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Hand preference and Mathematical Learning Difficulties: New data from Greece, the United Kingdom, and Germany and two meta-analyses of the literature

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Abstract

Increased rates of atypical handedness are observed in neurotypical individuals who are low-performing in mathematical tasks as well as in individuals with special educational needs, such as dyslexia. This is the first investigation of handedness in individuals with Mathematical Learning Difficulties (MLD). We report three new studies ($N = 134$; $N = 1{,}893$; $N = 153$) and two sets of meta-analyses (22 studies; $N = 3{,}667$). No difference in atypical hand preference between MLD and Typically Achieving (TA) individuals was found when handedness was assessed with self-report questionnaires, but weak evidence of a difference was found when writing hand was the handedness criterion in Study 1 ($p = .049$). Similarly, when combining data meta-analytically, no hand preference differences were detected. We suggest that: (i) potential handedness effects require larger samples, (ii) direction of hand preference is not a sensitive enough measure of handedness in this context, or that (iii) increased rates of atypical hand preference are not associated with MLD. The latter scenario would suggest that handedness is specifically linked to language-related conditions rather than conditions related to cognitive abilities at large. Future studies need to consider hand skill and degree of hand preference in MLD.

Keywords: ALSPAC, meta-analysis, handedness, mathematical abilities, PC mouse

1. Introduction

Within cognitive neuroscience there is growing attention on mathematical skills (e.g., Grabner & Ansari, 2010) and associate difficulties, such as Mathematical Learning Difficulties (MLD) (e.g., Ashkenazi, Rosenberg-Lee, Tenison, & Menon, 2012). A number of studies link the existence of MLD to right-hemispheric structural deficits, such as abnormalities in the microstructure of the white matter in the temporo-parietal cortex (Rykhlevskaia, Uddin, Kondos, & Menon, 2009), as well as with functional deficits, such as weaker activation in the intraparietal sulcus (Ashkenazi et al., 2012; Price et al., 2007; Rotzer et al., 2009). Furthermore, support for the idea that atypical handedness, a measure informative of cerebral laterality for language, is associated with low mathematical ability in the general population (i.e., individuals without a formal diagnosis of MLD) is growing (Johnston et al., 2013). However, when it comes to individuals that have received an MLD diagnosis, no study has focused on the handedness patterns of their participants as its main research question, although a few do report handedness data for MLD individuals (e.g., Bucca, 2018; Jovanovic et al., 2014; Rubinstein & Henik, 2006). The present study addresses the question of whether atypical handedness is associated with MLD for the first time, by presenting three new studies and by using meta-analytic methods to provide an overview of the literature.

Combining evidence using meta-analytic techniques, even if they were collected and reported in studies without having the meta-analysis research question as their primary objective, means that no data are wasted and new resources are not allocated to the investigation of the same research questions for which data are already available. Moreover, meta-analysis has increased statistical power and accuracy compared to each individual study. At the same time, it allows for the estimation of possible heterogeneity between the included studies, and, in the case heterogeneity does exist, to identify possible moderator variables (Egger & Smith, 1997; Rosenthal & Di Matteo, 2001; Walker, Hernandez, & Kattan, 2008). Furthermore, small study bias, a form of publication bias (the latter also referred to as ascertainment bias), can be investigated. Importantly, meta-analyses are vital in order to address the reproducibility issues troubling psychological research (e.g., Open Science Collaboration, 2015). Indeed, there is a growing body of meta-analytic literature on the existence of elevated levels of atypical handedness in conditions such as schizophrenia (Tran & Voracek, 2015), autism spectrum disorder (ASD) (Markou, Ahtam, Papadatou-Pastou, 2017), deafness (Papadatou-Pastou & Sáfár, 2016), and intellectual disability (Papadatou-Pastou & Tomprou, 2015).

