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Handedness in ADHD: Meta-Analyses

Evgenia Nastou¹, Sebastian Ocklenburg², Hoogman, Martine³, Marietta Papadatou-Pastou^{1,4}

¹: National and Kapodistrian University of Athens, Greece

²: Institute of Cognitive Neuroscience, Ruhr University Bochum, Germany

³: Radboud University Nijmegen The Netherlands

⁴: Biomedical Research Foundation, Academy of Athens, Greece

Corresponding author:

Marietta Papadatou-Pastou, Department of Primary Education, National and Kapodistrian University of Athens, 13A Navarinou Street, Athens 10680, Greece

E-mail: marietta.papadatou-pastou@seh.oxon.org

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Abstract

Meta-analyses have shown that several neurodevelopmental and psychiatric disorders, such as autism spectrum disorder and schizophrenia, are associated with a higher prevalence of atypical (left-, non-right-, and/or mixed-) handedness. One neurodevelopmental disorder for which this association is unclear is attention deficit hyperactivity disorder (ADHD). Here, some empirical studies have found evidence for a higher prevalence of atypical handedness in individuals with ADHD compared to neurotypical individuals. However, other studies failed to establish such an association. Therefore, meta-analytic integration is critical to estimate whether or not there is an association between handedness and ADHD. We report the results of three meta-analyses (left-, mixed-, and non-right-handedness) comparing handedness in individuals with ADHD to controls (typically developing individuals). The results show evidence of a trend towards elevated levels of atypical handedness when it comes to differences in left- and mixed-handedness ($p = 0.09$ and $p = 0.07$, respectively), but do show clear evidence of elevated levels of non-right-handedness between individuals with ADHD and controls ($p = 0.02$). These findings are discussed in the context of the hypothesis that ADHD is a disorder in which mostly right-hemispheric brain networks are affected. Since right-handedness represents a dominance of the left motor cortex for fine motor behavior, such as writing, as well as a left-hemispheric dominance for language functions, and about 90% of individuals are right-handers, this hypothesis might explain why there is not stronger evidence for an association of left-handedness with ADHD. We suggest that the mechanisms involved in the pathogenesis of ADHD might show an overlap with the mechanisms involved in handedness strength, but not handedness direction.

Keywords: Handedness; ADHD; ADD; Meta-analysis; Hand preference; Hand skill

PROSPERO preregistration ID = 122621

Introduction

Hemispheric asymmetries, that is functional or structural differences between the left and the right half of the brain, are an important organizational feature of the nervous system of vertebrates (Bisazza et al. 1998; Güntürkün and Ocklenburg 2017; Güntürkün et al. 2020; Miletto Petrazzini et al. 2020; Schmitz et al. 2017; Vallortigara and Rogers 2020). Hemispheric asymmetries have been observed in several cognitive systems in the human brain including language processing (Corballis and Häberling 2017; Hugdahl and Westerhausen 2016), emotion processing (Gainotti 2019; Lindell 2018), face processing (Harrison and Strother 2019), and visuo-spatial attention (Brooks et al. 2014). On the behavioral level, the most widely investigated form of hemispheric asymmetries are limb preferences, for example handedness in humans (Ocklenburg et al. 2013) or pawedness and similar concepts in non-human animals (Ocklenburg et al. 2019; Ströckens et al. 2013).

Handedness reflects a preference to use one hand over the other for everyday activities, such as writing or drawing (Brandler and Paracchini 2014; Corey et al. 2001; Ferre et al. 2020; Madalena et al. 2020; Paracchini et al. 2016), or the fact that one hand is more skilled than the other for unimanual actions. While right-handedness appears to be the norm in humans (Papadatou-Pastou et al., 2020b), non-typical handedness includes different manifestations, such as left-handedness, mixed-handedness, and non-right-handedness, the latter term typically including all former categories. Mixed-handedness typically refers to the preferred use of different hands for different activities. A recent meta-analysis estimated that the prevalence of left-handed preference lies between 9.3% and 18.1%, with the best overall estimate being 10.6%,

the prevalence of mixed-handedness lies between 6.7% and 12.0% (best overall estimate: 9.3%) and the prevalence of non-right-handedness lies between 13.9% and 22.3% (best overall estimate: 18.1%) (Papadatou-Pastou et al. 2020b). Importantly, several factors have been shown to affect the chances of being a left-hander, such as sex (Papadatou-Pastou et al. 2008), geographical location (Raymond and Pontier 2004), year of birth (Faurie and Raymond 2004), breastfeeding (Hujoel 2019), and birthweight (Kovel et al. 2019).

