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Handedness in Mental and Neurodevelopmental Disorders: A Systematic Review and Second-Order Meta-Analysis

Julian Packheiser[1, 2], Jette Borawski[3, 4], Gesa Berretz[5], Sarah Alina Merklein[3, 4], Marietta Papadatou-Pastou[6, 7], and Sebastian Ocklenburg[3, 4]

[1] Department of Social Neuroscience, Faculty of Medicine, Ruhr University Bochum
[2] Research Center One Health Ruhr of the University Alliance Ruhr, Ruhr University Bochum
[3] Department of Psychology, Medical School Hamburg
[4] ICAN Institute for Cognitive and Affective Neuroscience, Medical School Hamburg
[5] Computational Neuroscience Lab, Donders Institute for Brain, Cognition and Behavior, Radboud University
[6] School of Education, National and Kapodistrian University of Athens
[7] Biomedical Research Foundation, Academy of Athens, Athens, Greece

Several meta-analyses on hand preference in mental and neurodevelopmental disorders have been published in the last decade. Some disorders, like schizophrenia, have been associated with increased rates of atypical hand preference (i.e., non-right-, left-, or mixed-hand preference)—but others, like depression, have not. To identify overarching patterns between hand preference and psychopathology and estimate the influence of potential moderators independent of diagnosis, we need to leverage rich information in the databases of these meta-analyses and conduct a higher level of analysis of meta-analytic data across diagnoses. To this end, we performed a second-order meta-analysis after reviewing, updating, and reanalyzing previously published meta-analyses on hand preference in various mental and neurodevelopmental disorders. In total, this study includes 402 data sets totaling 202,434 individuals. On average, atypical hand preference had a significantly higher frequency in cases compared to controls (nonright odds ratio [*OR*]: 1.46, 95% CI [1.35, 1.59]; left *OR*: 1.34, 95% CI [1.22, 1.48]; mixed *OR*: 1.63, 95% CI [1.38, 1.93]). Further analyses indicated that case–control differences varied with diagnosis. Some diagnoses, like schizophrenia, are associated with a high frequency of atypical hand preference (nonright *OR*: 1.50, 95% CI [1.32, 1.70]; left *OR*: 1.37, 95% CI [1.17, 1.61]; mixed *OR*: 1.70, 95% CI [1.19, 2.44]). Moderator analyses showed that neurodevelopmental conditions, nonneurodevelopmental conditions with an early age of onset, and conditions that include symptoms related to language were all associated with higher rates of atypical hand preference. This finding suggests that the association between handedness and clinical conditions is best understood from a transdiagnostic, developmental, and symptom-focused perspective.

Public Significance Statement

This preregistered second-order meta-analysis of previously published meta-analyses strongly suggests that case–control differences in handedness vary with diagnosis. Neurodevelopmental conditions, nonneurodevelopmental conditions with an early age of onset and conditions that include language symptoms showed higher rates of non-right-hand preference and left-hand preference. This suggests that the association between handedness and clinical conditions is best understood from a transdiagnostic, developmental, and symptom-focused perspective. From a public health perspective, our study illustrates the potential and the limitations of using handedness as a biomarker for mental and neurodevelopmental conditions. Furthermore, our study highlights that leveraging databases from existing systematic reviews and meta-analyses while applying identical analysis pipelines as performed in this study is an essential step to improve public trust in scientific findings due to the increased robustness of the findings.

Keywords: handedness, lateralization, brain asymmetry, mental health, meta-analysis

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Blair T. Johnson served as action editor.
Julian Packheiser https://orcid.org/0000-0001-9805-6755
Jette Borawski https://orcid.org/0009-0004-2703-9754
Gesa Berretz https://orcid.org/0000-0002-3513-1946
Sarah Alina Merklein https://orcid.org/0009-0002-7952-8088
Marietta Papadatou-Pastou https://orcid.org/0000-0002-2834-4003
Sebastian Ocklenburg https://orcid.org/0000-0001-5882-3200
Papadatou-Pastou and Sebastian Ocklenburg shared last authorship.

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continued

One of the most intriguing features of the human motor system is the fact that almost everyone prefers to use one hand over the other for fine motor tasks like handwriting (McManus, 2019; Ocklenburg & Güntürkün, 2024). At first glance, handedness appears to be a straightforward construct, when in fact it is a multifactorial trait conceptualized in various ways. The two primary conceptualizations are hand preference, the individual's preference to use one hand predominantly in unimanual tasks, and hand skill difference, reflecting the relative efficiency, speed, or strength of one hand compared to the other. Handedness is typically employed as the umbrella term to encompass both of these concepts (Ocklenburg & Güntürkün, 2024; Papadatou-Pastou, 2011; Vingerhoets et al., 2023). Additionally, handedness can be understood in terms of both direction (e.g., left vs. right) and degree (e.g., weak vs. strong).

Handedness can be quantified continuously as well as categorically (Vingerhoets et al., 2023). For studies that classified individuals categorically and used a binary classification system for hand preference, a large-scale meta-analysis on handedness showed that 10.6% of people are left-handed and 89.4% are right-handed (Papadatou-Pastou et al., 2020). For studies that used a three-category classification scheme of handedness (left-handedness, mixed-handedness, and right-handedness), the meta-analysis showed that 9.49% of people were mixed-handed, 9.33% were left-handed, and the remaining 81.18% were right-handed. The proportion of left-handed females compared to right-handed females in the population is estimated to be around 10%. In males, this proportion is estimated to be around 12% (Papadatou-Pastou et al., 2008).

There is a substantial amount of evidence indicating that handedness is an early developmental trait, both from a phylogenetic and an ontogenetic perspective. In terms of phylogenesis, evidence suggests that the development of the right-hand bias occurred over the last 7 million years (Uomini & Ruck, 2018). Ontogenetically, hand preference appears prenatally, with prenatal thumb sucking being related to postnatal hand preference (Hepper et al., 2005). Moreover, handedness seems to be a unique characteristic of humans, as they appear to be almost the only species that exhibits such a strong population-level tendency to favor one limb over its opposite (Guerra et al., 2024). That being said, handedness, or more generally limb preferences, can also be observed in nonhuman animal species, albeit more often at the level of the individual organism rather than the population level (e.g., Güntürkün & Ocklenburg, 2017).

There are several reasons why psychologists, neuroscientists, and medical practitioners investigate handedness in their research. For example, handedness is highly relevant for research on the organization of the motor system (Sha et al., 2021). It is also necessary to address applied questions such as whether special training programs are needed for left-handed surgeons (Denison et al., 2023). Moreover, handedness represents a frequently used phenotype in research on the genetics of brain asymmetries, as it is easy to assess, and is thus included in many large-scale biomedical databases, such as the U.K. Biobank (Cuellar-Partida et al., 2021). Furthermore, handedness can be of interest in educational psychology, as left-handed pupils may have specific demands when learning how to write (Kula, 2008). Handedness is also relevant in neuroimaging research on cognitive functions as it shows correlations with other functional hemispheric asymmetries, mainly in the language domain. Left-handed individuals show atypical rightward language lateralization to a greater extent than right-handed individuals (Knecht et al., 2000).

In addition to the above, one of the core reasons why there is a continued interest in handedness research in the scientific community engaged in psychological research is the potential clinical relevance of handedness (Ocklenburg et al., 2024). It is an intriguing observation that in several mental and neurodevelopmental disorders, such as schizophrenia, posttraumatic stress disorder (PTSD), or attention deficit hyperactivity disorder (ADHD), as well as learning disabilities, such as stuttering, or dyslexia, handedness is altered compared to the general population (Mundorf & Ocklenburg, 2021). Over the course of the last decades, several case–control meta-analyses, focused on investigating handedness in a single disorder or learning disability, have been published. The investigated conditions include ADHD (Nastou et al., 2022), autism (Markou et al., 2017), depression (Packheiser et al., 2021), dyscalculia (Papadatou-Pastou et al., 2021), dyslexia (Packheiser et al., 2023), intellectual disability (ID; Papadatou-Pastou & Tomprou, 2015), pedophilia (Stein et al., 2023), PTSD (Borawski et al., 2023), schizophrenia (Hirnstein & Hugdahl, 2014), and stuttering (Papadatou-Pastou et al., 2023). Importantly, most, but not all, of these meta-analyses reported significant case–control differences in handedness in the same direction. Although no meta-analysis found an increase in right-handedness in cases, the majority of studies reported a significant increase in atypical handedness (non-right-, mixed- and/or left-handedness). Interestingly, for some conditions, like depression and dyscalculia, the meta-analyses did not report any significant case–control differences regarding handedness.

Handedness is determined by both genetic and nongenetic factors (Medland et al., 2009). The major psychiatric disorders show moderate to high genetic correlations, but also independent genetic contributions (Grotzinger et al., 2022). Molecular genetic studies in both common genetic variants (Cuellar-Partida et al., 2021) and rare genetic variants (Schijven et al., 2024) have shown genes relevant

Papadatou-Pastou and Sebastian Ocklenburg conceptualized the study, searched for and collected data, supervised the study, and wrote the article. All authors reviewed and edited the article.

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Correspondence concerning this article should be addressed to Sebastian Ocklenburg, Department of Psychology, Medical School Hamburg, Am Kaiserkai 1, 20457 Hamburg, Germany. Email: sebastian.ocklenburg@medicalschool-hamburg.de

for several specific conditions are also relevant for the ontogenesis of handedness. In the largest genome-wide association study on handedness to date (Cuellar-Partida et al., 2021), a positive genetic correlation between left-handedness and schizophrenia disorder was reported. A recent exome-wide analysis of rare genetic variants implicated that rare variants in genes previously associated with autism and schizophrenia are also relevant for left-handedness (Schijven et al., 2024). Thus, some disorders, like autism and schizophrenia, may show a stronger genetic overlap with handedness than others, which may explain why these disorders show a strong link to atypical handedness though others do not.

In parallel to genetic factors, environmental factors may play a role in the link between handedness and clinical conditions. For example, early life stress is an environmental factor that has been implicated in both the pathogenesis of various psychiatric disorders and the development of handedness (Berretz et al., 2020). From a developmental perspective, there is clear evidence that the development of handedness starts early in life, even prenatally (Michel et al., 2013). This fact strongly suggests that neurodevelopmental disorders that cause substantial early life stress may be a relevant factor for the association between handedness and clinical conditions (Berretz & Packheiser, 2022). Therefore, neurodevelopmental conditions that typically have an early age of onset could be predicted to have a higher rate of atypical handedness than other disorder groups that are not affecting neurodevelopment. Also, focusing on nonneurodevelopmental conditions and thus stressors emerging in later life stages, those conditions with an earlier age of onset should on average have a higher level of atypical handedness than those with a later age of onset. This is because earlier-onset conditions affect neurodevelopment to a larger degree as neurodevelopment is typically considered to last until early adulthood (de Graaf-Peters & Hadders-Algra, 2006).

It has also been suggested that within a transdiagnostic Research Domain Criteria perspective, certain symptoms that can be part of several different diagnoses may be linked to brain asymmetries (Nusslock et al., 2015). Research Domain Criteria is a classification framework for research on mental disorders (Insel et al., 2010; Williams et al., 2024) that is based on the biology underlying mental disorders. It is not focused on diagnoses like traditional classification systems for mental disorders but focuses on six functional domains that underlie behavior and brain function (arousal, positive valence, negative valence, social processes, sensorimotor functions, and cognitive functions). The strengths of this approach in research and clinical practice are preventing issues related to diagnostic heterogeneity and comorbidity due to symptoms overlapping between diagnoses. Moreover, in the context of clinical research on handedness, it can help identify overarching environmental influences or developmental processes that affect handedness independent of diagnosis.

The language system is well-known to be asymmetrically organized within the brain as most individuals show a left-hemispheric dominance in language processing and production (Corballis et al., 2012). Previous studies have shown that language asymmetries and motor asymmetries in the brain show substantial correlations (Karlsson et al., 2023) and are thus likely strongly interlinked (Steinmetz et al., 1991). It is, therefore, reasonable to assume that conditions that especially impact the language system, that is, show symptoms that affect language processing, comprehension, production, and display disruption of the usually left-sided language dominance (Bishop, 2013), might also affect the development of hand preferences. It should be noted that this association is correlational and there is so far no evidence of a causal link between these two variables as it might be caused through currently unknown third variables affecting both systems.

Overall, an important question the existing research has left unresolved is what factors affect whether individuals with a specific condition would be more likely to manifest atypical handedness compared to individuals from the general population. It is not possible to answer this important question based on the published meta-analytic literature, as each meta-analysis focuses on a single disorder. What is needed is a systematic cross-disorder research synthesis of the data published in previous meta-analyses on handedness in clinical groups. This is the scope of the present study. By leveraging existing databases from existing meta-analyses and supplementing them with data from primary research articles published after the publication date of each respective meta-analysis and then reanalyzing these data across conditions a so-called second-order meta-analysis will be performed (Johnson, 2021). Integration of data from published meta-analyses also has the further advantage of allowing for the testing of transdiagnostic moderator variables, which is not possible in meta-analyses focused on a single disorder, as mentioned above. Because the previously published meta-analyses operationalized handedness as hand preference due to the scarcity of primary studies on hand skill, we will also focus on hand preference in the second-order meta-analysis.

Aims and Hypotheses

Taken together, the overarching aim of the present study was to leverage existing databases to illuminate whether hand preference differs between individuals with mental or neurodevelopmental disorders and the general population and if so, to estimate the influence of potential moderators independent of diagnosis. We broke down this aim into three steps. First, we aimed to identify and review all published meta-analyses on hand preference differences between cases and controls in mental and neurodevelopmental disorders (including learning disabilities). Second, our study aimed to update the literature search of the meta-analyses identified in the first step, whereby new empirical studies published up to 2024 were included in their database and the effect sizes of the primary meta-analyses were recalculated using a streamlined and identical analysis pipeline. The purpose of this update was to ensure comparability across these meta-analyses, check their robustness using state-of-the-art analysis methods, and increase the statistical power of the analyses. Finally, we aimed to enter the updated meta-analyses into a second-order meta-analysis to test both typical moderators of hand preference (i.e., age, sex ratio, hand preference classification system, hand preference assessment, and study location) in a large data set and test new hypotheses through moderators that pertain specifically to the second-order meta-analysis. Within the second-order meta-analysis, we tested the following preregistered hypotheses:

1. The investigated conditions will vary concerning their atypical hand preference; thus, conditions that have demonstrated notable differences between cases and controls from the general population in previous primary meta-analyses (e.g., schizophrenia or autism) will demonstrate stronger differences compared to conditions that have shown no significant associations in primary meta-analyses (e.g., depression).

