22} The present study also clearly demonstrated that there is a surplus of non-right-handers in schizophrenia, if handedness is assessed behaviourally. In fact, there was a trend for higher ORs when handedness was assessed behaviourally than compared with other forms of handedness, of which the vast majority were self-report handedness questionnaires. Thus, if anything, the excess of non-right-handedness is even bigger than self-report questionnaires suggest. Finally, even when possible confounding gender and handedness assessment effects were controlled for simultaneously, we observed a significant excess of non-right-handedness in females, a trend in males, and a highly significant combined effect.

Converging evidence

The ORs obtained in the present study were in the range of 1.4–2.0. This very well matches the findings from two previous meta-analyses.^{11,12} One might wonder whether this is simply the consequence of including similar studies. However, although there is naturally some overlap across the three meta-analyses, the difference in study selection is considerable. This is due to different inclusion criteria, new studies (at least 15 studies between 2005 and 2013 were added), and a different research focus (gender differences). Thus, there is compelling converging evidence that the excess of non-right-handedness in schizophrenia truly exists and that it has a magnitude centring around OR = 1.6. That is, if 10% of the healthy population is non-right-handed,

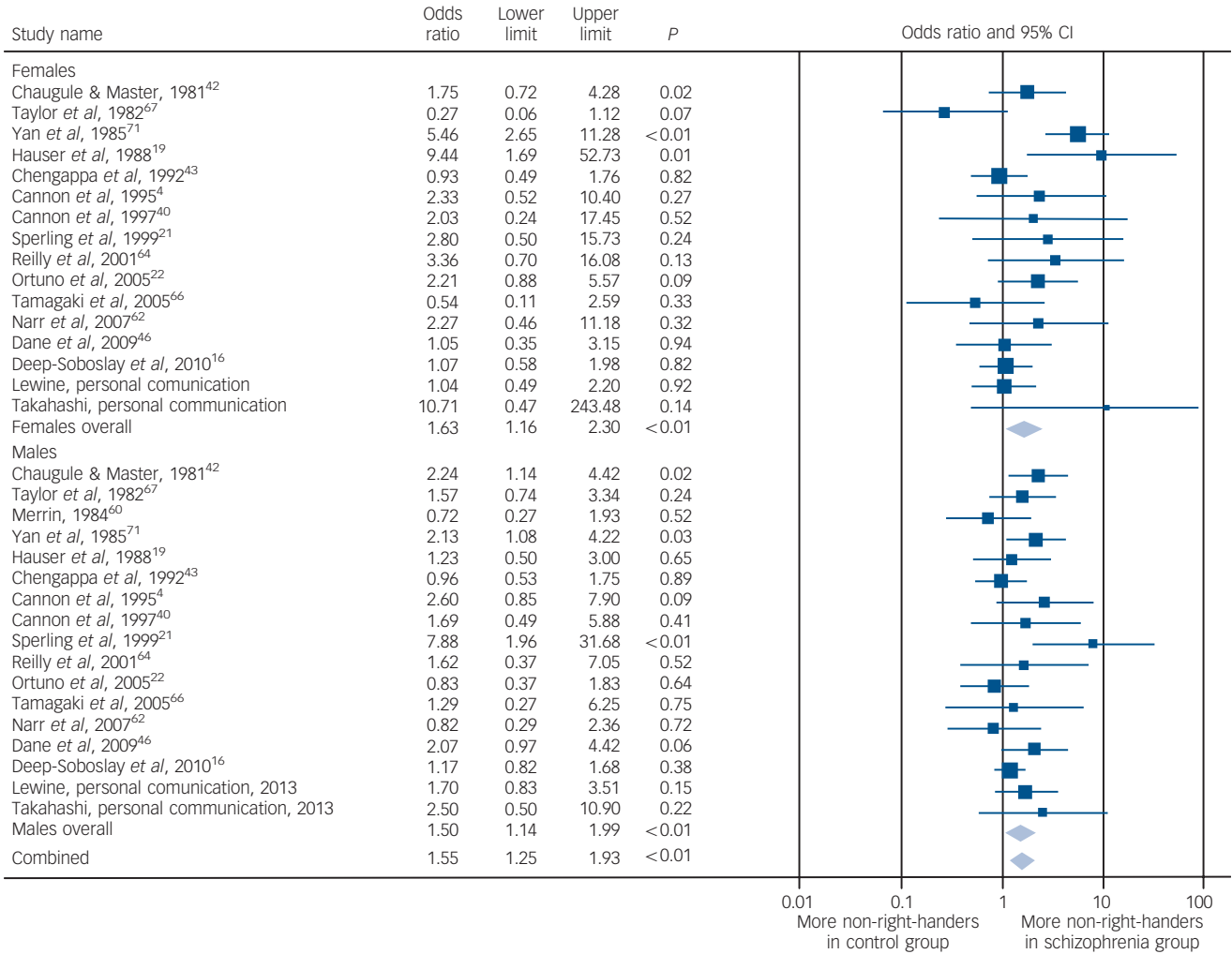


Fig. 2 Forest plot for non-right-handedness in males v. females.