One of the most striking findings in this regard is the fact that several neurodevelopmental and psychiatric disorders have been associated with a higher prevalence of left-handedness and/or mixed-handedness than what has been observed in neurotypical individuals (Mundorf and Ocklenburg 2021). These include autism spectrum disorders (Markou et al. 2017; Escalante-Mead et al. 2003), intellectual disability (Papadatou-Pastou and Tomprou 2015), schizophrenia (Dragovic and Hammond 2005; Hirnstein and Hugdahl 2014; Sommer et al. 2001), dyslexia (Eglinton and Annett 1994), and others.

One neurodevelopmental disorder for which the empirical evidence for a relation with handedness is somewhat ambiguous is attention deficit hyperactivity disorder (ADHD). ADHD is a rather common and clinically heterogeneous neurodevelopmental disorder with complex etiology that implicates both genetic and environmental factors (Cabral et al. 2020). ADHD is reflected by a persistent pattern of difficulties in paying attention with or without hyperactivity and impulsiveness, which prevents a person's stable development and functioning (American Psychiatric Association, 2013). There are three subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and the combined type (American Psychiatric

Association 2013). The prevalence of ADHD has been estimated to be around 5.9% to 7.1% in children and adolescents and 5.0% in young adults (Willcutt 2012).

Evidence for atypical lateralization in people with ADHD comes from several different fields of research. For example, several studies reported atypical asymmetries in EEG alpha and beta band in individuals with ADHD compared to neurotypical individuals (Hale et al. 2010a; Hale et al. 2009b; Hale et al. 2010b; Keune et al. 2015). Moreover, neuroimaging studies have shown that individuals with ADHD show atypical asymmetries in both grey matter and white matter structure (Douglas et al. 2018; Li et al. 2019). However, a recent mega-analysis of subcortical and cortical asymmetries in people with ADHD across the lifespan did not show differences for this brain phenotype in comparison to controls (Postema et al. 2021).

However, what is still unclear is whether or not there is an increased prevalence of atypical lateralization on the behavioral level, namely whether there are increased levels of left-handedness and/or mixed-handedness in individuals with ADHD compared to neurotypical controls. There is some empirical evidence that suggests that this might be the case. For example, in the BBC internet study that contained data from 255,100 individuals, there was evidence that mixed-handedness was related to a higher prevalence of hyperactivity (Peters et al. 2006).

Regarding studies that directly compared handedness rates in individuals with ADHD and neurotypical individuals there are some studies that present findings indicating a higher prevalence of left-handedness and/or mixed-handedness in individuals with ADHD. For example, a study in 56 individuals with ADHD reported a higher prevalence of left-handedness than in the general population (Niederhofer 2005) and a Finnish study reported that mixed-handed children were more likely to

display ADHD symptoms (Rodriguez et al. 2010). In contrast to these findings, a study in 520 children did not find any significant association between handedness and inattentiveness score or hyperactivity-impulsivity score (Ghanizadeh 2013). Moreover, there might be differential relations of ADHD symptoms with handedness, as a Taiwanese study in 505 male and 645 female patients with ADHD (Lin and Tsuang 2018) found that mixed-handers showed higher inattentiveness than left- or right-handers. In contrast, no associations with handedness were found for hyperactivity and impulsivity.

Several reasons could potentially explain these conflicting results, including differences in cohort age, handedness assessment, and cut-off criteria for handedness groupings. Moreover, low statistical power due to small sample sizes might have affected the ability of some study designs to detect small, but existing, effects. In order to determine whether there is a reliable association between handedness and ADHD a meta-analytic integration of findings is needed (Egger and Smith 1997; Rosenthal and DiMatteo 2001; Walker et al. 2008). In addition, meta-analytic techniques allow for the investigation of small study bias, which could be due to publication bias, and the evaluation of studies' heterogeneity. Importantly, meta-analysis has been put forward as a tool that could help towards dealing with the reproducibility crisis that psychological science has been recently facing (e.g. Open Science Collaboration, 2015).

Here we report meta-analyses that integrate research findings from empirical studies that assessed handedness in individuals with ADHD and neurotypical individuals. Our aim was to produce a reliable estimate of the prevalence of atypical handedness categories, namely left-, non-right-, and mixed-handedness, in individuals

with ADHD as compared to controls. Finally, the presence of possible small study bias was also assessed.

Methods

Study selection

Studies that were included in the meta-analysis were identified in a multi-step approach following the PRISMA guidelines (Moher et al. 2009).