2. Neurodevelopmental conditions will have a higher prevalence of atypical hand preference compared to conditions that are not associated with neurodevelopment.
3. Language-related conditions will show higher atypical hand preference prevalence compared to language-unrelated conditions.
4. When it comes to conditions that are not neurodevelopmental, the age of onset will be predictive of the level of atypical hand preference. Conditions that show an earlier onset are predicted to show higher atypical hand preference prevalence compared to conditions with a later onset.

Method

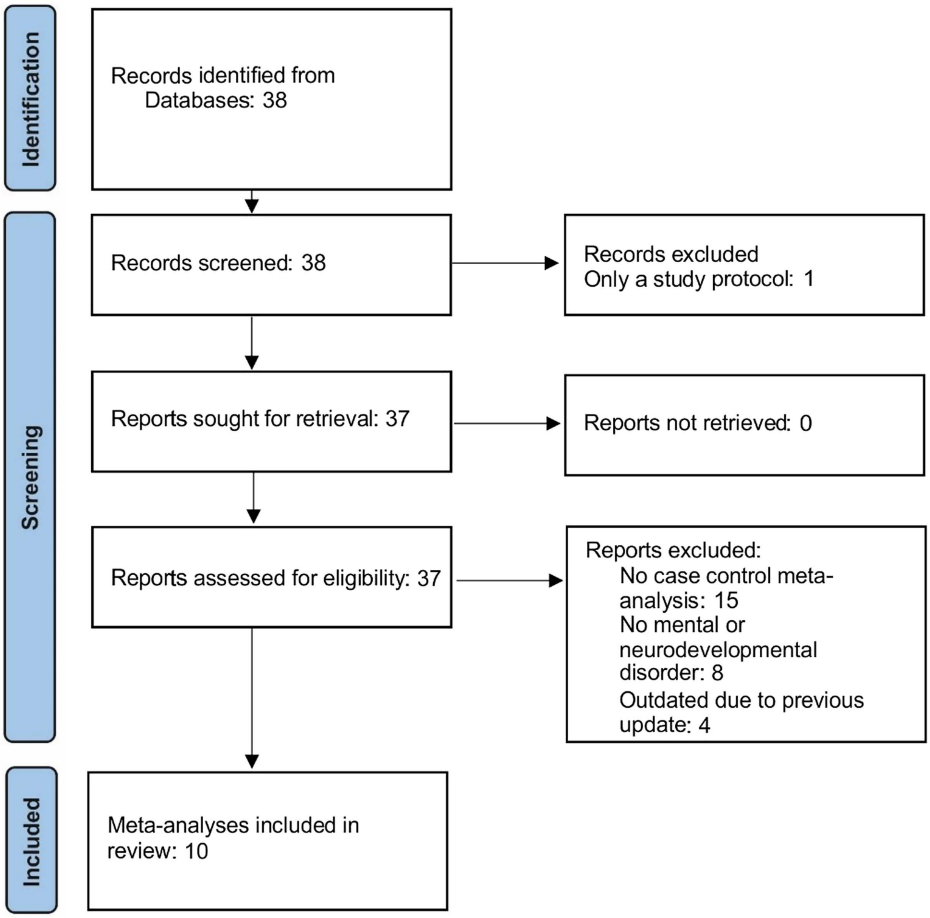
Search Strategy

The present study aimed to identify and review existing meta-analyses on the topic of handedness across various conditions and update all identified meta-analyses before conducting the second-order meta-analysis. Therefore, two different search strategies were followed, each corresponding to a different stage of our study:

1. Search for existing meta-analyses on handedness: Existing meta-analyses comparing cases and controls across mental and neurodevelopmental conditions, including learning disabilities, were searched online in the computerized reference databases Pubmed MEDLINE, APA PsycInfo, Google Scholar (first 200 hits), and Scopus using the search term ("meta-analysis" *OR* "meta analysis" *OR* "systematic review" AND handedness *OR* "hand preference" *OR* "hand use" *OR* lateralization *OR* "side bias" *OR* "hand skill") in "All Fields," from database conception. The cited literature of eligible articles for inclusion was scanned and their references were searched for potentially eligible articles as well. Furthermore, a prospective search of studies citing these meta-analyses was conducted to identify further relevant meta-analyses. The search for eligible meta-analyses concluded in January 2024. The flowchart for the search of existing meta-analyses is depicted in Figure 1.

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Flowchart Detailing the Identification and Screening of Identified Records for the Identification of Existing Meta-Analyses

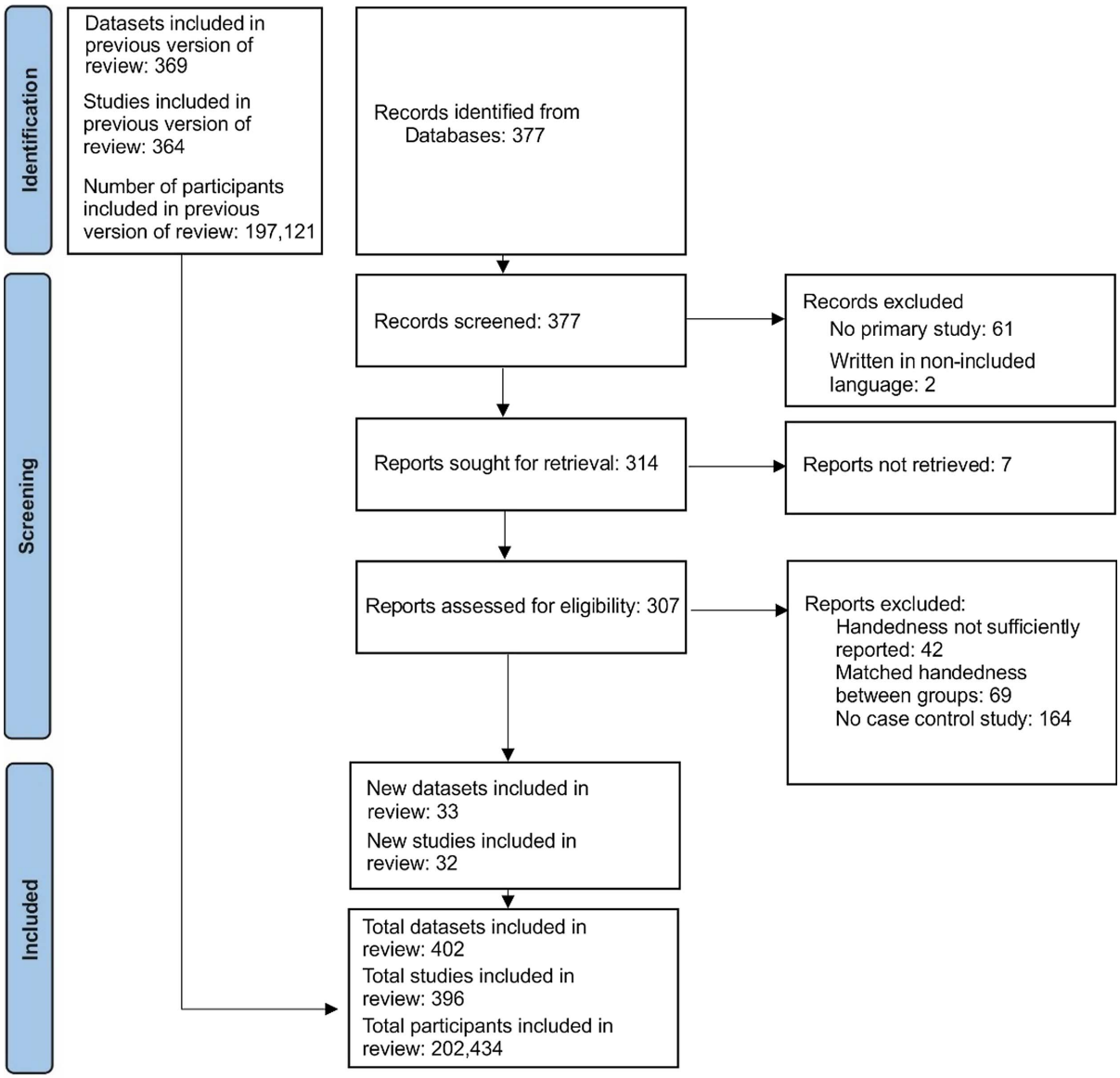


Note. Only the most recent version of a meta-analysis was included in this review. Thus, meta-analyses that had been updated previously were excluded. See the online article for the color version of this figure.

2. Updating of existing meta-analyses: To update existing meta-analyses, the search terms used in each original publication were entered into Pubmed MEDLINE, APA PsycInfo, Google Scholar (first 200 hits), and Scopus. For example, the ADHD meta-analysis used the terms ("handedness" OR "hand skill" OR "hand preference" OR "functional laterality") AND ("ADHD" OR "ADD" OR "Attention Deficit Hyperactivity Disorder" OR "Attention Deficit Disorder") and those terms were also used for the updating of this meta-analysis. Additionally, we identified the year in which the search was concluded in the original publications. This served as our starting year for the updating search. The search was concluded in April 2024. In addition to the search of reference databases, email requests for data were sent to the authors of the articles if a study clearly measured hand preference but incidences were not reported (e.g., if they were only used as a covariate in a larger model). Reminders were sent after 10 days, if no reply was received from the authors, as per our preregistration. The search strategy aimed for completeness. The flowchart for the updating of existing meta-analyses is depicted in Figure 2.

Figure 2

Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 Flowchart Detailing the Identification and Screening of Records for the Update of Existing Meta-Analyses



Note. See the online article for the color version of this figure.

Study Selection

Inclusion and Exclusion Criteria

The preregistered inclusion criteria for the second-order meta-analyses only stated that it had to be a case–control meta-analysis, that is, a study comprising both cases of a mental or neurodevelopmental condition (including learning disabilities) and a control group. A complete list of meta-analyses deemed eligible for inclusion in the second-order meta-analysis as well as meta-analyses found during the search that were ultimately not included in the second-order meta-analysis can be found in Supplemental Table 1. The inclusion of meta-analyses into the second-order meta-analysis was discussed and agreed upon by all authors.

For the updating of the eligible meta-analyses (identified with the process described above), the inclusion criteria reported in each of these meta-analyses were used. Some inclusion criteria were employed in all eligible meta-analyses as they were essential for the validity of the handedness data. These were the following criteria:

1. Studies needed to report handedness in cases as well as a control group. Studies without a control group were excluded.
2. Studies in which the cases and the controls were matched for handedness were excluded.
3. No selection of participants on the basis of handedness: Studies that either encouraged or discouraged left-handers to participate were excluded.
4. Studies had to clearly report handedness data, such as numbers of left- and right-handers in both the case and the control group, which could be used for meta-analytic calculations.

Although not affecting the validity of handedness data, the following criterion was also present across all included meta-analyses:

5. All eligible meta-analyses included studies available in the English language; some allowed other languages, namely the ones focused on dyscalculia (Papadatou-Pastou et al., 2021; Greek), depression (Packheiser et al., 2021; Greek, German, and French), dyslexia (Packheiser et al., 2023; German, and Greek), pedophilia (Stein et al., 2023; Greek, Spanish, and German), and stuttering (Papadatou-Pastou et al., 2023; Greek and German). Yet, no new studies were located in languages other than English, with the exception of Jovanović et al. (2013); this author kindly translated the report from Serbian (included in the dyscalculia meta-analysis, Papadatou-Pastou et al., 2021).

Specific meta-analyses that were deemed eligible for inclusion in the second-order meta-analysis had the following inclusion criteria in addition to the general ones.

ADHD (Nastou et al., 2022):

1. Studies including individuals with ADHD who presented comorbidity with other disorders were excluded.
2. Studies that relied on self-report diagnosis were excluded.

Autism (Markou et al., 2017):

1. Studies including individuals with autism who presented comorbidity with other disorders were excluded.
2. Studies with case groups including high-functioning individuals with autism or Asperger's disorder were excluded.

Dyscalculia (Papadatou-Pastou et al., 2021):

1. Dyscalculia needed to have been diagnosed by a third party. Diagnosis through self-report was excluded.
2. Studies including individuals with dyscalculia who presented comorbidity with other disorders were excluded.

Dyslexia (Packheiser et al., 2023):

1. Studies were excluded if no information on intelligence quotients (IQ) was given. Furthermore, the IQ of individuals had to be at least IQ $\geq$ 70.
2. Studies had to report that the reading level was below the mental age or chronological age.
3. Studies that only ascertained a risk for dyslexia based on, for example, the family history were excluded.

ID (Papadatou-Pastou & Tomprou, 2015):

1. Studies including individuals with an ID who presented comorbidity with other disorders were excluded.

Pedophilia (Stein et al., 2023):

1. Only participants aged 18 or older were included in the meta-analysis.

Studies that were included or excluded during the updating process were always checked by two independent reviewers from the author list. There were no disagreements about whether a study should be included or excluded. All data sets that were included in the updating process and the second-order meta-analysis can be found in Supplemental Table 2. A list of excluded studies can be found on the Open Science Framework (OSF: https://osf.io/975dq/) under "Exclusion list." As primary studies from different meta-analyses studied different diagnoses, there was no overlap (data sets reported multiple times across different meta-analyses) between included data sets from different meta-analyses.

Data Extraction

For almost all meta-analyses included in the second-order meta-analysis, we had direct access to the raw data prior to the updating process. As all extractions for these studies were already performed by at least two independent reviewers, no further review of this data was necessary. Only the meta-analysis by Hirnstein and Hugdahl (2014) was not coauthored by one of the authors of the present study. Here, we used the Supplemental Table that provided all relevant handedness data for the studies to extract data. As we also needed to extract variables such as sex ratios or the mean age of the sample not reported in the Supplemental Table, extracting data for

this meta-analysis was handled by two independent reviewers (J. P. and J. B.).