1.1. Handedness and cerebral lateralization

Handedness is the most prominent and widely studied behavioral asymmetry (Güntürkün & Ocklenburg, 2017; Michel, Babik, Nelson, Campbell, & Marcinowski, 2018; Papadatou-Pastou, 2011; Uomini & Ruck 2018). It can be defined as the preference to use one hand over the other for manual tasks and/or the ability to perform these tasks more efficiently with one hand (Corey, Hurley, & Foundas, 2001). Thus, handedness has two different manifestations, hand preference and hand skill, respectively. Two additional conceptualizations of handedness are direction and degree. Direction indicates whether an individual is right- or left-handed (with a third category oftentimes being a mixed-hander) either for preference or skill, whereas degree defines how strongly an individual prefers one hand to the other or how skilled one hand is compared to the other (Steenhuis & Bryden, 1989). Worldwide the majority of individuals is right-handed and the prevalence of left-hand preference in the general population is estimated to be 10.6% (Papadatou-Pastou et al., 2020). Sex differences are observed in handedness, with males showing a higher prevalence (Papadatou-Pastou, Martin, Munafo, & Jones, 2008). Cerebral lateralization for language in particular is the most extensively demonstrated functional laterality and has been shown to be associated, albeit weakly, with handedness (e.g., Bishop, Watt, & Papadatou-Pastou, 2009; Floris et al., 2016; Gonzalez & Goodale, 2009; Isaacs, Barr, Nelson, & Devinsky, 2006; Khedr, Hamed, Said, & Basahi, 2002; Sommer, Ramsey, Mandl, & Kahn, 2002). The link between handedness and language was robustly shown by a seminal study by Knecht et al. (2000b) who showed a linear increase in the prevalence of right-hemisphere language dominance with an increase in the degree of left-handedness from 4% of strongly right-handed individuals, to 15% in ambidextrous individuals and 27% in strong left-handers, using functional transcranial Doppler sonography (fTCD) in 326 healthy individuals. Mazoyer et al. (2014) claimed that most of the association between dominant hemispheres for language and hand use is due to left-handedness being found in strongly atypical individuals. Somers et al. (2015) showed that degree of hand preference and degree of language lateralization fit a cubic regression model, where stronger left-hand preference results in a higher chance for atypical language lateralization.

1.2. Mathematical Learning Difficulty

Many terms have been used to date to describe difficulties in mathematics. These include the terms dyscalculia (e.g., Hsieh, Lai, Lin, & Huang, 2017), developmental dyscalculia (DD) (e.g., Träff, Olsson, Östergren, & Skagerlund, 2016), mathematical learning difficulty (MLD) (e.g., Karagiannakis, Baccaglini-Frank, & Papadatos, 2014), mathematics learning disability (e.g., Dennis, Sorrells, & Falcomata, 2016), mathematical disability (e.g., Evans & Ullman, 2016), mathematics disorder (e.g., American Psychological Association [APA], 1994), mathematical learning disorder (e.g., Capano et al., 2008), specific learning disorder with impairment in mathematics (e.g., APA, 2013), mathematics difficulties (e.g., Wong, Ho, & Tang, 2017), mathematical impairment (e.g., Jastrzebski, Crewther, & Crewther, 2015), low mathematical ability (e.g., Skeide, Evans, Mei, Abrams, & Menon, 2018), arithmetic learning disability (e.g., Koontz, 1996), specific arithmetic difficulties (e.g., McLean & Hitch, 1999), specific disorder of arithmetical skills (e.g., Hein, Bzufka, & Neumärker, 2000), arithmetic deficiency (e.g., Greiffenstein & Baker, 2002), calculation difficulties (e.g., Isaacs, Edmonds, Lucas, & Gadian, 2001), and low numeracy (e.g., Galesic, Garcia-Retamero, & Gigerenzer, 2009). Although the literature is riddled with different terminology we will use the term MLD to refer to learning difficulties in mathematics inclusively, following Karagiannakis et al. (2014).