1. Study identification: Studies were identified using the scientific databases Pubmed, Scopus, and PsycInfo. The following search terms were used: ("handedness" OR "hand skill" OR "hand preference" OR “functional laterality”) AND ("ADHD" OR "ADD" OR "Attention Deficit Hyperactivity Disorder" OR “Attention Deficit Disorder”).
2. All published papers that were cited in the studies identified in step 1 were screened.
3. The authors that had published the included studies were contacted, if their email addresses could be retrieved, in order to enquire whether they could contribute previously missing or unpublished data to the meta-analysis.

Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were used to select the studies suitable for inclusion in the meta-analysis:

- a) Participants: Studies needed to report handedness in individuals with ADHD and a control group of neurotypical individuals with no age restriction. Studies without a control group were excluded.
- b) No handedness matching: Studies in which the individuals with ADHD and the controls were matched for handedness were excluded.
- c) No studies explicitly excluding left-handers: Studies that reported to only test right-handed individuals with ADHD and controls were excluded.
- d) No comorbidity: Studies including individuals with ADHD who presented comorbidity with other disorders were also excluded, as potential handedness effects could have been driven by the comorbidity. Neurodevelopmental disorders, such as autism (Markou et al., 2017), and psychiatric disorders, such as schizophrenia (Dragovic & Hammond, 2005), have been shown to be associated with elevated levels of atypical handedness. Therefore, excluding individuals with ADHD who also present with comorbidities was considered optimal in order to avoid misinterpreting any handedness-disorder associations found in our dataset as led by ADHD, when they could have been led by a comorbid disorder.
- e) ADHD diagnosis: ADHD needed to have been diagnosed by a third party and not have been self-reported.
- f) Sufficient reporting of statistical information: Only studies reporting the statistical information needed for the meta-analytic calculations were considered.
- g) Language: Only studies available in English were included.

Included studies

Data collection ended in April 2021 and a total of $k = 16$ studies and $d = 6$ databases were included in the meta-analysis. With regards to the databases, through the literature search we were able to locate the ADHD-200 database (Alexander et al., 2017), which provides handedness data for ADHD and control participants. The ADHD-200 database is partially used in other publications (e.g., Tomasiello, 2020; Wang et al., 2019; Wyciszewicz et al. 2017), so we opted to include the full database as provided to us in January 2021 instead of those publications. Moreover, we came across the ENIGMA ADHD working group (Hoogman et al., 2017), via which we were able to locate six more databases (namely, Würzburg, Niche, ACPU, NICAP, IMpACT2) that were not used in any of the included studies. Details about literature search and data extraction are shown in Figure 1. Table 1 shows details of included studies. Overall, the total number of participants included in the meta-analyses was $n = 2371$, including $n = 1114$ individuals with ADHD and $n = 1257$ controls.

Please insert Figure 1 about here

Please insert Table 1 about here

Preregistration

The study was preregistered on PROSPERO before the authors started to identify eligible studies for inclusion according to the criteria above. (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=122621).

The time-stamped date of registration in PROSPERO was February 5th, 2019. Preregistration was conducted in order to ensure unbiased data analysis.

Statistical analysis

Meta-analysis was carried out using R and R Studio, following an established protocol (Harrer et al., 2021). Due to variation in the classification schemes used in the original studies it was not possible to conduct one single meta-analysis without losing important information. For example, some studies reported two categories (left-handedness and right-handedness), while others reported three categories (left-handedness, right-handedness and mixed-handedness). We therefore conducted three different meta-analyses. In the first meta-analysis, we compared percentage rates of left-handedness between individuals with ADHD and controls. Overall, $k=13$ studies were included (Dramsdaahl et al. 2012; Hotham et al. 2018; Neely et al. 2016; Neely et al. 2017; Pluck et al., 2020; Rolfe et al. 2006; Robaey et al. 1992; Scharoun et al. 2013; Soliva et al. 2010; ter Huurne et al. 2013; Tucha et al. 2008; Tucha et al. 2006; Xia et al. 2012) and $d = 6$ databases (ADHD-200, Würzburg, Niche, ACPU, NICAP, IMpACT2).