For all studies that were eligible for inclusion as part of the updating process, at least two of the authors extracted raw handedness data as well as the relevant moderators. Interrater reliability was very high (Cohen's $\kappa > .95$). Any inconsistencies were resolved by discussion. Data extraction for the updating process started in January 2024 and was completed in May 2024. In line with most existing meta-analyses on the topic, we only extracted categorical hand preference data (e.g., frequency of occurrence for left-, mixed, or non-right-handed individuals in both case and control groups) because continuous measures, such as scores from the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), were extremely rarely reported and could thus not be analyzed meaningfully. The extracted moderating variables have been established in previous meta-analyses on the topic and were extracted in accordance with our preregistration. Note that the numbers on how often a moderating variable could be extracted pertain to extracted data sets rather than studies as a few studies provided multiple data sets for the analysis ($k = 2$ from Barry & James, 1978; $k = 2$ from McCaskey, 2018; $k = 3$ from Papadatou-Pastou et al., 2021; $k = 2$ from Samara & Caravolas, 2017; $k = 2$ from Jahnke et al., 2022). Furthermore, the numbers reflect the number of data sets after the updating process as these moderators were only tested in the scope of the second-order meta-analysis.

1. M_{age}: Mean age was calculated across the case and control group. If the mean age was reported for both groups separately, a weighted mean age based on the respective sample sizes of each group was computed. Mean age could be extracted for 311 data sets.

2. Sex ratio: As most studies did not break down handedness by sex, we used the female-to-male sex ratio as a proxy to investigate the influence of sex, similar to previous hand preference meta-analyses (dyscalculia, Papadatou-Pastou et al., 2021; depression, Packheiser et al., 2021; dyslexia, Packheiser et al., 2023; autism, Markou et al., 2017; ID, Papadatou-Pastou & Tomprou, 2015; stuttering, Papadatou-Pastou et al., 2023). Sex ratios were calculated across the case and control groups and could be extracted for 336 data sets.

3. Handedness classification: Handedness was classified across five different classification schemes. The most widely used classifications were by categorizing individuals into right-handed and non-right-handed individuals (Non-Right/Right or NR-R, 85 data sets), categorizing individuals into left- and right-handed individuals (Left/Right or L-R, 157 data sets), and categorizing individuals into left-, mixed-, or right-handed individuals (Left/Mixed/Right or L-M-R, 150 data sets). Two rarely used classification systems categorized individuals either into left- and nonleft individuals (Left/Nonleft or L-NL, seven data sets) or into mixed- and right-handed individuals (Mixed/Right or M-R, three data sets).

4. Handedness assessment: The method of assessing hand preference has been shown to influence the classification rates into left- or right-hand preferences (Papadatou-Pastou et al., 2020). The two most used inventories in our data sets to assess hand preferences were the EHI (141 data sets) and Annett's Handedness Questionnaire (Annett, 1970; 20 data sets). Because handedness assessment through other means was highly variable, another third category was created including all the studies that reported how they assessed handedness, but this assessment was not done via the EHI or Annett's Questionnaire (154 data sets). Studies that did not report how hand preference was assessed were excluded from this moderator analysis.

5. Study location: Ancestry has been shown to moderate the overall hand preference prevalence (Papadatou-Pastou et al., 2020). Study location was used as a proxy for ancestry and assessed based on what continent the study was conducted. Cohorts were sampled for the most part in North America (141 data sets) and Europe (169 data sets). Other locations were Asia (26 data sets), Oceania (15 data sets), Africa (four data sets), and South America (one data set). Africa and South America were excluded due to the scarcity of data sets available for analysis.

6. Study quality: To assess the individual study quality in more detail, we extracted relevant aspects that could influence case–control differences in handedness. Matching biases were ascertained through matching of age as well as sex/gender between cases and controls, the diagnostic assessment of cases, how handedness was measured, and whether comorbidities that are common in mental and neurodevelopmental disorders were an exclusion criterion. Specifically, we attributed each study with either a 1 or 0 rating depending on whether they fulfilled the quality checks for each category. For age matching, we checked if studies matched their case to the control groups with a maximum of 5% deviation in either direction for both the mean age and the error (e.g., *SD*). For sex/gender matching, we applied the same methodology: studies were sex/gender matched if the control group deviated with a maximum of 5% from the cases in either direction. For diagnosis, we checked if studies applied the *Diagnostic and Statistical Manual of Mental Disorders/International Statistical Classification of Diseases and Related Health Problems* (*DSM/ICD*) criteria or used a trained psychologist/psychiatrist/specialist for diagnosis. For handedness assessment, we checked whether a dedicated handedness inventory or comparable tasks were used to determine hand preferences. Finally, the criterion for comorbidity control was fulfilled if studies excluded Axis 1 disorders specifically or all psychiatric disorders in both cases and controls. Interrater reliability between two raters (J.P. and S.A.M) was substantial (Cohen's $\kappa = .71$). Disagreements were resolved via a third rater (G.B.).

To test our hypotheses, we furthermore extracted the following moderator variables:

1. Diagnosis: The underlying diagnosis (i.e., depression, dyslexia, stuttering) was used as a moderator to identify differences in atypical hand preferences between conditions.

2. Association with language: Each included condition or disability was assessed with respect to whether its symptomatology is associated with the domain of language. To this end, the diagnostic criteria of the *DSM*-5-Text Revision (TR) (American Psychiatric Association, 2022) were independently reviewed by three coders (J.P., G.B., and M.P.P.), and the three assessments were highly consistent. According to these assessments, autism, dyslexia, ID, schizophrenia, and stuttering were categorized as language-associated. Depression, dyscalculia, pedophilia, and PTSD were not found to be language-associated. Only for ADHD did one coder determine a language association whereas the others did not determine an association. Following an assessment of a fourth coder, ADHD was determined not to be categorized as language-associated.

3. Neurodevelopmental status: Each included condition or disability was assessed as to whether it constitutes a neurodevelopmental disorder. Two independent coders again reviewed the *DSM*-5-TR criteria (M.P.P. and S.O.). Based on the *DSM*-5-TR classification, autism, ADHD, dyslexia, dyscalculia, ID, and stuttering were classified as neurodevelopmental disorders. Depression, pedophilia, PTSD, and schizophrenia were not classified as neurodevelopmental disorders. There were no disagreements between coders.

4. Age of onset: We originally intended to use the age of onset as a moderator. Nonetheless, after careful consideration, we only applied this to conditions that were not classified as neurodevelopmental. Age of onset was extracted from Solmi et al. (2022) for depression (age of onset = 31 years), PTSD (age of onset = 30 years), and schizophrenia (age of onset = 25 years). For pedophilia (age of onset = 18.5 years), we used data collected by Tozdan and Briken (2019). All deviations from the preregistration are described under the Transparency and Openness section.

Statistical Analysis

Data were analyzed using R (v. 4.3.3 for Windows) and RStudio (2022.07.2 Build 576; R Core Team, 2023) using the metafor package (Viechtbauer, 2010) and the RoBMA package (Maier et al., 2023). Data analysis was conducted using all available data, that is, we included both the data that had been already collected by previous meta-analyses and the data that was extracted during the updating process. Our analysis was a two-step process, corresponding to the updating of existing meta-analyses and the second-order meta-analysis, as follows:

Updating of existing meta-analyses: As data analysis approaches differed across the eligible meta-analyses, we ran an updated analysis protocol using an identical processing pipeline for each individual diagnosis that was eligible for inclusion in the second-order meta-analysis. To this end, we ran three models that differed in terms of inclusivity due to different classification systems, following previous work (Borawski et al., 2023; Markou et al., 2017; Nastou et al., 2022; Packheiser et al., 2021, 2023).

1. First, we investigated whether the prevalence of non-right-hand preference differed between cases and controls. This analysis was the most inclusive as all studies except for the studies using a Left/Nonleft classification system could be converted to an NR-R classification by assigning left-handers from the L-R classification, left- and mixed-handers from the L-M-R classification, and mixed-handers from the M-R classification into the nonright category.

2. Second, we investigated whether the prevalence of left-hand preference differed between cases and controls, by excluding the studies that did not quantify the numbers of left-handed individuals in their respective cohorts. Thus, studies using an M-R or NR-R classification were removed.

3. Third, we investigated the prevalence of mixed-hand preferences between cases and controls. Only studies using an M-R or L-M-R classification were included in this analysis.

As measures of effect size, we used *OR*s. *OR*s are defined as the ratio of the odds of an event occurring in one group (cases) relative to the odds of the event occurring in another group (controls). Specifically, the events refer to non-right-hand preference (Meta-Analysis 1), left-hand preference (Meta-Analysis 2), or mixed-hand preference (Meta-Analysis 3). *OR*s and their corresponding variances were calculated for each extracted cohort independently. Note that all these calculations are directly implemented in the escalc function within the metafor package.

*OR*s lend themselves to the study of handedness differences between cases and controls, as they are independent of the base rate of handedness in each study. The latter can vary according to factors like the handedness assessment employed or the cutoff scores used to group participants into the different handedness categories. An *OR* equal to 1 indicates no difference between cases and controls. An *OR* greater or less than 1 indicates increased or decreased rates of atypical (i.e., non-right-, left-, or mixed-) hand preference in cases compared to controls, respectively. *OR*s and their variances were then combined using a random effects model to provide a pooled effect size and a test for the overall effect. We exclusively used random-effects models as previous research has demonstrated that there is abundant variability in the handedness literature, reflecting factors like the different hand preference measures used (Papadatou-Pastou et al., 2020; Vingerhoets et al., 2023). Additionally, robust variance estimation with cluster-robust inference was used at the study level, a step that is recommended to accurately determine the confidence intervals of multilevel and multivariate meta-analytic models (Pustejovsky & Tipton, 2022). We used cluster-robust inference as the data were clustered in a hierarchical manner with data sets being nested in studies due to some studies providing multiple data sets. The cluster-robust inference increases the precision of error estimates for models that have hierarchical structures and serves as a small-sample adjustment improving error estimation when the number of clusters is small (McCaffrey & Bell, 2003). *OR*s and their 95% confidence intervals were complemented by prediction intervals. Prediction intervals estimate the range of effects that are to be expected from new studies sampled at random from the same population taking both effect size variation and between-study heterogeneity into account (Spineli & Pandis, 2020). To assess small-study bias, we visually inspected the funnel plot. Furthermore,

we used precision effect test and precision effect estimate with standard errors (PET-PEESE) to apply a small-study bias correction by using either the standard error or the effect size variance as a moderator (Pustejovsky & Rodgers, 2019).

*OR*s of the overall models were additionally tested using robust Bayesian approaches to provide a complementary robustness check and quantify evidence for both the null and the alternative hypothesis. For Bayes factor interpretation, we used the terminology and guidelines established by Lee and Wagenmakers (2013). According to their recommendations, a BF_{10} of > 3 represents moderate evidence in favor of the alternative hypothesis, that is, that there are increased rates of atypical hand preference in cases compared to controls, and a BF_{10} of < 0.33 represents moderate evidence in favor of the null hypothesis, that is, that there is no difference between cases and controls. Values ranging between 0.33 and 3 would indicate the absence of evidence for an effect. Any BF_{10}s exceeding a value of 100 mark extreme and thus decisive evidence for the alternative hypothesis. Recent literature has suggested the use of a prior sensitivity approach, and thus a variety of priors to provide a more comprehensive picture of the data (Harrer et al., 2022). Effect sizes in meta-analyses are typically lower compared to individual experimental data sets suggesting the usage of small effect size priors (Harrer et al., 2022). *OR*s were transformed to Cohen's *d* as effect sizes in the RoBMA function require Cohen's *d* as input. We tested a small ($d = 0.3$), medium ($d = 0.5$), and large effect size prior ($d = 0.707$) centered around 0 in accordance with Packheiser et al. (2023). All priors followed a Cauchy distribution that is generally recommended in Bayesian approaches (Ghosh et al., 2018). Bayesian approaches through the RoBMA function further allow for direct quantification of publication bias beyond small-study bias by averaging across selection models as well as PET-PEESE models.

To determine whether individual effects were particularly influential, we calculated Cook's distance *D*. A threshold of $D > 0.5$ was used to qualify a study as influential (Cook, 1977). Heterogeneity in the present study was assessed using Cochran's *Q* as well as I^2, which indicates if the extracted effect sizes estimate a common population effect size. Because multilevel models estimate heterogeneity at all included random effects levels in the model, we furthermore computed σ^2 as an estimator of heterogeneity both at the study and data set level. These values for all models can be found on the OSF (https://osf.io/975dq/) under "Heterogeneity estimates." For the overall models, the presence of heterogeneity could also be calculated via a Bayes factor through the RoBMA function. No moderators were tested for the updated meta-analyses individually as they were globally assessed in the second-order meta-analysis.

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021), a risk of bias assessment is necessary for meta-analyses. As outlined, we assessed both small-study bias through PET-PEESE and publication bias via the RoBMA function. Even though previous meta-analyses on this topic could not identify a significant risk of bias, we comprehensively assessed study quality with respect to matching bias, comorbidity assessment, handedness measurements, and diagnostic tool (see Supplemental Table 3). The overall quality rating for each study was used as an exploratory metaregressor in the second-order meta-analysis.

Second-order meta-analysis: For the calculation of the overall models, we followed the identical procedure as for the updating process using a subdivision by handedness classification system (i.e., non-right-, left-, and mixed-hand preference). As before, the *OR* was used as a measure of effect and the log*OR* as a tool for visualization. As single studies provided multiple data sets across conditions in the second-order meta-analysis, random effects were implemented at the study and data set level. In addition, the variance–covariance matrix was calculated to account for dependencies of measured effect sizes coming from the same study. The variance–covariance matrix requires an assumption regarding the correlation of effect sizes. We assumed a value of $\rho = 0.6$ which has been demonstrated to be a conservative measure (Packheiser, Hartmann, et al., 2024). We calculated sensitivity analyses at $\rho = 0$, $\rho = 0.2$, $\rho = 0.4$, $\rho = 0.8$, and $\rho = 1.0$ as outlined in the preregistration. In the second-order meta-analysis, we also tested the standard moderators typically investigated in hand preference research, namely age, sex ratio, hand preference classification system, hand preference assessment, and study location. In addition to the standard moderators and to test our hypotheses, we ascertained moderation effects of (a) diagnosis, (b) status as a language-associated condition, (c) status as a neurodevelopmental condition, and (d) the age of onset of the condition. For moderator analyses, we exclusively applied frequentist statistics (see the Transparency and Openness section). The significance of moderators was determined using omnibus *F* tests. For categorical moderators, the intercept was removed from the analysis for interpretation of all factor levels. Effect size differences between moderator levels and their confidence intervals were assessed via *t* tests. In case of more than two moderator levels, we used a more conservative significance threshold ($\alpha = 1\%$) to reduce the number of Type 1 errors due to multiple comparisons.