Worldwide MLD has been estimated to affect between 1.3% to 13.8% of school-aged children with a mean of about 6% (Morsanyi, Bers, McCormack, & McGourty, 2018). Studies have been conducted in a number of countries, such as the United States of America (5%-8%; Geary, 2004), Greece (6.3%; Koumoula et al., 2004), Serbia (9.9%; Jovanović et al., 2013), Germany (6.6%; Hein et al., 2000), Belgium (3% - 8%; Desoete, Roeyers, & De Clercq, 2004), Brazil (7.8%; Bastos, Cecato, Martins, Grecca, & Pierini, 2016), Slovakia (6.4%; Kosc, 1974), Israel (6.5%; Gross-Tsur, Manor, & Shalev, 1996), and India (5.98%, 5.54%; Ramaa & Gowramma, 2002). A review of 164 studies revealed a lack of consensus for an operational definition of MLD, as showcased by the variability in the assessment methods and in the cutoff criteria used to identify students with MLD (Lewis & Fisher, 2016). Specifically, in 90% of the studies reviewed by Lewis and Fisher

(2016) the cutoff scores for identification of students with an MLD ranged from the 2nd percentile to the 46th percentile, while the rest of the studies did not use achievement on a maths test as a criterion. This could explain the wide range of MLD prevalence found in the literature. When it comes to sex differences in MLD, White et al. (2016) showed that females are 32% less likely than males to present MLD (White, Ruther, & Kahn, 2016) and Reigosa-Crespo et al. (2012) reported a male to female ratio of 4:1. Other studies have also reported a similar sex difference in the prevalence of MLD (Devine, Soltész, Nobes, Goswami, & Szűcs, 2013; Koumoula et al., 2004).

1.3. Handedness and MLD

Only one study to date has investigated the relationship between senses and limbs laterality and MLD as its main research question, but without focusing on handedness per se (Jovanovic et al., 2014). It studied 140 fifth-grade pupils (83 with dyscalculia [term as used by Jovanovic et al., 2014] and 57 typically developing) from all the elementary schools in Kragujevac, Serbia, and found no relationship between dominant hand and dyscalculia. However, there was evidence of a more frequent occurrence of mixed laterality in students with dyscalculia. Of note, this study was not published in the English language, but in Serbian.

In the absence of studies reporting on the handedness of individuals with MLD, we turn our attention to studies using general population samples that have reported on the mathematical abilities of different handedness groups. Johnston et al. (2013) used a large sample of 6,566 individuals aged less than 14 years old from the USA and showed that left-handers had lower test scores in mathematics, compared to their right-handed counterparts (7% of a standard deviation lower). The handedness of the participants was reported by their mothers and mathematical ability was assessed by the Peabody Individual Achievement Test (PIAT). Similar findings have also been reported by Johnston, Nicholls, Shah, and Shields, (2009) who studied an Australian sample of 4,942 children aged 4-5 years and found that both left- and mixed-handed children had lower performance in all measures of child development including mathematics, compared to right-handed ones. A recent series of five studies with 2,314 student participants in Italian schools reported that the variance in mathematic scores explained by handedness was between 3-10%, although neither linear nor quadratic functions could capture this relationship sufficiently. Moreover, gender, age, and type of mathematical task influenced the shape of this relationship (Sala, Signorelli, Barsuola, Bolognese, & Gobet, 2017).

Corballis, Hattie, and Fletcher (2008) further showed that ambidextrous individuals show worse performance than left- or right-handers on the arithmetic subscales of the New Zealand IQ Test, using a sample of 1,353 adults aged from 18 to over 60 years of age from New Zealand. Similar findings were reported by Crow, Crow, Done and Leask (1998) in their study totaling 11,700 11-year-olds from the UK. Rodriguez et al. (2010) studied 7,871 8-16 year-old children in Finland, and found that mixed-handers are more likely to develop mathematics-related problems. However, Sherman (1979) reported that handedness did not affect math achievement in a general population sample of 281 students in 9th, 10th, and 11th grades.

Furthermore, mathematically talented children tend to have twice as many odds to be left–handed compared to typically achieving (TA) children (Bower, 1985). Benbow (1988) further supported that there is an increased prevalence of non-right-handedness among children with mathematical giftedness, while arithmetic skill was strongly associated with the skill of the left hand. However, a recent study of 7,525 children in Ireland showed no evidence of an association between mathematical scores and handedness (O'Connell, 2018).