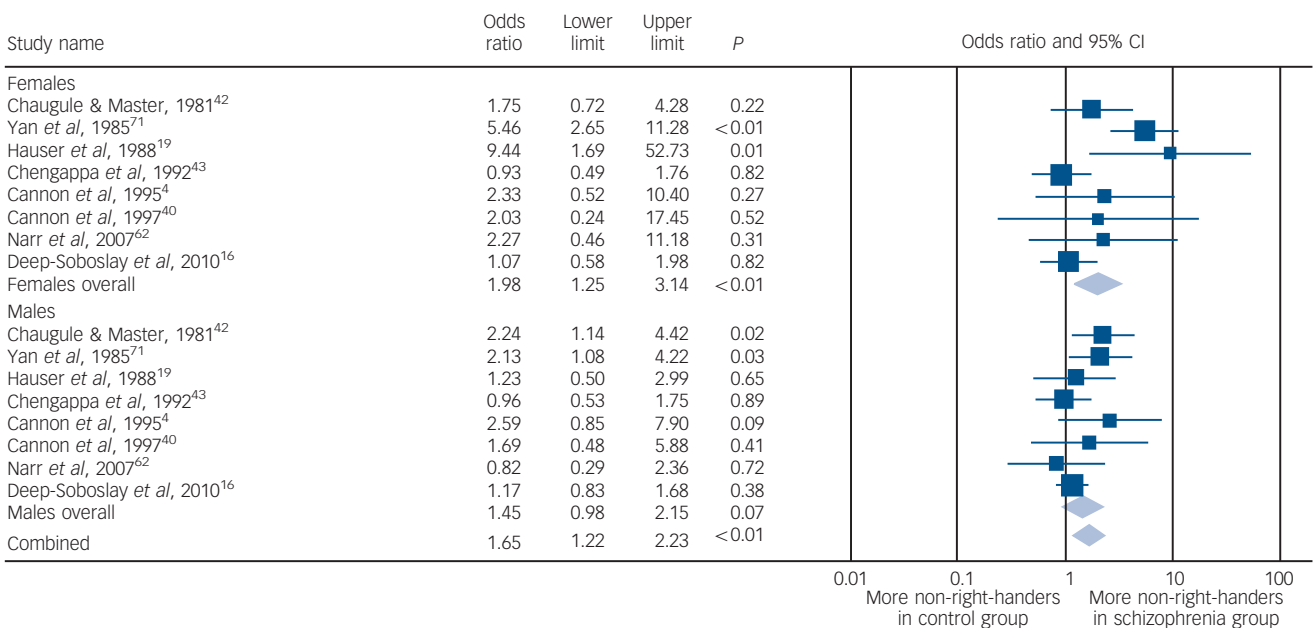


Fig. 3 Forest plot for non-right-handedness in males v. females when handedness was assessed behaviourally.

then approximately 15% of patients with schizophrenia are non-right-handed. An OR=1.6 is a small effect (Cohen's $d=0.26$) but Rosenthal's fail-safe n suggest that it is fairly robust. For instance, it would require 78 studies with null findings to abolish the excess of non-right-handedness when the participants' gender is included and handedness assessed behaviourally. The number is even higher for gender ($n=216$) and behavioural handedness assessment alone ($n=481$).

No excess in consistent left-handers

The main focus of the present study was on non-right-handedness, but the results for left- and mixed-handedness revealed similar results (see online supplement). Interestingly, however, there was no excess of patients with schizophrenia when strong left- *v.* strong right-handers was compared (with all mixed-handers excluded). This would suggest that the excess in left-handedness is mainly driven by left-handers with a weak hand preference and that degree not direction of handedness is linked to schizophrenia, supporting the notion that schizophrenia is mainly characterised by an 'absence' or 'lack' of hemispheric specialisation.² On the other hand, statistical power to detect an excess was much lower in the strong left- *v.* strong right-handers as compared with the general left- *v.* right-handers analysis. Thus we are a bit cautious with claiming that the excess of non-right-handedness in schizophrenia is only present in mixed- and not left-handers.