For visualization of moderation effects, forest plots were used to depict the individual moderator-level *OR*s. Please note that forest plots of individual eligible meta-analyses use the log*OR* instead of the *OR* because visualization of large confidence intervals is difficult otherwise. Log*OR*s center around 0 instead of 1 for a null effect and range from minus to plus infinity instead of from 0 to plus infinity. Thus, log*OR*s center symmetrically around 0. In addition to forest plots, we also used orchard plots (Nakagawa et al., 2023) that allow for a visual representation of each data set included on each moderator level as well as their precision (1/*SE*). For the visualization of continuous moderators, we used scatterplots with fitted regression lines and confidence intervals.

Transparency and Openness

The present study was fully preregistered at https://osf.io/xg7wt/. All procedures were conducted following the PRISMA statement (Page et al., 2021). All data and code for analysis are available at https://osf.io/975dq/ (Packheiser, Papadatou-Pastou, et al., 2024). The PRISMA 2020 Main Checklist as well as the PRISMA 2020 Abstract Checklist can be found under this link as well. The following items were deviations from the preregistration:

1. The first hypothesis of our study was slightly rephrased as the preregistered hypothesis was formulated too vaguely. The original phrasing was as follows: "We expect that the investigated conditions will vary concerning their atypical hand preferences (i.e., certain conditions will demonstrate

higher atypical hand preferences compared to healthy controls whereas others will not show differences compared to healthy controls)."

2. In the preregistration, we aimed to use the age of onset of any condition included in the second-order meta-analysis as a metaregressor. However, we concluded during a later discussion that any neurodevelopmental condition has an age of onset at birth or even prenatally, even if it is only diagnosed later when symptoms manifest more clearly. Thus, we decided to only use the age of onset for conditions that were not categorized as neurodevelopmental.

3. The preregistration outlined that frequentist statistics may be complemented with Bayesian approaches if possible using the RoBMA function. To our knowledge, complex metaregression of multivariate and multilevel models is not yet implemented in the RoBMA function. We thus only used the RoBMA function for overall estimates of case–control odds ratios and publication bias analyses, and not for moderator analyses.

Results

In the following, we will first provide an overview of the existing meta-analyses that were deemed eligible for inclusion in the second-order meta-analysis. In the next step, we provide an overview of the updating process of these meta-analyses. Finally, we describe the results of the second-order meta-analysis.

Review of Meta-Analyses

After application of the inclusion criteria of the second-order meta-analysis, 10 meta-analyses were deemed eligible for inclusion. The meta-analyses were all case–control meta-analyses on the following conditions: ADHD (Nastou et al., 2022), autism (Markou et al., 2017), depression (Packheiser et al., 2021), dyscalculia (Papadatou-Pastou et al., 2021), dyslexia (Packheiser et al., 2023), ID (Papadatou-Pastou & Tomprou, 2015), pedophilia (Stein et al., 2023), PTSD (Borawski et al., 2023), schizophrenia (Hirnstein & Hugdahl, 2014), and stuttering (Papadatou-Pastou et al., 2023). Studies in these ten meta-analyses were published between 1921 and 2022. The ratings of study quality of individual studies can be found in Supplemental Table 3. Study locations of the included data sets comprised mostly Western countries (i.e., 157× Europe and 113× North America). Asian samples comprised 17 data sets with both West Asia (e.g., Israel) and East Asia (e.g., Japan) being represented. Data sets coming from Africa (three data sets) or South America (one data set) were very rarely observed.

Before the updating as part of the second-order meta-analysis, these meta-analyses comprised $k = 369$ individual data sets from 364 individual studies (see Table 1 for detailed information about

Table 1
Number of Data Sets, Cases, Controls, and the Results From the Respective Meta-Analysis for Each Included Meta-Analysis

Meta-analysis	Number of data sets	Number of cases	Number of controls	*OR*	95% CI
ADHD nonright	22	1,077	1,186	1.49	[1.07, 2.07]
ADHD left				1.34	[0.95, 1.90]
ADHD mixed				1.59	[1.07, 2.07]
ASD nonright	12	400	364	3.48	[1.66, 7.29]
ASD left				2.49	[1.14, 5.46]
ASD mixed				2.34	[1.13, 4.82]
Depression nonright	87	9,801	25,700	1.05	[0.96, 1.15]
Depression left				1.04	[0.95, 1.15]
Depression mixed				1.64	[0.98, 2.74]
Dyscalculia nonright	22	747	1,906	1.04	[0.79, 1.37]
Dyscalculia left				1.06	[0.79, 1.42]
Dyscalculia mixed				1.2	[0.67, 2.17]
Dyslexia nonright	67	4,631	40,833	1.37	[1.14, 1.65]
Dyslexia left				1.25	[1.02, 1.50]
Dyslexia mixed				1.55	[1.23, 1.96]
ID nonright	13	5,795	7,949	2.66	[1.63, 4.35]
ID left				1.98	[1.24, 3.15]
Pedophilia nonright	14	1,194	5,648	1.25	[1.00, 1.55]
Pedophilia left				1.25	[0.86, 1.83]
Pedophilia mixed				0.96	[0.43, 2.14]
PTSD nonright	14	747	2,192	1.81	[1.29, 2.54]
PTSD left				0.95	[0.49, 1.83]
PTSD mixed				2.42	[1.66, 3.52]
Schizophrenia nonright	81	8,280	68,479	1.55	[1.25, 1.93]
Stuttering nonright	45	1,774	8,418	1.42	[1.11, 1.81]
Stuttering left				1.56	[1.11, 2.20]
Stuttering mixed				1.12	[0.54, 2.34]

Note. An *OR* equal to 1 indicates no difference between cases and controls. An *OR* greater or less than 1 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. *OR* = odds ratio; CI = confidence interval; ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorders; ID = intellectual disability; PTSD = posttraumatic stress disorder.

included data sets and number of cases and controls). Note that we only describe the number of participants and data sets that were included in the second-order meta-analysis. In the next section, we first shortly describe the included meta-analyses with respect to their methodology and outcome before the updating process. Numeric results from these meta-analyses are also presented in Table 1. A quality assessment and results for each meta-analysis prior to the update can be found in Supplemental Table 4.

ADHD

The meta-analysis on ADHD was preregistered. The study found small but significant effects that cases differed from controls for non-right-hand preferences but no significant effect for left-hand and mixed-hand preferences. Because neither the left-hand nor the mixed-hand preference analysis reached significance, it remains unclear whether the effect in the non-right-hand preference analysis is due to a reversal (left-hand preference) or absence of asymmetry (mixed-hand preference). There was no significant between-study heterogeneity or small-study bias in any analysis.

Autism Spectrum Disorder

The meta-analysis found evidence that cases differed from controls for non-right-hand, left-hand, and mixed-hand preferences suggesting that individuals with autism show higher rates of atypical hand preferences and thus both reversed but also reduced asymmetries. Between-study heterogeneity was significant across all three classification systems. Small-study bias could be detected for non-right- and mixed-hand preferences.

Depression

The meta-analysis on depression found no significant differences between cases and controls for non-right-hand, left-hand, and mixed-hand preferences suggesting that individuals with depression show no alterations in hand preferences. Neither between-study heterogeneity nor small-study bias was evident in any analysis.

Dyscalculia

The meta-analysis on dyscalculia found no significant differences between cases and controls for non-right-hand, left-hand, and mixed-hand preferences suggesting that dyscalculia does not affect hand preferences. Neither between-study heterogeneity nor small-study bias was evident except for small-study bias in the left-hand preference meta-analysis.

Dyslexia

The meta-analysis on dyslexia found evidence that cases differed from controls for non-right-hand, left-hand, as well as mixed-hand preferences suggesting that individuals with dyslexia show both reversed and reduced asymmetries. Between-study heterogeneity was significant for the meta-analysis on non-right-hand preference. Small-study bias could not be detected in any meta-analysis.

ID

The meta-analysis on ID found evidence that cases differed from controls for non-right-hand and left-hand preferences suggesting that intellectual disabilities are associated with changes in asymmetries. As no analysis was conducted for mixed-hand preferences, it remains unclear if this effect is associated exclusively with a reversal of right-hand preferences. Between-study heterogeneity was significant for both the non-right-hand and left-hand preference meta-analysis. Small-study bias was calculated for the non-right-hand preference meta-analysis. No small-study bias was detected.

Pedophilia

The meta-analysis on pedophilia found small but significant differences between cases and controls for non-right-hand preferences. The meta-analyses for left-hand and mixed-hand preferences did not reveal any differences between cases and controls. Because the results for the non-right-hand preference meta-analysis did not survive a leave-one-out sensitivity analysis, the finding of changes in hand preferences in pedophilia does not seem robust. Neither between-study heterogeneity nor small-study bias was evident in any analysis.

PTSD

The meta-analysis on PTSD found evidence that cases differed from controls for non-right-hand and mixed-hand preferences. No effect was observed for left-hand preferences suggesting that PTSD is mostly associated with a reduction in asymmetry. Between-study heterogeneity and small-study bias were not detected in any meta-analysis.

Schizophrenia

The meta-analysis on schizophrenia found evidence that cases differed from controls for non-right-hand preferences suggesting that schizophrenia is linked to alterations in hand preference. No analyses were conducted for left-hand preferences or mixed-hand preferences separately. Heterogeneity between studies was found to be present. Small-study bias was not assessed.

Stuttering

The meta-analysis on stuttering found evidence that cases differed from controls for non-right-hand and left-hand preferences. For mixed-hand preferences, no significant differences were detected suggesting that stuttering seems to be associated with the reversal rather than a reduction of asymmetries. Between-study heterogeneity was significant for the non-right-hand and mixed-hand preference meta-analyses. Small-study bias was absent across all meta-analyses.

Updating of Meta-Analyses

In total, 33 new data sets were added through the updating process (see Table 2 for details). Studies that were added after the updating search were published between 2014 and 2024. One unpublished data set was provided through personal communication (S. Brederoo, personal communication, October 29, 2024). Study locations of the included data sets comprised mostly Europe (12×), North America

Table 2
Number of Added Data Sets, Cases, and Controls for the Updating Process per Individual Meta-Analysis

Meta-analysis	Number of added data sets	Number of added cases	Number of added controls
ADHD	5	498	324
ASD	8	978	844
Depression	8	253	297
Dyscalculia	2	32	28
Dyslexia	2	49	57
ID	2	54	180
Pedophilia	1	51	55
PTSD	0	0	0
Schizophrenia	5	187	548
Stuttering	0	0	0

Note. ADHD = attention deficit hyperactivity disorder; ASD = autism spectrum disorders; ID = intellectual disability; PTSD = posttraumatic stress disorder.

(7×) as well as Asian countries (9×). Only a single data set from Africa could be identified for inclusion. To follow the best practice and update each meta-analysis using an identical data analysis pipeline, we also processed the meta-analyses individually using both frequentist and Bayesian approaches. The results for these calculations can be found on the OSF (https://osf.io/975dq/) under Update Table.

Second-Order Meta-Analysis

After applying the study-specific inclusion criteria as part of the updating process, another $k = 33$ data sets could be added. Thus, a total of 402 data sets from 396 studies were included in the second-order meta-analysis. In total, the second-order meta-analysis comprised $n = 202{,}434$ individuals; there were $n = 36{,}902$ cases and $n = 165{,}532$ controls. There was no overlap in cases and controls across the different meta-analyses. Descriptive details for the non-right-hand, left-hand, and mixed-hand preference meta-analyses within the second-order meta-analysis are presented in Table 3. Relevant meta-data for each study included in the second-order meta-analysis can be found in Supplemental Table 5.

Overall Model Estimates and Standard Moderators

The meta-analysis on non-right-hand preference showed significantly higher rates of non-right-hand preferences across conditions in cases compared to controls, $t(389) = 9.08$, $p < .001$. Bayesian estimates with a small effect prior confirmed extreme evidence for an effect ($BF_{10} > 100$ for all prior settings). The prediction interval was substantially wide suggesting large heterogeneity. This was confirmed via the Q test for heterogeneity, $Q(396) = 833.67$, $p < .001$, $I^2 = 54.96\%$, and Bayesian estimates for heterogeneity ($BF_{10} > 100$). To test for small-study bias, we visually inspected the funnel plot (see Supplemental Figure 1) and used the standard error as well as the variance as moderator. In both cases, there was a trend that lower estimates of precision were associated with smaller *OR*s, PET: $F(1, 388) = 2.59$, $p = .109$; PEESE: $F(1, 388) = 2.86$, $p = .091$. Bias-adjusted *OR*s were 1.63 (95% CI [1.38, 1.93], see Supplemental Figure 2) for PET and 1.55 (95% CI [1.39, 1.73], see Supplemental Figure 3) for PEESE. Bayesian estimations provided strong evidence against publication bias ($BF_{10} = .014$). No data set was classified as influential (Cook's $D < 0.5$) for all data sets.

We first calculated the effects of typically investigated moderators in handedness research. For continuous moderators, we found a significant negative association of case–control *OR*s with the mean age of the sample, $\beta = -0.007$, $F(1, 298) = 5.39$, $p = .021$, suggesting that younger samples show higher differences in non-right-hand preference between cases and controls. A metaregression plot examining the *OR*s across ages can be found in Supplemental Figure 4. In the case of the sex ratio, a nonsignificant trend could be observed that fewer females in the sample were linked to higher *OR*s between cases and controls, $\beta = —0.301$, $F(1, 318) = 2.85$, $p = .092$. A metaregression plot examining the *OR*s across sex ratios can be found in Supplemental Figure 5. For categorical moderators, no effect of the assessment method nor of the study location could be detected, $F(2, 303) = 0.89$, $p = .412$; $F(3, 337) = 0.21$, $p = .892$, respectively. For classification systems, the omnibus test revealed a significant effect, $F(4, 385) = 2.55$, $p = .039$. No post hoc comparison remained significant using a threshold of $p < .01$.