The possible relationship of atypical handedness and MLD is not just suggested by some published evidence, but there are also theoretical reasons making this investigation worthwhile. Recent work suggests that the same genes that are involved in structural laterality also contribute to behavioral laterality, as manifested by handedness, and neurodevelopmental disorders (Brandler & Paracchini, 2014). The involvement of the same genes in handedness and neurodevelopmental disorders is further supported by the latest Genome Wide Association Studies (GWAS) on handedness, which found that genes that are involved in handedness formation are involved in cellular cytoskeleton and schizophrenia (Cuellar-Partida et al., 2020; Wiberg et al., 2018).

The putative relationship between handedness and MLD could be explained by left hemisphere dysfunction. Faults and malfunctions of the left hemisphere have been suggested to cause changes in the execution of tasks, difficulties in maintaining and recalling basic sizes, and problems in understanding the concept of numbers (Drigas & Pappas, 2015). Shalev, Manor, Amir, Wertman-Elad and Gross-Tsur (1995) examined the relationship between arithmetic dysfunction and brain laterality in 25 children with developmental dyscalculia and found that dysfunction of both hemispheres hinder the learning process of arithmetics. Yet, left-hemisphere dysfunction can result in more severe difficulties suggesting that arithmetic functions are left-hemisphere dependent. Pinel and Dehaene (2010) in an fMRI study of 209 French adults, showed that performance of calculation tasks resulted in approximately equal levels of activations in both hemispheres, but with more extended activations in the left hemisphere . Isaacs et al. (2001) further showed using voxel-based morphometry that impaired calculation ability in adolescents of preterm birth was associated with less gray matter density in the left parietal lobe.

1.4. Present scope

The purpose of the present article is twofold: (i) to present new data on the handedness prevalence in individuals with MLD (Studies 1-3) and (ii) to synthesize statistically all old and new data on handedness levels in MLD, using meta-analytic techniques (Study 4). More specifically, Study 1 reports data from primary school students in Greece, and compares 45 MLD students, with 89 TA students. Study 2 draws data from the ALSPAC longitudinal study, taking place in the UK and compares 445 MLD children, with 1,448 TA children. Study 3 reports data from Germany on 19 children at risk of MLD and 134 non at risk of MLD on hand preference for writing and line tracing. Study 4 presents meta-analyses that combine the data of Studies 1-3 as well as data from 19 already published studies totaling 3,667 participants, although these studies were not designed to directly investigate the question at hand. More specifically, Study 4 comprises two sets of meta-analyses of studies that have assessed the prevalence of handedness among individuals with MLD. The main goal is to explore and quantify the handedness prevalence in individuals with MLD compared to TA individuals. Another goal is to investigate heterogeneity among studies and possible sources of it. Candidate factors examined include year of publication of the study, location where the study took place, participant sex ratio, participant age, handedness classification and instruments used to measure handedness and to diagnosed MLD, following similar meta-analyses which examined handedness in individuals with special educational needs (e.g., deafness; Papadatou-Pastou & Sáfár, 2016; ASD; Markou et al., 2017; and intellectual disability; Papadatou-Pastou & Tomprou, 2015). Moreover, small study bias will be investigated.

2. Study 1: Collection of primary data in Greece

2.1. Method

2.1.1. Participants

This study included 134 fourth-grade students (73 female, mean age = 9.75 yrs., SD = 0.33 and 61 males, mean age = 9.77 yrs., SD = 0.35), recruited from public schools and after-school learning centers in the wider area of Athens. Students in the after-school learning centers faced math-related difficulties. Participants with a diagnosis of autism spectrum disorder, attention deficit disorder, or mental disability and participants with an extremely low raw Raven's Coloured Matrices score were excluded, in order to make sure that any students with undiagnosed mental disability were not included in the sample. All participants had raw scores of 13 or above (mean score = 27.88, SD = 4.42, range = 13-35). Parents gave written informed consent prior to their child's participation in the study. The study was approved by the local ethics committee.

The MLD group consisted of forty-five students (19 males, mean age = 9.79 yrs., SD = 0.32; 26 females, mean age = 9.79 yrs., SD = 4.79) who were diagnosed as having MLD according to the NUCALC battery (von Aster, 2001; Koumoula, et al., 2014). The TA group included 89 students without MLD (42 males, mean age = 9.79 yrs., SD = 0.37; 47 females, mean age = 9.73, SD = 0.29). Groups were matched for age, $t(132) = .64$, $p = .52$, sex, $\chi^2(1) = .30$, $p = .59$, and intelligence according to WISC-III Vocabulary subscales, $t(132) = -1.16$, $p = .25$, and WISC-III Digit Span, $t(132) = -.26$, $p = .79$, but not according to WISC-III Digit Span (reverse order), $t(132) = -4.16$, $p < .001$, and Raven's Coloured Matrices, $t(132) = -5.04$, $p < .001$.