In the second meta-analysis, we compared non-right-handedness rates (i.e., left-handedness and mixed-handedness combined) between individuals with ADHD and controls. Overall, $k = 16$ studies were included (Dramsdaahl et al. 2012; Groen et al. 2009; Hotham et al. 2018; Neely et al. 2016; Neely et al. 2017; Martel et al. 2008; Pluck et al., 2020; Robaey et al. 1992; Rolfe et al. 2006; Shaw and Brown 1990; Scharoun et al. 2013; Soliva et al. 2010; ter Huurne et al. 2013; Tucha et al. 2008; Tucha et al. 2006; Xia et al. 2012) and $d = 6$ databases (ADHD-200, Würzburg, Niche, ACPU, NICAP, IMpACT2).

In the third meta-analysis, we compared mixed-handedness rates between individuals with ADHD and controls. Overall, $k = 9$ studies were included (Groen et al. 2009; Martel et al. 2008; Neely et al. 2017; Pluck et al., 2020; Robaey et al. 1992; Shaw and Brown 1990; Soliva et al. 2010; Tucha et al. 2006; Tucha et al. 2008) and $d = 5$

databases (ADHD-200, Würzburg, Niche, ACPU, IMpACT2).

As a secondary analysis, we repeated the analysis for all subgroups, this time including only those studies and datasets that had used the Edinburgh Handedness Inventory (Oldfield, 1971) to measure handedness, as this is the most used hand preference inventory in the literature (Papadatou-Pastou et al., 2020b). This analysis was not preregistered.

In the PROSPERO preregistration we had stated: “In case handedness is reported as a continuous variable in at least five studies, we will further compute the standardized difference in handedness mean score between individuals with ADHD/ADD and neurotypical individuals”. However, we could only identify three studies that reported handedness as a continuous variable and fulfilled all inclusion criteria. Therefore, this analysis was not carried out.

For all three meta-analyses, the odds ratio (OR) between individuals with ADHD and the control group of neurotypical (NT) individuals with a 95% confidence interval were used as the effect size measure. The OR can also be transformed to a simple proportion, using the formula $ADHD = NT \times OR / [1 + NT(OR - 1)]$, so that the findings can be more intuitively grasped. To investigate the presence of small study bias, funnel plots and Egger’s *t* test were used, as well as Duval and Tweedie’s Trim-and-Fill method (Duval and Tweedie, 2000). In addition, the presence of heterogeneity was investigated using the *Q* test, the *I*² index and the Tau² test. The *I*² index level was considered low if it was up to 25%, medium if it was up to 50% and high if it was up to 75% (Higgins et al., 2003). Effect sizes were calculated using a random-effects model in all meta-analyses. Data are available in <https://osf.io/97vra/>.

Results

Meta-analysis 1: Left-handedness

Overall, $k = 13$ studies and $d = 6$ databases with an overall n of 2,039 participants (953 individuals with ADHD and 1,086 controls) were included in this analysis (see Figure 2). The ADHD-to-neurotypical left-handedness odds ratio was 1.34 (95% Confidence Interval [CI] lower limit: 0.95, upper limit: 1.90). Weak evidence of a difference in left-handedness prevalence between individuals with ADHD and controls was found ($t = 1.77$, $p = 0.09$). No evidence of heterogeneity was detected ($Q(18) = 18.29$, $p = 0.44$, $\text{Tau}^2 = 0.01$, $I^2 = 1.6\%$).

Please insert Figure 2 about here

Egger's test indicated that there was no evidence for small study bias ($t_{(18)} = -0.048$, $p = 0.96$). Visual inspection of the funnel plot graphical test (see Figure 3) also did not reveal any evidence for small study bias, as the plot looked rather symmetrical. Duval and Tweedie's Trim-and-Fill method added two studies on the right (ORs = 7.72 and 10.99).

Please insert Figure 3 about here

Meta-analysis 2: Non-right-handedness

Overall, $k = 16$ studies and $d = 6$ databases with an overall n of 2,371 participants (1,114 individuals with ADHD and 1,257 controls) were included in this analysis (see Figure 4). The ADHD-to-neurotypical non-right-handedness odds ratio was 1.49 (95% CI lower limit: 1.07, upper limit: 2.07). Strong evidence for a difference in non-right-handedness prevalence between individuals with ADHD and controls was found ($t = 2.49$, $p = 0.02$). Therefore, it can be shown using the formula $ADHD = NT \times OR / [1 + NT(OR - 1)]$, that, for an estimate of non-right-handedness of 18.1% for the general population (Papadatou-Pastou et al., 2020b), individuals with ADHD show a non-right-handedness prevalence of 27.32%. No evidence of heterogeneity was detected ($Q(21) = 26.24$, $p = 0.20$, $\tau^2 = 0.13$, $I^2 = 20\%$).