The meta-analysis on left-hand preference showed significantly higher rates of left-hand preferences across conditions in cases

Table 3
Number of Data Sets, Cases, and Controls as Well as ORs for the Second-Order Meta-Analysis

Meta-analysis	Number of data sets	Number of cases	Number of controls	*OR*	95% CI	95% PI
Nonright	397	36,711	165,358	1.46	[1.35, 1.59]	[0.57, 3.75]
Left	314	30,279	122,745	1.34	[1.22, 1.48]	[0.59, 3.06]
Mixed	153	10,263	24,398	1.63	[1.38, 1.93]	[0.44, 6.03]

Note. An *OR* equal to 1 indicates no difference between cases and controls. An *OR* greater or less than 1 indicates increased or decreased rates of atypical (i.e., non-right-, left-, or mixed-) hand preference in cases compared to controls, respectively. *OR* = odds ratio; CI = confidence interval; PI = prediction interval.

compared to controls, $t(306) = 5.87$, $p < .001$. Bayesian estimates with a small effect prior confirmed extreme evidence for the presence of an effect ($BF_{10} > 100$ for all prior settings). The prediction interval was large suggesting considerable heterogeneity. We confirmed the presence of between-study heterogeneity via the Q test, $Q(312) = 511.05$, $p < .001$, $I^2 = 39.24\%$, and Bayesian estimates for heterogeneity ($BF_{10} > 100$). To test for small-study bias, we again visually inspected the funnel plot (see Supplemental Figure 6) and used the standard error as well as the variance as moderator. In both cases, we found significant negative associations between error magnitude and the size of the *OR*s, PET: $F(1, 305) = 4.74$, $p = .030$; PEESE: $F(1, 305) = 5.05$, $p = .025$. Bias-adjusted *OR*s were 1.59 (95% CI [1.31, 1.94], see Supplemental Figure 7) for PET and 1.46 (95% CI [1.28, 1.67], see Supplemental Figure 8) for PEESE. Bayesian estimations overall provided strong evidence against publication bias ($BF_{10} = .02$). No data set was classified as influential (Cook's $D < 0.5$) for all data sets.

As for the non-right-hand preference comparison, we initially investigated the effects of standard moderators in handedness research. For continuous moderators, we found a significant negative association of case–control *OR*s with the mean age of the sample, $\beta = -0.007$, $F(1, 236) = 4.30$, $p = .039$, suggesting that younger samples show higher differences in left-hand preference between cases and controls. A metaregression plot examining the *OR*s across mean ages can be found in Supplemental Figure 9. For sex ratio, there was no significant relationship with *OR* magnitude, $\beta = -0.241$, $F(1, 243) = 0.82$, $p = .367$. A metaregression plot examining the *OR*s across sex ratios can be found in Supplemental Figure 10. For categorical moderators, no effect of handedness assessment nor of study location was detected, $F(2, 238) = 1.05$, $p = .353$; $F(3, 262) = 1.08$, $p = .359$, respectively. The same was true for a moderation test of classification systems, $F(2, 304) = 0.27$, $p = .761$.

The meta-analysis on mixed-hand preference showed significantly higher rates of mixed-hand preferences across conditions in cases compared to controls, $t(147) = 5.71$, $p < .001$. Bayesian estimates with a small effect prior confirmed overwhelming evidence for the presence of an effect ($BF_{10} > 100$ for all prior settings). The prediction interval was substantially larger than the confidence interval suggesting considerable heterogeneity. We confirmed the presence of between-study heterogeneity via the Q test, $Q(152) = 350.51$, $p < .001$ $I^2 = 58.97\%$, and Bayesian estimates for heterogeneity ($BF_{10} > 100$). To test for small-study bias, the funnel plot was visually inspected (see Supplemental Figure 11) and the standard error as well as the variance were used as moderators. There was no evidence of small-study bias for mixed-hand preference, PET: $F(1, 146) = 0.15$, $p = .703$; PEESE: $F(1, 146) = 0.07$, $p = .797$. Bias-adjusted *OR*s were 1.56 (95% CI [1.13, 2.15], see Supplemental Figure 12) for PET and 1.61 (95% CI [1.28, 2.01], see Supplemental Figure 13) for PEESE. Bayesian estimations showed anecdotal evidence against the presence of publication bias ($BF_{10} = 0.68$). No data set was classified as influential (Cook's $D < 0.5$) for all data sets.

For continuous moderators, neither mean age, $\beta = 0.002$, $F(1, 114) = 0.08$, $p = .773$, nor sex ratio demonstrated any significant relationship with *OR* magnitude, $\beta = -0.581$, $F(1, 111) = 2.23$, $p = .138$. A metaregression plot examining the *OR*s across mean ages and sex ratios can be found in Supplemental Figures 14 and 15, respectively. The same was true for categorical moderators as there was no effect of the used inventory, $F(2, 126) = 0.90$, $p = .408$, the study location, $F(3, 122) = 0.11$, $p = .953$, respectively, or the hand preference classification systems, $F(1, 146) = 1.48$, $p = .225$.

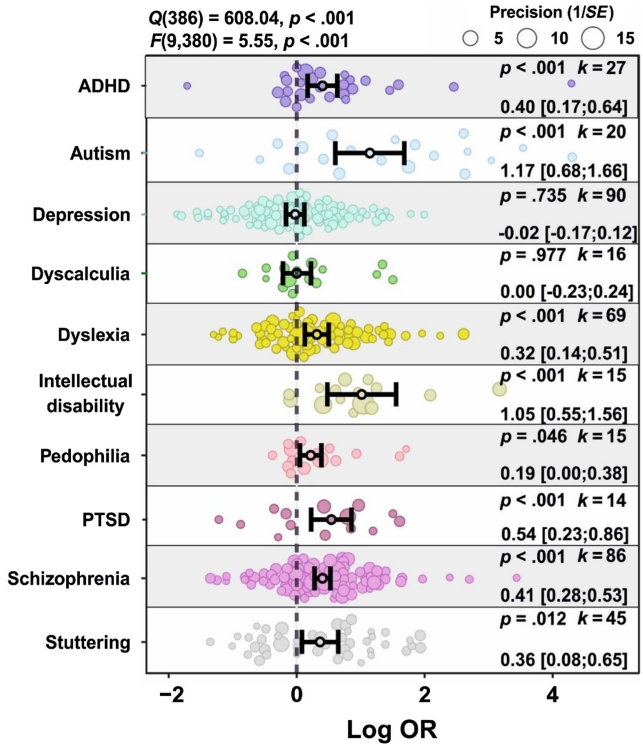
Hypothesis 1: Case–Control Differences in Hand Preference Vary With Diagnosis

To test our first hypothesis, we integrated all updated meta-analyses and used the diagnosis as a moderator. We hypothesized that different conditions would vary with respect to their *OR*s between cases and controls.

In the case of the non-right-hand preference meta-analysis, the underlying diagnosis reached significance when used as a moderator, $F(9, 380) = 5.55$, $p < .001$. Overall, all included diagnoses except for depression and dyscalculia showed a significant effect between cases and controls (all ps $< .013$, see Figure 3). Using a more conservative significance threshold for post hoc comparisons

Figure 3

Orchard Plot Illustrating the Differences in Non-Right-Hand Preference Between Cases and Controls for Each Diagnosis Included in the Second-Order Meta-Analysis



Note. Each dot reflects a data set, and the number of data sets (k) included in the analysis is depicted on the right. Mean effects (log*OR*) and 95% CIs are presented below the number of data sets and are further indicated by the central black dot (mean effect) and its error bars (95% CI). The heterogeneity Q and moderator F statistics are presented in the top left. Note that the figure illustrates log*OR*s that center symmetrically around 0. A log*OR* equal to 0 indicates no difference between cases and controls. A log *OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., non-right-, left-, or mixed-) hand preference in cases compared to controls, respectively. *SE* = standard error; ADHD = attention deficit hyperactivity disorder; PTSD = posttraumatic stress disorder; *OR* = odds ratio; CI = confidence interval. See the online article for the color version of this figure.

between different diagnoses ($p < .01$), we found higher *OR*s in data sets investigating autism, ID, PTSD, and schizophrenia compared to data sets investigating dyscalculia (all ps $< .008$). *OR*s in autism, ADHD, dyslexia, ID, PTSD, and schizophrenia were all higher compared to the *OR* in depression (all ps $< .005$). Autism furthermore demonstrated higher *OR*s compared to dyslexia, pedophilia, schizophrenia, and stuttering (all ps $< .006$). Finally, we found that ID showed higher *OR*s in non-right-hand preference compared to pedophilia ($p = .002$).

For left-hand preference, diagnosis as a moderator also reached significance, $F(9, 297) = 3.19$, $p = .001$. In contrast to non-right-hand preferences, only five diagnoses showed a significant difference from a zero effect (ADHD: $OR = 1.38$, 95% CI [1.05, 1.80], $p = .019$; autism: $OR = 2.76$, 95% CI [1.56, 4.90], $p < .001$; dyslexia: $OR = 1.26$, 95% CI [1.04, 1.54], $p = .021$; ID: $OR = 2.14$, 95% CI [1.39, 3.29], $p < .001$; schizophrenia: $OR = 1.37$, 95% CI [1.16, 1.61], $p < .001$, see Figure 4). We found higher *OR*s in data sets investigating autism and ID compared to data sets investigating depression as well as PTSD (ps $< .006$).

As for the other two classification systems, diagnosis as a moderator reached significance for mixed-handedness, $F(9, 138) = 2.96$, $p = .003$. Five diagnoses revealed a significant difference from a zero effect (autism: $OR = 2.22$, 95% CI [1.44, 3.42], $p < .001$; dyslexia: $OR = 1.51$, 95% CI [1.16, 1.96], $p = .002$; ID: $OR = 3.56$, 95% CI [1.80, 7.04], $p < .001$; PTSD: $OR = 2.52$, 95% CI [1.70, 3.74], $p < .001$, schizophrenia: $OR = 1.70$, 95% CI [1.19, 2.42], $p = .004$, see Figure 5). Post hoc comparisons revealed higher *OR*s in data sets investigating autism, dyslexia, ID, PTSD, and schizophrenia compared to data sets investigating dyscalculia (all ps $< .007$).

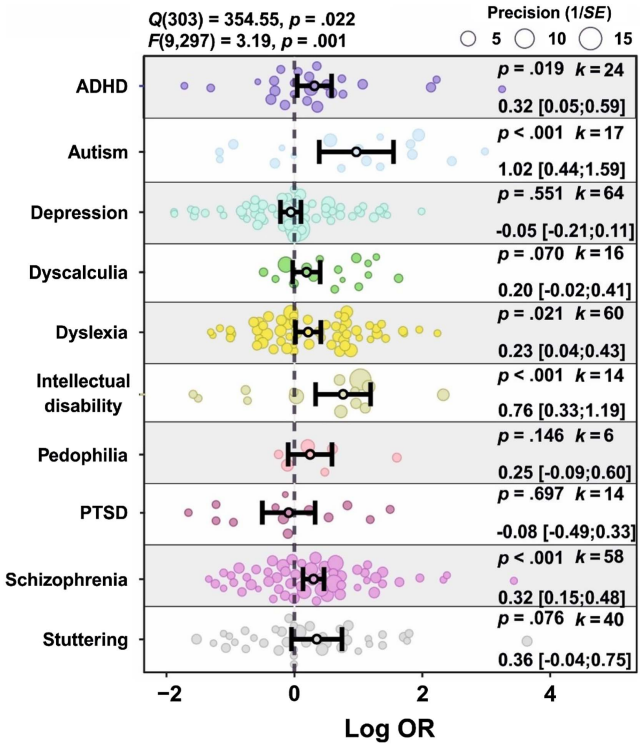
Hypothesis 2: Stronger Case–Control Hand Preference Differences in Neurodevelopmental Conditions

Our second hypothesis proposed that case–control differences in hand preferences are more pronounced for neurodevelopmental conditions compared to nonneurodevelopmental conditions. To test this hypothesis, we categorized each eligible diagnosis into either category using *DSM*-5-TR criteria (see Method) and used this binary classification as a moderator variable.

For non-right-hand preference, both conditions with and without neurodevelopmental status demonstrated significant case–control differences in *OR*s (neurodevelopment: $OR = 1.66$, 95% CI [1.44, 1.91], $p < .001$; no neurodevelopment: $OR = 1.31$, 95% CI [1.20, 1.43], $p < .001$). The *OR*s for neurodevelopmental conditions were significantly higher, $F(1, 388) = 7.62$, $p = .006$, Figure 6A. Analyzing left-hand preferences revealed a similar result pattern as conditions with and without neurodevelopmental status demonstrated significant case–control differences in *OR*s (neurodevelopment: $OR = 1.52$, 95% CI [1.31, 1.77], $p < .001$; no neurodevelopment: $OR = 1.16$, 95% CI [1.04, 1.30], $p = .010$). Again, the *OR*s for neurodevelopmental conditions were significantly higher, $F(1, 305) = 7.86$, $p = .005$, Figure 6B. Contrasting the findings from non-right- and left-hand preferences, the meta-analysis for mixed-hand preference did not reveal an effect based on status as a neurodevelopmental condition. Although conditions with and without neurodevelopmental status demonstrated significant case–control differences in *OR*s (neurodevelopment: $OR = 1.61$, 95% CI [1.28, 2.03], $p < .001$; no neurodevelopment: $OR = 1.69$, 95% CI [1.31, 2.13], $p < .001$) there was no significant difference among them, $F(1, 146) = 0.05$, $p = .832$, Figure 6C.

Figure 4

Orchard Plot Illustrating the Differences in Left-Hand Preference Between Cases and Controls for Each Diagnosis Included in the Second-Order Meta-Analysis



Note. Each dot reflects a data set, and the number of data sets (k) included in the analysis is depicted on the right. Mean effects (log*OR*) and 95% CIs are presented below the number of data sets and are further indicated by the central black dot (mean effect) and its error bars (95% CI). The heterogeneity Q and moderator F statistics are presented in the top left. Note that the figure illustrates log*OR*s that center symmetrically around 0. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. *SE* = standard error; ADHD = attention deficit hyperactivity disorder; PTSD = posttraumatic stress disorder; *OR* = odds ratio; CI = confidence interval. See the online article for the color version of this figure.