2.2.2. Material

Neuropsychological Test Battery for Number Processing and Calculation for Children (*NUCALC*): Mathematical abilities were assessed using the Greek standardized version of the NUCALC (Koumoula et al., 2014). The NUCALC is an untimed paper-and-pencil arithmetic fluency test which consists of six subtests: Dictation of Numbers, Mental Addition, Reading Numbers, Oral Comparison, Problem Solving, and Written Comparison. Children with low achievement, i.e. below the 30th percentile (which corresponds to a score of 60), were classified as MLD students. The cut-off score was based on the Greek standardized norms of the NUCALC battery.

Wechsler Intelligence Scale for Children (WISC) - III: The Vocabulary and Digit Span subscales from the WISC-III (Wechsler, 1991) were administered. For the Vocabulary scale, each student was asked to define a provided word. For the Digit Span scale, each student was asked to repeat orally sequences of numbers, as heard and in reverse order.

Raven's Coloured Matrices (Sideridis, Antoniou, Simos & Mousaki, 2015): The non-verbal (IQ) of participants was measured with Raven's Coloured Matrices Test. It is a normed untimed visual-spatial reasoning test for children in the age range of 4-12 years. Children saw a coloured pattern and were asked to select the missing piece out of 6 options.

Handedness inventory: A 4-item questionnaire was used for hand preference assessment, including hand used for writing, drawing, throwing a stone, and using a computer mouse. A recent meta-analysis showed that short questionnaires give the same handedness estimates as longer ones and should thus be preferred (Papadatou-Pastou et al., 2020). The first three items are typically found in hand preferences inventories, including the most popular one in the handedness literature, namely the Edinburgh Handedness Inventory (Oldfield, 1971) according to the Papadatou-Pastou et al. (2020) meta-analysis. Using a computer mouse was introduced because it reflects an activity that it performed nearly everyday in western societies during the last decades, yet hand preference for computer mouse use has not been assessed to date, to the best of our knowledge. The participants could respond with the right hand (scored with 0), both hands (scored with 1), or the left hand (scored with 2). A handedness index describing degree of hand preference was calculated by adding the responses to the questionnaire, with higher scores indicating stronger left-handedness. Moreover, participants were grouped into left-handers (scores 4-8) and right-handers (scores 0-3), using the midpoint of the handedness index as the cut-off point, as it is typical in the literature when dividing participants in two handedness groups (e.g., Kumar, Voracek, & Singh, 2020). A second grouping consisting of left-handers (scores 6-8), mixed-handers (scores 3-5), and right-handers (scored 0-2) was also followed, in order to capture the middle category of participants with weak or no preferences.

2.2.3. Procedure

Each child was tested individually at their school or afterschool learning center. All assessments were conducted by trained research assistants in the following order: Vocabulary, Raven, Digit span, Handedness, and NUCALC. The duration of the evaluation was approximately forty-five minutes.

2.2.4. Statistical analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) v. 25 (IBM Corporation, 2017). A univariate ANOVA was run with sex (male and female) and presence of MLD (MLD and TA) as the grouping factors and with the continuous handedness score as the dependent variable. The η^2 statistic was used as an estimate of power. In order to test if handedness frequencies differ between the MLD and TA group, chi square tests were used. Moreover, Pearson's *r* was used to test for a correlation between the score in the NUCALC test and the continuous handedness score of the participants.