Please insert Figure 4 about here

Egger's test indicated that there was no evidence for small study bias ($t_{(21)} = 1.70$, $p = 0.11$). Visual inspection of the funnel plot graphical test (see Figure 5) also did not reveal any evidence for small study bias. Using Duval and Tweedie's Trim-and-Fill method showed that four studies needed to be added on the left of the plot to achieve symmetry (ORs = 0.02, 0.12, 0.29, 0.48)

Please insert Figure 5 about here

Meta-Analysis 3: Mixed-handedness

Overall, $k = 9$ studies and $d = 5$ databases with an overall n of 1,284 participants (886 individuals with ADHD and 986 controls) were included in this analysis (see Figure 6). The ADHD-to neurotypical mixed-handedness odds ratio was 1.59 (95% CI lower limit: 0.96, upper limit: 2.66). Evidence indicating weak evidence of a difference in mixed-handedness prevalence between individuals with ADHD and controls was detected ($t = 1.97, p = 0.07$). No evidence of heterogeneity was detected ($Q_{(13)} = 18.79, p = 0.13, \text{Tau}^2 = 0.23, I^2 = 31$).

Please insert Figure 6 about here

Egger's test indicated that there was evidence for small study bias ($t_{(13)} = 2.28, p = 0.042$). Visual inspection of the funnel plot graphical test (see Figure 7) revealed asymmetry with the right side showing a more scattered distribution of studies than the left. Using Duval and Tweedie's Trim-and-Fill method showed that four studies needed to be added on the left side of the plot to achieve symmetry (ORs= 0.002, 0.11, 0.22, 0.35)

Please insert Figure 7 about here

Secondary analysis (EHI studies)

As a secondary analysis, we repeated the above meta-analyses for the subgroup of studies and datasets that used the Edinburgh Handedness Inventory (Oldfield, 1971) to assess hand preference. The number of datapoints included in each of the comparisons was limited to 6 (out of 19) for the left-handedness comparison, 7 (out of

22) for the non-right-handedness comparison, and 3 (out of 14) for the mixed-handedness comparison. For none of the comparisons was there evidence of a difference in atypical handedness between ADHD and neurotypical controls ($p = 0.77$; $p = 0.74$; $p = 0.75$, respectively) or evidence of heterogeneity ($p = 0.87$; $p = 0.54$; $p = 0.16$, respectively).

Discussion

The aim of the present study was to statistically integrate studies on handedness in individuals with ADHD and controls in order to determine whether or not ADHD shows an association with handedness. To this end, three meta-analyses were performed, investigating left-handedness, non-right-handedness, and mixed-handedness.

The results of our study indicate that the link between ADHD and handedness is weak. The meta-analyses revealed weak evidence for the idea that patients with ADHD show a higher prevalence of left-handedness ($p = 0.09$) and mixed-handedness ($p = 0.07$), but we did find stronger evidence for a higher prevalence of non-right-handedness ($p = 0.02$). In other words, the analysis revealed evidence that individuals with ADHD have a higher prevalence of non-right-handedness than neurotypical controls with an odds ratio of 1.49. Thus, if the non-right-handedness incidence is 18.1% in the general population (Papadatou-Pastou et al., 2020b), then it is 27.3% for individuals with ADHD. For all meta-analyses, all heterogeneity tests failed to reach significance. This makes it unlikely that there is a subgroup of studies showing a result pattern differing from the main result.

Egger's t test failed to show evidence that these results were affected by small study bias, except for the mixed-handedness comparison. This result, however, should

be interpreted cautiously for two reasons. First, this analysis was based on the smallest set of studies with $k = 9$ studies and $d = 5$ data sets. Moreover, the measurement of handedness was not the main purpose of any of the included studies, let alone the measurement of mixed-handedness per se. We would not therefore consider publication bias (which could be one of the causes of small study bias) a major determinant. More empirical studies and additional meta-analytic integration of future studies on mixed-handedness in ADHD are needed to draw any final conclusions.

As a secondary analysis, we replicated our analyses but restricted the included studies and datasets to those that used the Edinburgh Handedness Inventory (Oldfield, 1971) to measure handedness. For none of the comparisons was there evidence of handedness differences between ADHD and neurotypical control participants. We note that heterogeneity was not significant in our main analysis, therefore we did not directly explore the possible moderating effects of different variables, such as the way handedness was measured. Nevertheless, given the importance of good-quality phenotyping (the phenotype being handedness in this case) the analysis focusing only on EHI studies was reported. These analyses should be treated with caution, however, as they rely on considerably fewer datapoints compared to the main analysis and have considerably lower power. Therefore, it is not possible to disentangle whether these results indicate that the findings of the main analysis are due to bad phenotyping (no EHI) and do not hold with good phenotyping (EHI) or whether they are the result of low power (indicatively, only three datapoints in the mixed-handedness comparison). In other words, the findings of this secondary analysis could be an artefact due to the analyses being underpowered.