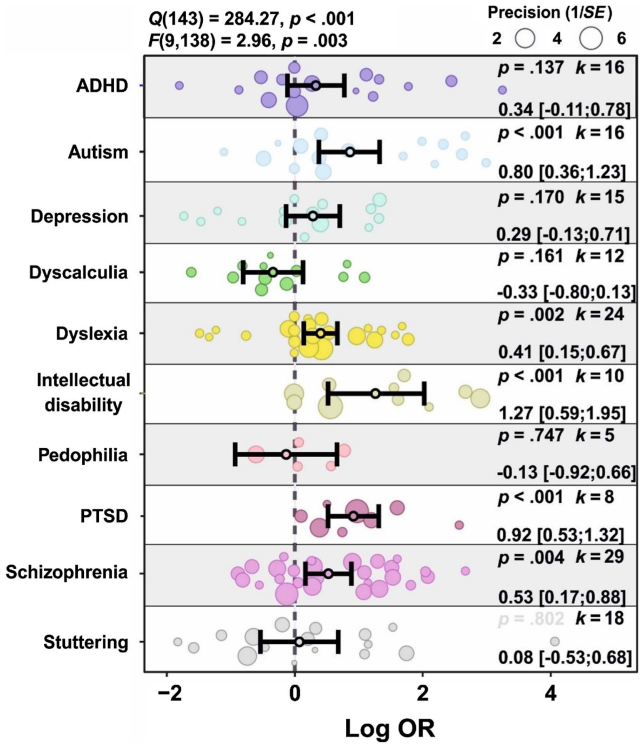
Hypothesis 3: Stronger Case–Control Hand Preference Differences in Language-Associated Conditions

Our third hypothesis pertained to the expectation that conditions whose symptomatology is associated with the domain of language would be linked to higher differences in *OR*s between cases and controls. As for neurodevelopmental status, we used a binary categorization of all eligible conditions being either language- or non-language-associated. This was then used as a moderator to test the hypothesis.

For non-right-hand preference, both conditions with and without language association showed significant non-right-hand preference differences between cases and controls (language

Figure 5

Orchard Plot Illustrating the Differences in Mixed-Hand Preference Between Cases and Controls for Each Diagnosis Included in the Second-Order Meta-Analysis



Note. Each dot reflects a data set, and the number of data sets (*k*) included in the analysis is depicted on the right. Mean effects (log*OR*) and 95% CIs are presented below the number of data sets and are further indicated by the central black dot (mean effect) and its error bars (95% CI). The heterogeneity *Q* and moderator *F* statistics are presented in the top left. Note that the figure illustrates log*OR*s that center symmetrically around 0. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. *SE* = standard error; ADHD = attention deficit hyperactivity disorder; PTSD = posttraumatic stress disorder; *OR* = odds ratio; CI = confidence interval. See the online article for the color version of this figure.

association: *OR* = 1.64, 95% CI [1.47, 1.84], $p < .001$; no language association: *OR* = 1.18, 95% CI [1.06, 1.30], $p < .001$). *OR*s in conditions with language association were significantly higher, $F(1, 388) = 18.57$, $p < .001$, Figure 7A. The results were slightly different for left-hand preference as we only found a significant effect for conditions with language association between cases and controls but no effect for conditions without language association (language association: *OR* = 1.52, 95% CI [1.33, 1.73], $p < .001$; no language association: *OR* = 1.07, 95% CI [0.95, 1.20], $p = .277$). Similar to non-right-hand preferences, *OR*s in conditions with language association were significantly higher, $F(1, 305) = 16.02$, $p < .001$, Figure 7B. For mixed-hand preferences, the result pattern again differed from the results for non-right- and left-hand preferences. The analysis showed significant nonzero effects for either moderator level (language association: *OR* = 1.74, 95% CI [1.40, 2.16], $p < .001$; no language association: *OR* = 1.43, 95% CI [1.10, 1.86], $p = .007$). As for neurodevelopmental status, no differences in *OR*s were found between moderator levels for mixed-hand preferences, $F(1, 146) = 1.27$, $p = .263$, Figure 7C.

Hypothesis 4: A Later Age of Onset Is Associated With Smaller Case–Control Differences in Hand Preference

For all conditions that were not classified as neurodevelopmental, we hypothesized that a later age of onset would be linked to lower *OR*s. Using the age of onset as a continuous moderator revealed a significant negative association with differences in non-right-hand preference between cases and controls, $\beta = -0.023$, $F(1, 202) = 4.04$, $p = .046$, Figure 8A, as well as left-hand preference, $\beta = -0.040$, $F(1, 139) = 6.65$, $p = .011$, Figure 8B, supporting our hypothesis for these two classification systems. For mixed-hand preference, no significant association was detected, $\beta = 0.035$, $F(1, 54) = 1.32$, $p = .256$, Figure 8C, suggesting that alterations in mixed-hand preferences between cases and controls are not related to the onset of a condition.

Exploratory Analyses

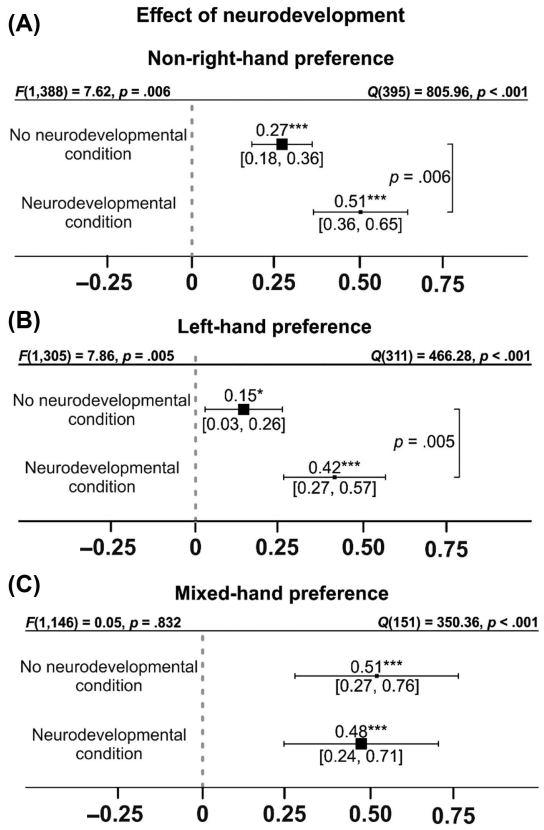
Although our results largely confirmed our initial hypotheses, we found in many cases that conditions not affecting the language system or not being considered neurodevelopmental still showed significant case–control differences. However, our analyses did not specifically compare conditions with neither link to these categories (e.g., depression), a single link (e.g., schizophrenia being only language-associated), or both links (e.g., autism). We therefore explored the data beyond the scope of the preregistration and tested the interaction between these two moderators.

The model of the interaction reached significance in the case of non-right-hand preference suggesting that moderator levels differed from another, $F(3, 386) = 6.89$, $p < .001$. Looking at each moderator level individually, we found that *OR*s for conditions with either neurodevelopmental, language, or a combination of both associations were significantly different from a zero effect (only neurodevelopmental: *OR* = 1.35, 95% CI [1.11, 1.63], $p = .002$; only language: *OR* = 1.51, 95% CI [1.33, 1.71], $p < .001$; both: *OR* = 1.75, 95% CI [1.48, 2.08], $p < .001$, Figure 9A). Only conditions with neither association did not demonstrate a significant effect (*OR* = 1.12, 95% CI [0.99, 1.27], $p = .077$). Post hoc comparisons revealed significant differences between conditions without any association and language-associated, $t(387) = 3.31$, $p = .001$, or language- and neurodevelopmental-associated conditions, $t(387) = 4.14$, $p < .001$.

For left-hand preferences, the model of the interaction also reached significance suggesting that moderator levels differed from another, $F(3, 303) = 7.62$, $p < .001$. Similar to the results in the non-right-hand preference comparison, we found that *OR*s for conditions with either neurodevelopmental, language, or a combination of both associations were significantly different from a zero effect (only neurodevelopmental: *OR* = 1.34, 95% CI [1.10, 1.63], $p = .004$; only language: *OR* = 1.42, 95% CI [1.21, 1.66], $p < .001$; both: *OR* = 1.58, 95% CI [1.31, 1.90], $p < .001$, Figure 9B). Only conditions with no language and no neurodevelopmental association did not demonstrate a significant effect (*OR* = 0.96, 95% CI [0.83, 1.10], $p = .546$). Post hoc comparisons revealed significant differences between conditions without any association and neurodevelopmental-associated, $t(303) = 2.73$,

Figure 6

Forest Plot for (A) Non-Right-, (B) Left-, and (C) Mixed-Hand Preference Analysis Differentiated by Neurodevelopmental Status of the Included Conditions in the Second-Order Meta-Analysis



Note. Numbers above and below the whiskers represent the mean effect (log*OR*) and its 95% CI in brackets, respectively. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. The significance of each moderator level individually against a zero effect is indicated by the number of asterisk symbols. Overall effects of moderator impact were assessed via an *F* test, and post hoc comparisons were done using *t* tests (two-sided test). An α level of 1% was used for post hoc comparisons. The *F* value in the top left represents a test of the hypothesis that all effects within the subpanel are equal. The *Q* statistic in the top right represents the heterogeneity estimate. Vertical lines indicate significant post hoc tests between moderator levels. The corresponding orchard plots can be found in Supplemental Figures 16–18. *OR* = odds ratio; CI = confidence interval.
$^{*}p < .05$. $^{***}p < .001$.

$p = .007$, language-associated, $t(303) = 3.63$, $p < .001$, as well as neurodevelopmental- and language-associated conditions, $t(303) = 4.24$, $p < .001$.

Finally, an exploration of the interaction between neurodevelopmental and language associations did not reveal any significant moderation effect for mixed-hand preferences, $F(3, 144) = 1.54$, $p = .206$. We found that *OR*s for conditions with neither a neurodevelopmental nor language association showed a difference from a zero effect (*OR* = 1.74, 95% CI [1.23, 2.45], $p = .002$). The same was true for conditions with a language association as well as conditions with both a language- and neurodevelopment-association (only language: *OR* = 1.62, 95% CI [1.15, 2.28], $p = .006$; both: *OR* = 1.80, 95% CI [1.36, 2.39], $p < .001$, Figure 9C). Only conditions with an exclusive neurodevelopmental association did not demonstrate a significant effect (*OR* = 1.14, 95% CI [0.80, 1.61], $p = .464$). Post hoc comparisons did not reveal any significant differences among moderator levels using the conservative significance threshold (all *p*s > .044).

Robustness Check

The results were robust against sensitivity checks for different values of ρ as no result pattern changed if ρ values of 0, 0.2, 0.4, 0.6 (default value used during analysis), 0.8, or 1.0 were used for calculation (see "Sensitivity analyses" on https://osf.io/975dq/).

As an additional exploratory robustness check, we also investigated classification systems in more detail by exclusively analyzing those data sets for non-right-hand preferences that used an NR-R classification system. Similarly, we differentiated left-hand preferences between studies that used an L-R and L-M-R classification system. For the overall analysis, studies using an NR-R classification system showed a significant effect suggesting the cases differed from controls overall with respect to their non-right-hand preferences (*OR* = 1.36, 95% CI [1.17, 1.58], $p < .001$). For studies using an L-R classification system, a significant effect was found as well for left-hand preferences (*OR* = 1.32, 95% CI [1.16, 1.50], $p < .001$). If left-hand preferences were assessed using a more extreme L-M-R classification, the results were comparable (*OR* = 1.38, 95% CI [1.18, 1.61], $p < .001$). The results for the moderator analyses can be found in Supplemental Figures 25–27. Overall, the findings for moderation effects did not differ from the observed result pattern if all studies are considered for non-right- and left-hand preferences as described before suggesting that the results are robust. Full model results can be found on the OSF (see "additional online material models" at https://osf.io/975dq/).

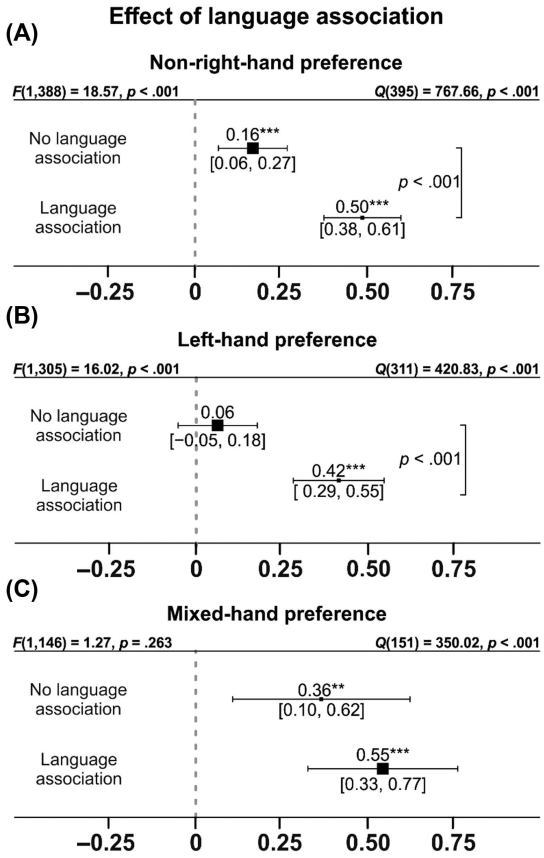
To identify if study quality influenced *OR*s between cases and controls, we used the overall quality rating of each study as a metaregressor. We did not find any evidence that study quality had a significant impact in the non-right-, $t(359) = 1.36$, $p = .173$; left-, $t(279) = 0.22$, $p = .828$, or mixed-hand preference meta-analysis, $t(127) = 0.41$, $p = .685$. A metaregression plot examining the *OR*s across study quality for non-right-, left-, and mixed-hand preferences can be found in Supplemental Figures 28–30, respectively.

Discussion

The present second-order meta-analysis aimed to leverage the databases from previously published meta-analyses on hand preference across diagnoses, identified through a systematic procedure and, after updating them, to investigate transdiagnostic patterns in hand preference prevalence. Moreover, the study aimed at statistically assessing the relevance of several potential moderators on the association between hand preference and clinical diagnoses. To this end, several sets of transdiagnostic case–control hand preference meta-analyses were conducted for three different types of hand preference classifications (non-right-hand preference, left-hand preference, and mixed-hand preference).