2.2. Results

Tables 1 and 2 present the handedness data for both groups of participants (MLD and TA), broken down by sex. The two groups were not found to differ with regards to the frequency of left- and right-handers they include, $\chi^2(1) = 1.30$, $p = .26$. Differences with regards to the frequency of left-, mixed-, and right-handers could not be tested as there were two cells with $n < 5$. However, when only writing hand was entered into the analysis (merging the participant who had responded "both hands" with those that had selected the left hand, in order to create a non-right-handedness group), then there was weak evidence of a relationship, $\chi^2(1) = 3.89$, $p = .049$. Moreover, there was statistical evidence that the NUCALC score correlates with the handedness score, over the whole sample, $r = -.35$, $p < .001$. Such evidence was further found within both groups, $r = -.49$, $p = .001$ and $r = -.22$, $p = .04$, for the MD and TA groups, respectively, thus the correlation was stronger within the MLD group. Moreover, the correlation held true for both males, $r = -.33$, $p = .009$, and females, $r = -.35$, $p = .002$. A 2 x 2 ANOVA was run with sex (male or female) and presence of MLD (MLD and TA) as the grouping factors and with handedness score as the dependent variable. No main effects of sex, $F(1,130) = .91$, $p = .34$, $\eta^2 = .01$, presence of MLD, $F(1,130) = 1.01$, $p = .32$, $\eta^2 = .01$, or interaction between sex and presence of MLD, $F(1,130) = .17$, $p = .68$, $\eta^2 = .01$, were found.

All data and analysis code is available at https://osf.io/p4e9h/.

Please insert Tables 1 & 2 about here

2.3. Discussion

Handedness data where compared between a group of students with MLD and an age- and sex-matched group of TA students, all attending the 4th grade of primary school. Handedness was operationalized as hand preference, using a 4-item self-report inventory.

Findings provide a mixed picture. When grouping the students into left- and right-handers using the midpoint of a handedness index that was calculated using all four items, then handedness frequency was not found to differ between MLD and TA students. However, when only writing hand was taken into account (merging those who use their left hand with those who reported using both of their hands for writing), then there was evidence of a difference, albeit weak (p = .049). A 2 x 2 ANOVA did not show any differences in the continuous handedness score between males and females or between MLD and TA students, nor an interaction between sex and mathematical achievement. Yet, when the continuous mathematical achievement score that was calculated using the NUCALC test was correlated with the continuous handedness score, then the evidence of this relationship was strong.

The present findings are representative of the handedness literature in that it is riddled with different assessment criteria for handedness as well as different cut-off points for the handedness categories that are employed in different studies. This lack of a consensus in the assessment of handedness has been pointed out as a factor that contributes to the discrepancies in the literature when discussing the relationship of handedness with other variables, such as intelligence (Papadatou-Pastou, 2018) or the prevalence rates of handedness in the general population (Papadatou-Pastou et al., 2020). For example, using the midpoint of the handedness index to group participants in left- and right-handers, as was the case here, could result in participants performing two tasks with the right hand and the remaining two with the left hand to be classified as left-handed. Acknowledging a middle handedness category could address this issue to some extent. Indeed, Papadatou-Pastou et al. (2020) recommend capturing the middle handedness category in order to address questions around handedness. In addition, the study illustrates how challenging it is to interpret handedness effects in small samples, even more so as only a small percentage of the sample presents with atypical handedness. Therefore, chance findings could be mistaken for true effects and vice versa.