Genetic link

It has been suggested that the excess of non-right-handedness in schizophrenia is the result of subtle brain damage,²⁹ but there is little support for this notion.¹² As McManus⁷⁵ pointed out, it is generally questionable whether pathological left-handedness exists. The genes and exact mechanism that underlie handedness have not been identified, but the empirical evidence clearly demonstrates that hand preference is under strong genetic influence.^{76,77} The most plausible explanation is thus that the genetic origin of non-right-handedness is linked to schizophrenia as suggested by Crow.^{2,78}

As with all meta-analyses, the findings of the present study are dependent on the studies that were included. We used quite restrictive selection criteria similar to Sommer *et al.*,¹¹ but the fact that Dragovic & Hammond¹² found similar results with more liberal criteria implies that the excess of non-right-handedness is a reliable finding. We did not include studies with psychiatric control participants, because we wanted to specifically investigate whether non-right-handedness is overrepresented in schizophrenia as compared with healthy controls. It would be interesting to examine, however, whether this excess is specific to schizophrenia or also emerges in other psychiatric patients. Dragovic & Hammond¹² included psychiatric samples but did not specifically compare them with patients with schizophrenia. A recent study⁷⁹ reported that the prevalence of left-handedness in schizophrenia is 40% compared with 11% for patients with mood disorder (OR=7.9), rather implying the excess of non-right-handedness is typical for schizophrenia. One may argue that due to the large variability in handedness assessment and categorisation, it is questionable whether those studies can be compared and aggregated. We tried to resolve this issue statistically by assuming a random-effects model, in which the true underlying effect can differ from study to study. Finally, it should be pointed out that handedness is only one marker of lateralisation and the finding of an excess of non-right-handedness in schizophrenia – however robust it is – only suggests that brain

lateralisation and schizophrenia are linked. The literature on neuroscientific evidence for abnormalities in structural or functional hemispheric asymmetries is less rich and consistent than the excess of non-right-handedness. Recently, however, Crow⁸⁰ provided an overview of neuropsychological and neuroimaging findings that, taken together, suggest anomalous lateralisation in schizophrenia also manifests in the brain.

We took great care to minimise the risk for the selection and reporting bias. On the individual study level, we checked whether samples had been pre-selected for handedness. Studies were excluded when samples consisted solely of right- or left-handers and when studies stated they had handedness-matched samples without specifying whether the matching was intended or coincidence. The vast majority of studies with only right-handers (or left-handers) were neuroimaging studies and from our own experience in this field we know that often only right-handers are recruited to keep the study design simple and to avoid large variance in the data. Moreover, since handedness is believed to be associated with schizophrenia, many researchers make sure that their studies have handedness-matched samples. We thus believe we had good reasons to exclude those studies to prevent a selection bias, but it may be argued that excluding them represents a selection bias itself, and the OR would be lower, if they were admitted to the meta-analysis. One may also argue that there is a risk of a reporting bias since publishing studies with significant handedness effects may be easier. We aimed to control for that statistically across all studies by calculating Rosenthal's fail-safe n and indeed find it hard to believe that up to 481 studies with null findings have been gathering dust in file drawers.

In summary, the present study clearly demonstrated that patients with schizophrenia are more often non-right-handed and that this cannot be attributed to a gender artefact or hidden biases in handedness questionnaires. With both points of criticism disproven, there is little doubt left that the excess of non-right-handedness truly exists, which strongly supports the view that there is a genetic link between handedness, brain lateralisation and schizophrenia.² In addition, the present data indicate that the excess of non-right-handedness is mostly the consequence of a higher proportion of mixed- rather than left-handers, suggesting that strength of handedness rather than direction is linked to schizophrenia.

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Marco Hirnstein, PhD, Department of Biological and Medical Psychology, University of Bergen; **Kenneth Hugdahl**, PhD, Department of Biological and Medical Psychology, University of Bergen, and Division of Psychiatry and Department of Radiology, Haukeland University Hospital, Bergen, Norway

Correspondence: Dr Marco Hirnstein, Department of Biological and Medical Psychology, University of Bergen, Jonas Lies vei 91, 5009 Bergen, Norway. Email: marco.hirnstein@psybpb.uib.no

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