Figure 7

Forest Plot for (A) Non-Right-, (B) Left-, and (C) Mixed-Hand Preference Analysis Differentiated by Language Association of the Included Conditions in the Second-Order Meta-Analysis



Note. Numbers above and below the whiskers represent the mean effect (log*OR*) and its 95% CI in brackets, respectively. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. The significance of each moderator level individually against a zero effect is indicated by the number of asterisk symbols. Overall effects of moderator impact were assessed via an *F* test, and post hoc comparisons were done using *t* tests (two-sided test). An α level of 1% was used for post hoc comparisons. The *F* value in the top left represents a test of the hypothesis that all effects within the subpanel are equal. The *Q* statistic in the top right represents the heterogeneity estimate. Vertical lines indicate significant post hoc tests between moderator levels. The corresponding orchard plots can be found in Supplemental Figures 19–21. *OR* = odds ratio; CI = confidence interval.

** $p < .01$. *** $p < .001$.

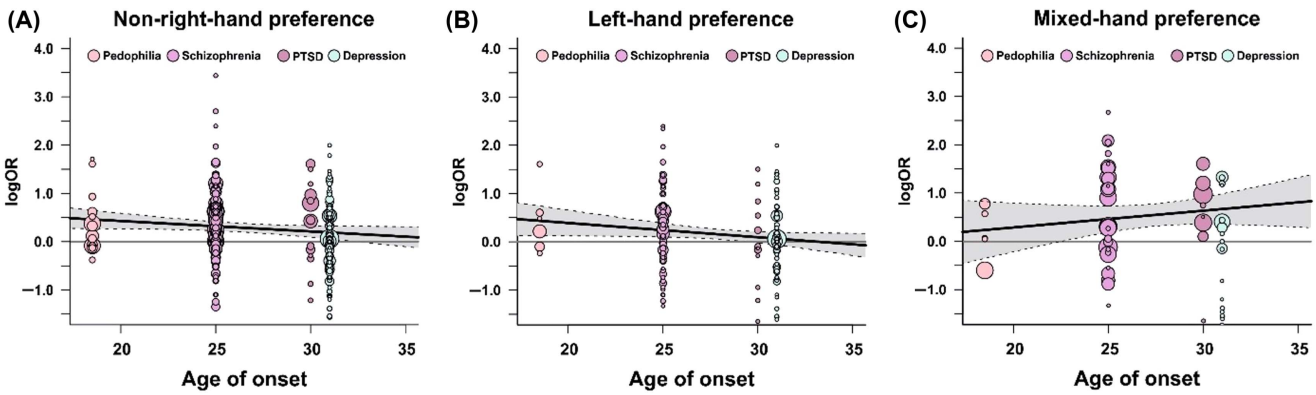
For all three main meta-analyses, the case–control *OR* reached significance indicating that cases on average showed higher rates of non-right-hand preference, left-hand preference, and mixed-hand preference than controls (see Table 3 for reference). For all three meta-analyses, the significant effect in frequentist meta-analysis was further supported by Bayesian meta-analysis indicating extreme evidence in favor of an effect. Thus, the overall effect of a higher rate of atypical hand preference in cases compared to controls is very robust. Although publication bias was not detected for any of the three comparisons, small-study bias was detected for the left-hand preference comparison (as well as a trend toward small-study bias in the non-right-hand preference comparison). Of note, the bias-adjusted estimates were higher than the original estimates. Specifically, the *OR* for the left-hand preference comparison was found to be $OR = 1.46$, whereas the bias-adjusted estimate was $OR = 1.63$ for the PET and $OR = 1.54$ for the PEESE adjustments. This finding translates into smaller studies reporting smaller hand preference differences than other studies. It could be that handedness matching between cases and control may have taken place without being reported or it could reflect what may be the lower methodological quality of smaller studies.

For the overall moderators tested across all diagnoses, we only found evidence that mean age was negatively associated with case–control differences in the non-right-hand and left-hand preference meta-analyses, suggesting that differences between cases and controls marginally decrease with increasing age. Although the effect was very small, it could fit our finding that a later age of onset is associated with smaller *OR*s between cases and controls if we assume that cohorts are tested relatively close to their diagnosis. This scenario seems likely given that studies often included participants with first-episode depression or tested children in their school-age following a diagnosis of dyslexia. Although we excluded neurodevelopmental disorders from the age of onset analysis, this finding could indicate that our results might generalize to these disorders as well since the highest *OR*s were observed in autism spectrum disorders, ID, and dyslexia, for all of which participants were typically assessed at a very young age in the primary studies. For the moderation effect of age of onset, we observed that this moderator showed nonsignificant differences in both the non-right- and left-hand preference meta-analyses at later ages of onset, suggesting that differences between cases and controls do not only decrease with a later age of onset of the underlying condition but also disappear. This effect could be explained by hand preferences becoming fixed and no longer being modifiable by external factors at later ages (Hamaoui et al., 2024). Another potential explanation could be that conditions with a very late age of onset, such as PTSD and depression, have genetic risk factors that do not overlap with genes associated with the development of lateral biases in humans. It should be noted though that large-scale genome-wide association studies have found positive genetic correlations for handedness and bipolar disorders pointing against this interpretation (Cuellar-Partida et al., 2021). Interestingly, no other moderator (sex ratio, classification system, handedness inventory, study location) reached significance despite all these factors affecting handedness in general (Papadatou-Pastou et al., 2008, 2020). This finding, however, fits the results from the primary meta-analyses in which these moderators, if investigated, also did not reach significance. Although this finding seems conflicting at first glance with all these factors modulating handedness, it can be explained as cases and controls are affected in a similar way since, for example, the use of a standardized inventory or assessing handedness via self-report is applied to cases and controls alike.

In the first preregistered hypothesis it was predicted that the investigated conditions would vary with regard to their atypical hand preferences. This hypothesis was confirmed by the statistical analyses that clearly showed that the overall case–control effect was not independent of diagnoses (see Figures 3–5). For all three

Figure 8

Metaregression Illustrating the Relationship Between the Age of Onset of Nonneurodevelopmental Conditions and the logORs Between Cases and Controls for (A) Non-Right-, (B) Left-, and (C) Mixed-Hand Preferences



Note. The age of onset is 18.5 years for pedophilia (Tozdan & Briken, 2019), 25 years for schizophrenia, 30 years for PTSD, and 31 years for depression (Solmi et al., 2022). Each dot represents an effect size from an individual data set. Its size indicates the precision of the study (larger dot indicates higher precision). The shaded area around the regression line represents the 95% CI. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. *OR* = odds ratio; PTSD = posttraumatic stress disorder; CI = confidence interval. See the online article for the color version of this figure.

meta-analyses, there was clear evidence for substantial heterogeneity suggesting that different subgroups may exist in the overall sample. The direct test of Hypothesis 1 using moderator analyses confirmed that diagnosis was a significant moderator of hand preference in all three meta-analyses. For non-right-hand preference, all included diagnoses except for depression and dyscalculia showed significant effects, whereas, for both mixed-hand preference and left-hand preference, four disorders did not show an effect. Especially individuals with autism spectrum disorder, ID, or schizophrenia demonstrated a higher prevalence of atypical hand preference compared to the rest of the conditions. In contrast, conditions such as dyscalculia or depression showed almost no changes in hand preferences between cases and controls.

In the second preregistered hypothesis, it was predicted that neurodevelopmental conditions would have a higher prevalence of atypical hand preference compared to conditions that are not associated with neurodevelopment. This hypothesis was confirmed for two out of the three analyses (see Figure 6). Specifically, moderator analyses indicated significantly higher *OR*s in neurodevelopmental conditions compared to other conditions supporting the notion that the neurodevelopmental status of the underlying conditions affects case–control differences. This only holds true when comparing non-right-hand and left-hand preferences and could not be observed for mixed-hand preferences, the latter generally linked to a reduction in brain asymmetry. Despite significant differences due to neurodevelopmental status, conditions without neurodevelopmental components still showed a nonzero effect for mixed-hand preference.

In the third preregistered hypothesis it was predicted that language-related conditions would show higher atypical hand preference prevalence compared to conditions without language-related symptoms. The third hypothesis was partly confirmed since for non-right-hand preferences and left-hand preferences, the *OR*s for atypical handedness in conditions with language association were significantly higher than in conditions without a language association (see Figure 7). Thus, the presence of symptoms affecting the language system is predictive of higher case–control differences as hypothesized. As for neurodevelopmental status, this difference did not emerge for mixed-hand preferences suggesting that mixed-hand preferences are not modulated by the condition having a language component.

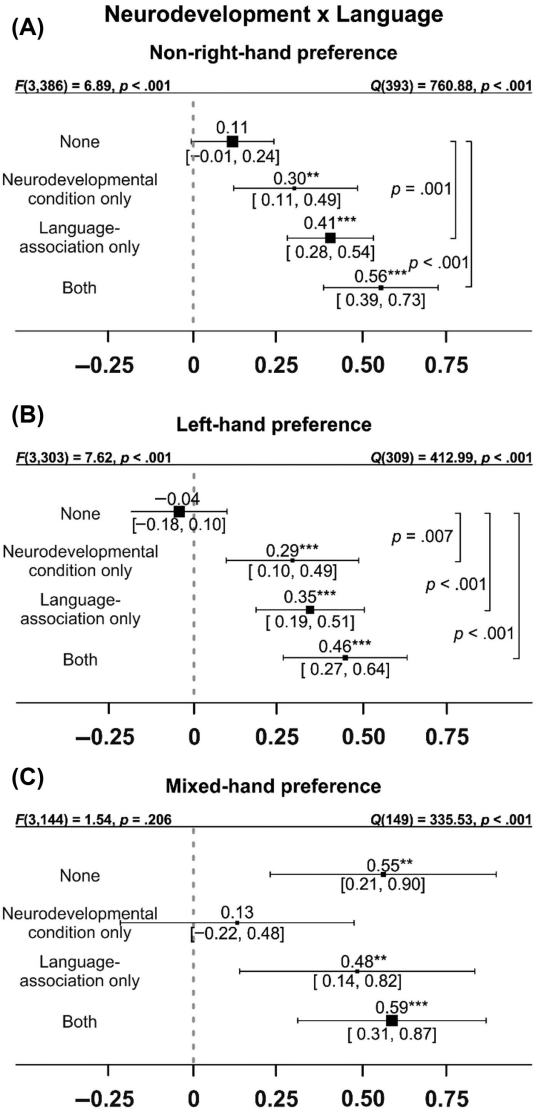
In the fourth preregistered hypothesis it was expected that the age of onset of nonneurodevelopmental conditions would be predictive of the prevalence of atypical hand preference. Specifically, it was expected that conditions that show an earlier onset would show higher atypical hand preferences compared to conditions with a later onset. The fourth hypothesis was confirmed for both non-right-hand preferences and left-hand preferences but not for mixed-hand preferences, again suggesting that mixed-hand preferences are not affected by altered neurodevelopment even in later life stages (see Figure 8).

Taken together, the statistical analyses, focused on testing the four preregistered hypotheses, reveal a clear pattern of results. On average, the clinical conditions investigated in the 10 previously published meta-analyses integrated in the present second-order meta-analysis were associated with increases in the frequency of atypical hand preference, which was moderated by diagnosis. Regarding the moderating effects of neurodevelopmental status, age of onset, and language association, significant effects were observed for non-right-hand preferences and left-hand preferences but not mixed-hand preferences. Because the non-right-hand preference category consists of a combination of left-hand preferences and mixed-hand preferences, it is likely that the results for non-right-hand preferences were primarily driven by left-hand preferences and not mixed-hand preferences.

In addition to the analyses that focused on testing the preregistered hypotheses, we also conducted an exploratory analysis focused on the interaction between two of the moderating variables, namely language status and neurodevelopmental status. For this analysis, the results suggest that conditions that neither affect the

Figure 9

Forest Plot Showing Mean Effect Sizes for (A) Non-Right-, (B) Left-, and (C) Mixed-Hand Preference Analysis Differentiated by the Interaction Between Neurodevelopmental Status and Language Association of the Included Conditions in the Second-Order Meta-Analysis



Note. Numbers above and below the whiskers represent the mean effect (log*OR*) and its 95% CI in brackets, respectively. A log*OR* equal to 0 indicates no difference between cases and controls. A log*OR* greater or less than 0 indicates increased or decreased rates of atypical (i.e., left-, mixed-, or non-right-) hand preference in cases compared to controls, respectively. The significance of each moderator level individually against a zero effect is indicated by the number of asterisk symbols. Overall effects of moderator impact were assessed via an *F* test, and post hoc comparisons were done using *t* tests (two-sided test). An α level of 1% was used for post hoc comparisons. The *F* value in the top left represents a test of the hypothesis that all effects within the subpanel are equal. The *Q* statistic in the top right represents the heterogeneity estimate. Vertical lines indicate significant post hoc tests between moderator levels. The corresponding orchard plots can be found in Supplemental Figures 22–24. *OR* = odds ratio; CI = confidence interval. ** $p < .01$. *** $p < .001$.

language system nor the neurodevelopmental trajectory do not show case–control differences in atypical handedness. However, this is again only the case for non-right-hand preference and left-hand preference (see Figure 9). The prevalence of mixed-hand preferences was affected by case–control status even in conditions without language association and neurodevelopmental status. Thus, it seems to be that the reversal of asymmetry—that is, higher rates of left-hand preferences in cases compared to controls—seems to be specific for neurodevelopmental or language-associated conditions. A reduction in asymmetry, as is the case for mixed-hand preferences, seems to be present across conditions irrespective of a connection to these factors.

Overall, these results have several important implications for clinical laterality research. They clearly suggest that case–control differences in hand preference vary with diagnosis. Focusing on the non-right-hand preference and left-hand preference findings, significant effects of a condition's neurodevelopmental status and age of onset could suggest that the developmental trajectory of a disorder is a critical component for the association of case–control status and atypical handedness. The finding that conditions developing earlier in life show a higher prevalence of atypical handedness suggests that there may be a period prenatally or early in life that is critical for an association between a clinical condition and handedness. As outlined before, handedness is determined by both genetic and nongenetic factors (Medland et al., 2009). Although pleiotropic genetic factors affecting both handedness and disorder pathogenesis (Cuellar-Partida et al., 2021; Schijven et al., 2024) may show their effect on both phenotypes at different points of life, timing may be more crucial regarding shared nongenetic influence factors.