3. Study 2: Data from the ALSPAC longitudinal study

3.1. Method

3.1.1. Participants

ALSPAC is a longitudinal cohort representing the general population living in the Bristol area. Pregnant women resident in the county of Avon, UK, with expected dates of delivery from 1st April 1991 to 31st December 1992 were invited to take part in the study, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age (Boyd et al., 2013; Fraser et al., 2013). From age seven, all children were invited annually for assessments on a wide range of physical, behavioural and neuropsychological traits. Informed written consent was obtained from the parents after receiving a complete description of the study at the time of enrolment into ALSPAC, with the option to withdraw at any time. Ethical approval for the present study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. The ALSPAC study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The cohort includes a vast collection of phenotypic data for probands at different time points, including those relevant to this study, such as cognitive assessment, educational attainment, and handedness (Buenaventura Castillo et al., 2020). For the scope of this study we applied the following exclusion criteria: i) a performance IQ < 85 to exclude possible conditions that might affect mathematical abilities as a secondary effect (Wechsler et al., 1992), ii) presence of other neurodevelopmental conditions (i.e., ASD, dyslexia, developmental language disorder, or ADHD) as defined before in the ALSPAC cohort (Newbury et al., 2014; Scerri et al., 2011), iii) individuals who had missing data for any of the measures necessary for this study. A total of 2,894 individuals (1,557 females, 1,337 males) entered the study. The MLD group consisted of 445 individuals (mean age = 11.2 yrs., SD = 0.31; 184 males [mean age = 11.2 yrs., SD = 1.69] and 261 females [mean age = 11.2 yrs. , SD =1.62], referring to the age at which probands undertook the math tests) selected for a Mathematical Achievement (MA) score (see below for details of the test) < -1 SD. Three individuals (females) presented inconsistent handedness between two time points (at age 7 and 11) and were excluded from the primary analysis (Table 3). The TA group included 1,664 individuals with a MA score > 0 (mean age = 11.2 yrs. , SD = 0.31; 800 males and 827 females, excluding 9 individuals reported with dyscalculia on a questionnaire filled by the mother). Since the MLD and TA groups were not matched for gender, a random gender-matching was carried out by eliminating 165 males in the TA group. This resulted in a sample of N = 1,448 TA individuals (mean age = 11.2 yrs, SD = 0.310; 590 males [mean age = 11.2 yrs., SD = 0.311] and 858 females [mean age = 11.2 yrs., SD = 0.309]).

Matching for gender was considered necessary, as robust sex differences in handedness have been documented (Papadatou-Pastou et al., 2008). Groups were not matched for age (measured in months; MLD group was 1.6 months younger than the TA one, Figure 1) at which the MA test was undertaken, $t\ (1891) = -.6117$, $p < 0.001$, WISC-III Digit Span, $t\ (1847) = -13.034$, $p < .001$, WISC-III Vocabulary, $t\ (835.79) = -13.333$, $p < .001$, and total IQ, $t\ (932.12) = -24.482$, $p < .001$).

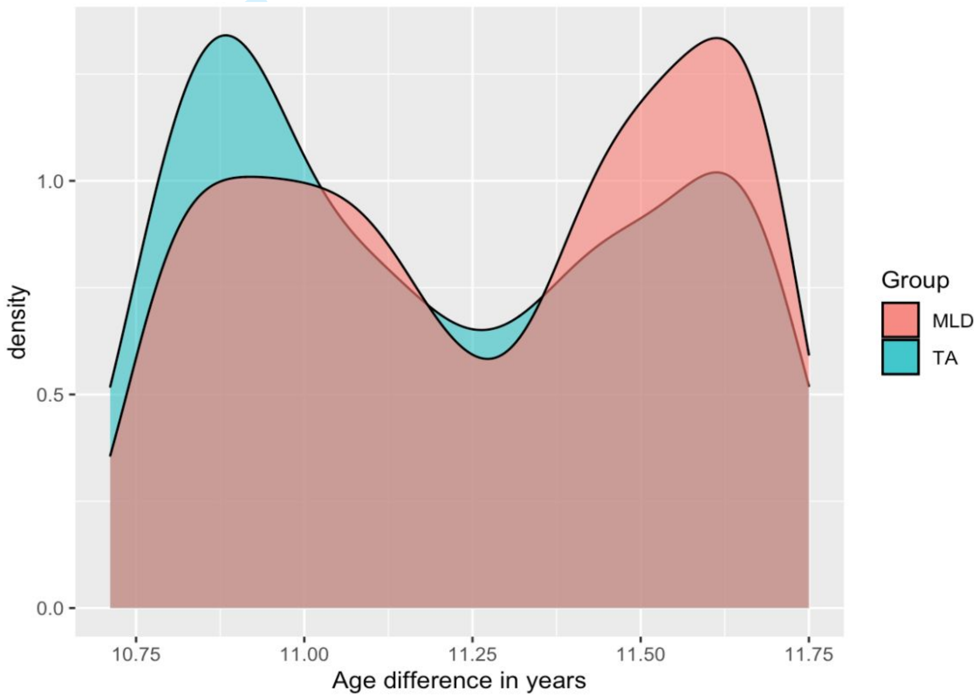

Figure 1. Age in difference between MLD and TA group

3.2.2. Material

Wechsler Intelligence Scale for Children (WISC) - III: The Vocabulary and Digit Span subscales from the WISC-III were used (Woolger, 2001) as described for Study 1. Total IQ was calculated as the sum of the verbal and performance IQ subtests (5 subtests each).