The results of the present study make it unlikely that the mechanisms and factors involved in ADHD and left-handedness overlap to a large extent. This is in line with

several papers in the published literature. A deficit in attention represents one of the core symptoms of ADHD, but a recent study did not find a link between left- and right-handedness and inattentiveness scores (Ghanizadeh 2013). Moreover, studies have reported a dominance of the right hemisphere for visuo-spatial attention (Heilman and van den Abell 1980). Based on this literature, several authors have suggested that ADHD is mainly a deficit of neural networks that are prevalently represented in the right hemisphere (Klimkeit and Bradshaw 2006; Rentería 2012; Stefanatos and Wasserstein 2001) or a deficit in the interaction of right-hemispheric networks with their left-hemispheric counterparts (Hale et al. 2009a). For handedness, most individuals are right-handed (Papadatou-Pastou et al., 2020b), which translates into a left-hemispheric dominance for fine motor movements. Moreover, right-handedness is highly correlated to left-hemispheric language dominance (Knecht et al., 2000). Therefore, a right-hemispheric dysfunction in ADHD should not lead to a switch in handedness in ADHD, as the hemisphere relevant for handedness is largely unaffected in individuals with ADHD. This might explain why we did not observe stronger evidence of an elevated rate of left-handedness in individuals with ADHD compared to controls.

We did, however, find evidence for a link between non-right-handedness and ADHD. The reason why non-right-handedness, but not left-handedness, is affected cannot be inferred from the present data. One reason for this specific pattern of results could lie in the fact that laterality has two different dimension that might be affected by different ontogenetic factors: direction (left and right) and strength (strong preference for one side, vs. weak preference for one side, also found in the literature under the term “degree”). Ontogenetic studies have suggested that in zebra fish, different genetic pathways underlie these two aspects of laterality (Ocklenburg and Güntürkün 2018;

Hüsken and Carl 2013). If handedness is measured as a continuous variable, direction and strength can be distinguished and some studies have reported differential genetic effects on these two dimensions of handedness (Arning et al. 2013). Left-handedness is mostly a reflection of handedness direction, while non-right-handedness could also reflect handedness strength (e.g., weakly right-handed individuals are often included in this group). Thus, it could be speculated that the mechanisms involved in the pathogenesis of ADHD might show an overlap with the mechanisms involved in handedness strength, but not handedness direction.

When discussing the results of the present study, it is of importance to consider methodological issues. Most importantly, a very substantial number of studies needed to be excluded from analysis in order to fulfill inclusion criteria. Out of 342 full text articles that were screened, only 16 were included in the final analyses. In particular, the presence of comorbidity was an issue in many excluded studies (Fassbender et al. 2011; Valera et al. 2010). Therefore, our findings can only generalize to those individuals with ADHD without comorbidity, when the majority of participants with ADHD do present with comorbidities. We are, however, convinced that this inclusion criterion is of utmost importance in order to gain a reliable estimate of the association between handedness and ADHD. Many neurodevelopmental and psychiatric disorders have been shown to affect handedness and not excluding individuals with ADHD with comorbidities could lead to severely misleading results. This finding also highlights the importance of collecting handedness data in ADHD individuals with no comorbidities in future studies. Moreover, we were unable to conduct the fourth analysis we had preregistered in PROSPERO, involving the analysis of continuous handedness data. There were only three studies reporting handedness as a continuous variable in individuals with ADHD and controls that fulfilled the inclusion criteria. As we had set

a minimum of five studies to conduct this analysis, we did not carry it out. This highlights the importance of reporting continuous handedness data for future ADHD studies or, optimally, sharing raw data in open-access repositories, such as the Open Science Framework (osf.io).