Hand preferences develop early in life (Nelson et al., 2013). Prenatal arm use at 10 weeks gestation is highly predictive of hand preference later in life (Hepper, 2013). Although no clear consensus on when hand preferences are fixed at an adult level exists, different time points between 3 and 6 years of age have been suggested by researchers (Scharoun & Bryden, 2014). Thus, after the age of 6 years, hand preference typically does not change anymore unless hand preference is actively retrained (Porac, 1996) or a major injury of the dominant hand takes place (Taras et al., 1995). Thus, if a nongenetic factor (e.g., a stressful or traumatic event) can potentially affect both handedness and the pathogenesis of a disorder, it likely needs to happen during a critical period before age 6 or potentially even earlier. This finding would be in line with comparative findings in rodents. In rats, it has been shown that motor asymmetries are affected by prolonged stress exposure in the early postnatal days (Mundorf et al., 2020). Importantly, we also observed significant case–control differences for nonneurodevelopmental conditions with a later age of onset. As it is unlikely that hand preference changes due to a traumatic event later in life (e.g., in adulthood), these effects may potentially be explained by pleiotropic genetic influences that affect hand preference and the likelihood to develop a clinical condition, although at different points in life.

The results also showed that for non-right-hand preferences and left-hand preferences, conditions that included language-associated symptoms had a higher rate of atypical handedness. Language lateralization and handedness are correlated, with left-handers being more likely to show atypical rightward language asymmetry (Bruckert et al., 2021; Karlsson et al., 2023). At the same time, it has been discussed that inconsistent language lateralization may represent a risk factor for language impairment (Bradshaw et al., 2020). Furthermore, it has been shown that the clinical severity of

language-based symptoms is related to the amount of atypical language lateralization. A meta-analysis on language lateralization assessed with the dichotic listening task in schizophrenia patients (Ocklenburg et al., 2013) revealed that patients experiencing auditory verbal hallucinations had a stronger reduction of the typical leftward asymmetry for auditory language processing than patients without auditory verbal hallucinations. The findings of the present study suggest that similarly there is an association between atypical handedness and language symptoms, likely due to strong correlations between handedness and language lateralization. We cannot make any inferences on whether atypical asymmetry may be a cause or a consequence of clinical conditions, or if a shared third factor contributed to both phenomena (see Bishop, 2013 for a discussion of this question). More generally, this finding implies that it could be meaningful to conceptualize the association between atypical handedness and clinical conditions less on a diagnosis level, but more within the framework of a symptom-driven transdiagnostic approach in that the severity of relevant symptoms is associated with laterality, not the diagnosis per se. Since individual patients could have rather diverse symptoms and still meet the diagnostic criteria for a specific disorder, a diagnosis-driven approach is not optimal from a neuroscientific perspective, even if our data suggest a significant effect of diagnosis on atypical handedness. Since specific cognitive systems may be affected in some people with the same diagnosis, but not in others, a symptom-driven approach may explain a larger amount of variance in handedness data than a diagnosis-based approach.

Importantly, the moderator effects observed for non-right-hand preferences and left-hand preferences were not observed for mixed-hand preferences. This suggests that left-hand preferences and mixed-hand preferences are distinct phenotypes. They need to be assessed and analyzed separately in clinical laterality studies. Our results show that although both left-hand preferences and mixed-hand preferences had significantly higher prevalence in cases than controls, moderator effects were specifically observed for left-hand preferences but not mixed-hand preferences. This suggests the different ontogenetic and developmental factors affect left-hand preferences and mixed-hand preferences and that these factors show differential associations with the pathogenesis of the analyzed conditions. This is in line with the findings of a recent handedness genome-wide association studies that identified 48 common gene variants associated with handedness (Cuellar-Partida et al., 2021). Of these variants, 41 showed statistically significant association with left-hand preferences and seven showed associations with mixed-hand preferences. If there are different neurobiological bases for left-hand preferences and mixed-hand preferences, it may explain the different moderation effects found in the present study. Moreover, on a more abstract level, left-hand preference represents a change in the direction of asymmetry for handedness from the typical right-hand preference. The strength of the preference itself remains largely unaffected by this change in asymmetry direction. Mixed-hand preference, in comparison, represents a reduction in the degree of the asymmetry leading to an almost symmetric preference, without a strong preference for either direction. Since different patterns of activation in the motor cortex have been associated with the direction and degree of handedness (Dassonville et al., 1997), left-hand preference and mixed-hand preference may be associated with distinct neural signatures.

Although our results highlight that a reversal rather than a reduction in asymmetry may be relevant regarding the investigated moderators, there could also be another explanation as to why the meta-analysis on mixed-hand preferences showed a contrasting result pattern. Even though categorizing individuals into left- and right-handers is usually straightforward, the criteria for categorizing individuals as mixed-handers are often inconsistent between studies. Mixed-handedness may reflect ambidexterity, that is, an equal skill level of both hands, or inconsistent hand use, that is, using different hands across different tasks (Vingerhoets et al., 2023). Unfortunately, studies included in this second-order meta-analysis that clarified whether they measured ambidexterity or inconsistent hand use were rare exceptions. Since the terminology is also used inconsistently in the literature, these reports might not even be reliable. Studies might have labeled a group as ambidextrous based on lateralization quotients. Yet, lateralization quotients per se are not informative of ambidexterity or inconsistent hand use as both phenotypes result in values around 0. The differences in the result pattern in the mixed-hand preference meta-analysis might therefore be grounded in a more heterogenous phenotype that is actually represented by these two different features of handedness, namely ambidexterity or inconsistency (Mundorf et al., 2024).

The findings of the present study show the methodological benefits of using second-order meta-analysis as a form of evidence synthesis in clinical psychology (Schmidt & Oh, 2013). Recent research has highlighted the need for second-order meta-analyses or umbrella reviews as these types of studies are even one step above first-order meta-analyses or systematic reviews in the evidence synthesis pyramid for multiple reasons. Beyond increasing statistical power, they can make complex topics comprising multiple meta-analyses and systematic reviews more digestible for the reader and minimize conflicting information from first-order meta-analyses (Ortega et al., 2016). Furthermore, second-order metastudies can illuminate previously undiscovered patterns across primary meta-analyses (Fusar-Poli & Radua, 2018). Pooling data gathered by previously published meta-analyses in different clinical conditions permits the synthesis to make conclusions on the transdiagnostic moderator effects that would have not been possible based on the data presented in any single meta-analysis. The methodological strategy used in the present study combined the integration of data across previously published meta-analyses with moderator analyses using moderators that were beyond the scope of each meta-analysis as well as analyses focused on the interaction between moderators. This general principle may also be useful for many other research questions in clinical psychology aimed at identifying the transdiagnostic influence of factors on different clinical entities or psychological phenotypes. Furthermore, this principle can be also applied in other fields within psychology, or other sciences, to discover higher level effects, not possibly be dealt with within first-order meta-analyses.

Part of the process that concluded in the second-order meta-analysis was updating previously published first-order meta-analyses and recalculating their effect sizes using an identical analysis pipeline. This procedure makes the findings of these meta-analyses not only up to date (and thus relevant for researchers and clinicians interested in a single disorder) but also directly comparable, as the same, state-of-the-art analytical decisions (e.g., tests used, corrections applied) were applied. Moreover, the overall effects of each

updated meta-analysis were the product of an omnibus analysis (and not of 10 separate meta-analyses), protecting against Type 1 errors.

Limitations

Although a second-order meta-analysis amplifies the advantages of meta-analysis, such as high statistical power due to a large number of integrated data points, it also can be negatively affected by the typical problems that can reduce the data quality in meta-analysis. Most importantly, problems with data quality in the empirical studies integrated into the meta-analyses that are the basis of the second-order meta-analysis may affect the results (the so-called "garbage in–garbage out" problem, Egger et al., 2001). In the present study, this issue may have mostly affected the mixed-handedness analysis, as it is a known issue in handedness research that there is high interstudy variability in the definition of mixed-handedness based on typical handedness questionnaires (Mundorf et al., 2024). Thus, phenotyping in studies with a three-category system (left, right, mixed) may have been much more variable than phenotyping in studies with a two-category system (left, right). Therefore, the findings for left-hand preferences may be more robust and replicable than those for mixed-hand preferences. Another point related to the quality of the included studies is that only four primary meta-analyses (pertaining to ADHD, autism, dyscalculia, and ID) explicitly used the absence of comorbidity as an exclusion criterion. This concern is especially important in a transdiagnostic perspective, as is the one adopted here.

A further shortcoming of the present study pertains to the fact that development, by definition, is a process of change over time. Cross-sectional studies as they were included in the present study are unable to illuminate whether disorders affecting neurodevelopment are linked to changes in handedness. Although we did not explicitly exclude longitudinal designs from the search, no primary study included in this second-order meta-analysis investigated the effects of (atypical) neurodevelopment using longitudinal designs on the development of handedness. To our knowledge, no such study has been conducted to this date. Thus, any interpretations regarding the influence of neurodevelopment on handedness need to be treated with caution as these links can only be hinted at using cross-sectional research.

As mentioned above, handedness manifests as both hand preference and hand skill difference. Individuals can further vary in terms of direction or degree of hand preference and they can be categorized categorically (e.g., left-handers vs. right-handers in each case or control group) or placed in a continuum, whereby handedness means and standard deviations of each group are reported. Still, hand skill data are scarce in the literature and even more so when it comes to case–control studies. Therefore, no meta-analyses on hand skill levels in different conditions have been conducted to date that would allow for a transdiagnostic second-order meta-analysis. Similarly to hand skill, degree of handedness and continuous scores of handedness are not typically reported, making it impossible to conduct a transdiagnostic analysis using these handedness variables.

With respect to the age of onset analyses, it should be noted that each diagnosis was attributed to discrete age values preventing a truly continuous approach that might also potentially reveal nonlinear associations. This deficit could be remedied if future primary studies start to report the age of onset for a given diagnosis in their sample. An even better solution involves individual participant data meta-analyses that use the raw primary data instead of sample averages as the age of onset will vary considerably between individuals. Using an individual participant data approach could therefore be extremely insightful to illuminate the relationship between age of onset and the development of atypical hand preferences. We hope that, in the future, authors provide the sample's mean age of onset, or ideally, the individual's age of onset. These data will allow for more detailed analyses into relations between the age of onset and the prevalence of atypical hand preference across mental and neurodevelopmental disorders.

An inherent limitation of conventionally conducted meta-analyses is that they do not truly elucidate mechanisms as they are a method of synthesizing existing data. Although causality can be approximated using structural equation modeling and mediation in meta-analyses, these approaches generally require appropriate underlying primary data controlling for confounding variables and strong theoretical grounding for meaningful mechanistic interpretation (Landis, 2013). For handedness research specifically, studies usually report handedness as a demographic variable without placing it at the center of their research question. Therefore, confounding variables affecting handedness are often not reported. In addition, the absence of primary longitudinal data on relationships between handedness and the onset of disorders makes such an approach difficult as of now. Our results nonetheless highlight critical transdiagnostic patterns that strongly hint at mechanistic processes related to neurodevelopment and language processing. Future research is needed that causally tests these patterns across species (both humans and other animals) to ascertain the true biological mechanisms at play in our findings.

Future Directions

The findings of the present second-order meta-analysis have several important implications for future research. Obviously, it is important to conduct more case–control meta-analyses on handedness in clinical conditions that have not yet been meta-analyzed, such as anxiety disorders and obsessive–compulsive disorders. Moreover, the present findings strongly suggest that more transdiagnostic empirical research on handedness is needed. In particular, studies are needed that directly compare handedness in disorders that have not yet been investigated in meta-analysis. Moreover, it is crucial to identify at what age the critical period for an association between handedness and clinical conditions takes place and how long it is. Doing so would probably require a combination of large-scale longitudinal studies in humans and controlled animal experiments. Given that the effects of neurodevelopment can only be disentangled using longitudinal designs, we hope that the research presented here will prompt future primary studies to specifically study the relationship between neurodevelopment and handedness in more detail. Although we did not find evidence that the overall study quality was influential with respect to hand preference differences between cases and controls, we nonetheless recommend that future studies carefully focus on high-quality research and carefully curated samples to ensure the absence of confounding variables.

In terms of methodology, we would like to urge researchers to measure and report both hand preference and hand skill, and share raw data in open science repositories, such as the OSF. Doing so allows meta-analysts to calculate both direction and degree scores and to treat handedness either as a categorical or a continuous variable. In turn, this procedure allows for a more holistic understanding of

the handedness phenomenon, as these handedness manifestations have different properties. At the same time, primary studies should report in their raw data set demographic variables, such as sex and specific age (instead of labeling their sample as, e.g., "college students"), and detail their methodological approaches (e.g., procedure used for diagnosis, severity of symptoms). The failure to report these variables happens more often than expected, resulting in fewer studies being included in moderator variable analyses and thus reducing their power. As mentioned above, limb preferences can also be observed in nonhuman animal species (Vallortigara & Rogers, 2020). Interestingly, animal models for the development of psychopathologies have been investigated in clinical laterality research (Mundorf et al., 2020; Mundorf & Ocklenburg, 2021). If more empirical laterality studies in nonhuman animal models for psychopathology are published in the future, cross-species meta-analysis (Ocklenburg et al., 2023) integrating such data with human data may yield interesting insights into an evolutionary perspective on handedness and clinical conditions. Furthermore, they are critical for the discovery of biological mechanisms at the circuit and genetic level that are utmost needed to fully understand handedness and its link to psychopathology in the future.

Conclusions

Our study concludes that the association of handedness and clinical conditions is best understood from a transdiagnostic, developmental, and symptom-focused perspective as case–control differences in hand preference vary with diagnosis. Moreover, neurodevelopmental conditions, conditions with an early age of onset, and conditions that included language symptoms showed higher rates of atypical handedness. Although our results do not provide causal and mechanistic insight, they nonetheless suggest that atypical hand preferences are likely linked to atypical neurodevelopment or language processing, especially in earlier life stages. We hope that our results prompt more primary research that can potentially test any causal relationships to further elucidate the role of handedness in psychological research in the future.

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