The present meta-analyses included studies that had investigated hand preference and not hand skill, as none of the included studies reported measuring the hand skill of their participants. These two different manifestations of handedness have been suggested to be independently lateralized (Triggs et al., 2000), but they do show medium size correlations of $r = .50$ to $.57$ (Triggs et al., 2000) or even lower ($r = .08$ to $.30$; Buenaventura, Lynch & Paracchini, 2019). We urge researchers to report both hand preference and hand skill measures, following previously voiced suggestions reported in handedness meta-analyses (Ntolka & Papadatou-Pastou, 2018; Markou, Ahtam, & Papadatou-Pastou, 2017; Papadatou-Pastou & Sáfár, 2016; Papadatou-Pastou & Tomprou, 2015; Papadatou-Pastou et al. 2020a) in order to achieve a more complete understanding of the phenomenon of handedness.

In conclusion, our study indicates that there is only weak evidence for a higher prevalence of left-handedness, but there is evidence for higher non-right-handedness in individuals with ADHD compared to neurotypical individuals. There is some limited evidence for a higher prevalence of mixed-handedness in individuals with ADHD compared to controls that might, however, have been affected by small study bias. In general, the study highlights the need for more empirical studies on handedness in individuals with ADHD without any comorbidities. Furthermore, it highlights the need to separately investigate direction and degree of handedness. Importantly, it highlights the importance of a disorder-specific approach when investigating the relation of neurodevelopmental and psychiatric disorders and handedness. Not all disorders are

linked to elevated rates of left-handedness. Understanding which specific pathologies affect handedness is crucial in order to understand the neurobiological mechanisms underlying the relationship of laterality and mental health.

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Studies marked with an asterisk (*) were included in the meta-analyses.

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Figure captions

Figure 1: Flow diagram for the literature search and the inclusion and exclusion criteria for studies included in the meta-analysis. The figure was created according to the guidelines of the PRISMA statement (Moher et al. 2009).

Figure 2: Forest plot for the left-handedness meta-analysis. In the plot the 95% confidence interval for each study is represented by a horizontal line and the point estimate is represented by a square. The size of the square is representative of the weight that each study has in the overall effect size estimate. The confidence interval for total (overall effect) is represented by a diamond shape at the bottom of the plot.

Figure 3: Funnel plot for small study bias for the left-handedness meta-analysis.

Figure 4: Forest plot for the non-right-handedness meta-analysis. In the plot the 95% confidence interval for each study is represented by a horizontal line and the point estimate is represented by a square. The size of the square is representative of the weight that each study has in the overall effect size estimate. The confidence interval for total (overall effect) is represented by a diamond shape at the bottom of the plot.

Figure 5: Funnel plot for small study bias for the non-right-handedness meta-analysis.

Figure 6: Forrest plot for the mixed-handedness meta-analysis. In the plot the 95% confidence interval for each study is represented by a horizontal line and the point estimate is represented by a square. The size of the square is representative of the weight that each study has in the overall effect size estimate. The confidence interval for total (overall effect) is represented by a diamond shape at the bottom of the plot.

Figure 7: Funnel plot for small study bias for the mixed-handedness meta-analysis

Table 1

Details of studies included in the meta-analyses. ADHD = Attention Deficit Hyperactivity Disorder, RH = Right-Handedness, LH = Left-Handedness, MH = Mixed-Handedness, IT = Inattentive Type, CT = Combined Type, HT = Hyperactive Type

	N (total)	N (ADHD)	N (control group)	Age means in years (ADHD)	Age means in years (control group)	Handedness measurement	Handedness classification	ADHD diagnosis	ADHD type
ACPU (2021), unpublished data set	35	7 (7 males)	28 (28 males)	13	14	Part of the Scored Developmental Neurological Examination (for 4 cases the Edinburgh Handedness Inventory, Oldfield, 1971)	RH-MH-LH	DSM-IV	Not reported
Dramsdahl et al. (2012)	66	29 (15 males)	37 (14 males)	32.9	30	Writing and drawing hand	RH-LH	ICD-10 or DSM-IV	IT: 7 CT: 19 HT: 3
Groen, et al. (2009)	50	32 (29 males)	18 (12 males)	ADHD (methylphenidate treatment group): 11.4 ADHD (no treatment group): 11.7	11.4	Self-report list for handedness (Van Strien, 2003)	RH-MH-LH	DSM-IV-TR	CT: 32 IT: 3
Hotham et al. (2018)	64	29 (27 males)	35 (32 males)	10.5	11.5	Edinburgh Handedness Inventory (Oldfield 1971)	RH-LH	DSM-IV-TR	CT: 26

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IMpACT2 (Jacobi et al., in preparation)	140	63 (25 males)	77 (39 males)	34.54	33.61	self-report	RH-MH-LH	Diagnostic Interview for ADHD in adults (DIVA; 6 or more symptoms)	Not reported
Neely, et al. (2016)	40	20 (8 males)	20 (7 males)	20.45	20.4	Edinburgh Handedness Inventory (Oldfield 1971)	RH-LH	Self-report short form (S:S) of the CAARS	Not reported
Neely, et al. (2017)	102	51 (22 males)	51 (29 males)	21.1	21	Edinburgh Handedness Inventory (Oldfield, 1971)	RH-MH	DSM-V, Conners' Adult ADHD Diagnostic Interview	Not reported
NICAP (Silk et al. 2016)	95	26 (22 males)	69 (39 males)	10	10	self-report	RH-LH	Diagnostic Interview Schedule for Children - IV	Not reported
Niche (de Zeeuw et al., 2012)	124	44 (38 males)	80 (67 males)	11	10	self-report	RH-MH-LH	DSM-IV clinical psychologist	Not reported
Martel, et al. (2008)	250	113 (72 males)	137 (77 males)	14.25	15.01	Edinburgh Handedness Inventory (Oldfield, 1971).	RH-MH-LH	ADHD Rating Scales (DuPaul, Power, Anastopolous, & Reid, 1998), Parent and Teacher Behavior Assessment System for Children (Reynolds & Kamphaus, 1992), and the Conners (1997) Parent and Teacher Rating	Not reported

Scales—Revised Short Forms.									
Pluck et al. (2020)	120	28 (12 males)	92 (47 males)	22.45	23.42	Edinburgh Handedness Inventory (Oldfield, 1971)	RH-LH (0 cut-off) RH-MH-LH (-80 and 80 cut-off)	Adult ADHD self-report scale v1.1. screener (ASRS-Screener) (>3 items positive)	Not reported
Robaey et al. (1992)	24	12 (12 males)	12 (12 males)	6-8 (separated into two groups < and > 7 years and 6 months)	6-8 (separated into two groups < and > 7 years and 6 months)	12-item list (Annett, 1970)	RH-MH-LH	DSM III-R	Not reported
Rolfe et al. (2006)	45	30 (28 males)	15 (14 males)	ADHD-I: 8.59 ADHD-C: 8.92	8.86	Edinburgh Handedness Inventory (Oldfield, 1971)	RH-LH	Integrated Visual and Auditory Continuous Performance Task; (IVA-CPT; Sanford & Turner, 2000) and the Brown ADD Scales	IT: 15 CT: 15
Scharoun et al. (2013)	116	58 (29 males)	58 (29 males)	10.1	10.1	Observation of several unimanual tasks, including throwing at a target, ringing a bell, cutting with a knife.	RH-LH	IPPP database of neurobehavioural disorders	Not reported
Shaw & Brown (1990)	32	16 (13 males)	16 (13 males)	12	12	Laterality was established with 10 common tasks, each assessed twice (Newton & Thompson, 1976)	RH-MH	Selection with and without a standardized rating scale, psychologists and teachers helped the selection	CT:16

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Soliva et al. (2010)	34	17 (15 males)	17 (15 males)	10.41	10.76	Not reported	RH-MH-LH	DSM-IV TR, Conners' Teacher and Parent's Rating Scale and the Child Behavior Checklist	IT:2 CT: 14 HT: 1
ter Huurne et al. (2013)	35	17 (7 males)	18 (10 males)	31.8	30.9	Edinburgh Handedness Inventory (Oldfield, 1971)	RH-LH	DSM-IV-TR, the Diagnostic Interview for Adult ADHD	Not reported
Tucha, et al. (2006)	32	16 (10 males)	16 (10 males)	31.13	32.25	Handedness questionnaire (Chapman and Chapman, 1987)	RH-MH-LH	DSM-IV	IT: 4 CT: 10 HT: 2
Tucha, et al. (2008)	188	94 (50 males)	94 (50 males)	ADHD-IT: 36.84 ADHD-HT: 33.17 ADHD-CT: 33	Control-IT: 36.79 Control-HT: 33.58 Control-CT: 33.49	Handedness questionnaire (Chapman and Chapman, 1987).	RH-MH-LH	DSM-IV	IT: 19 CT: 63 HT:12
Würzburg (Conzelmann et al., 2009)	74	23 (10 males)	51 (25 males)	42	39.6	Self-report	RH-MH-LH	DSM-IV clinical psychologist	Not reported
Xia et al. (2012)	38	19 (14 males)	19 (10 males)	10.9	12.2	Not reported	RH-LH	DSM-IV criteria for combined type ADHD	CT: 19