Math Achievement (MA) score: The math achievement score was computed as the sum of the Key Stage 2 tests, consisting of two written maths tests (45 minutes each) and a mental arithmetic test (20 minutes) (Nunes, Bryant, Barros, & Sylva, 2012; Pettigrew et al., 2015). The Key Stage 2 tests were designed by the British government to measure school achievement and were conducted and scored by teachers. The three tests assess arithmetic and mathematical reasoning, through problem-solving (i.e., 'A box contains trays of melons. There are 15 melons per tray. Each box has 3 trays. How many melons can a farmer sell?) and graph interpretation (i.e., counting the faces of a 3D geometric figure).

Handedness: Self-reported hand preference for writing was collected at two time points (age 7 and 11) as a categorical trait ('Right' or 'Left').

More details of all the data are available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

3.2.4. Statistical analysis

All analyses were performed using R Studio v.3 (R Core Team, 2018) using the packages robumeta and meta. Chi-square test was used to compare the frequency of handedness in the MLD and TA groups. The *t*-test and the Welch *t*-test (a *t*-test for distributions with unequal variances) were used to compare the differences of age, WISC-III Vocabulary, total IQ, and Digit Span between the MLD and TA groups.

3.2. Results

Table 3 presents the handedness data for both the MLD and the TA groups, excluding individuals with inconsistent handedness (N = 3), broken down by sex. Hand preference (right- vs. left-handedness) was not found to be associated with participants' group (presence of MLD, χ^2 (1) = .38421, p = .53) and, within the MLD group, with gender (χ^2 (1) =.055063, p = .81). When looking in the more severe subgroups (MA<-1.75SD) left-handedness frequency was slightly higher (11.5%), with this trend mainly driven by females (12.3%) (Table 4), but the data points were not sufficient for statistical comparisons with the TA group. All analysis code is available at https://osf.io/p4e9h/.

3.3. Discussion

Hand preference for writing was compared between individuals with MLD and a sex-matched group of TA probands. The results suggest that handedness frequency does not differ between the MLD and TA groups (p = .53). The presence of a gender difference for math abilities is debated in the current literature, with some studies supporting that such a sex-gap exists (Cimpian, Lubienski, Timmer, Makowski, & Miller, 2016), whereas others finding little or no evidence (Lindberg, Lindberg, Hyde, Petersen, & Linn, 2010; Miller & Bichsel, 2004; for a review see Devine et al., 2013). Sex was thus investigated for association with hand preference within the MLD group, but no association was found (p = .81). In other terms, the frequency of male and female left-handers is similar in the MLD and TA groups.

Several studies further report a slight advantage of older students in mathematics in Grades 4, 7, 8, and 9 (e.g., Cobley et al., 2009; Kawaguchi, 2011). In the case of the present study, the MLD and TA groups were not matched for age (p < .001), with the TA individuals being on average 7 weeks older (Figure 1). This showcases how even in large samples with detailed phenotypes (e.g., age measured in weeks, not years), as it was the case here, it remains a challenge to reach homogeneity across cases/controls. Therefore, the possibility of a bias in how the groups were defined exists. In other words, some children in the MLD group might be lower performing on the mathematical achievement tests because they are younger rather than because they present with MLD.

4. Study 3: Collection of primary data in German kindergarten children

4.1. Method

4.1.1. Participants

As part of a larger study investigating children's mathematical and fine motor skills, 155 children from kindergartens located in rural areas of Southern Germany were tested. Two children had to be excluded from the analysis due to missing data. None of the remaining children was diagnosed with or displayed any signs of neurodevelopmental or physical disorders. The final sample consisted of 74 girls (*M* = 5.4 years, *SD* = 9.2 months) and 79 boys (*M* = 5.5 years, *SD* = 8.2 months) from middle-class families. ~~Socioeconomic status was approximated from parents' educational attainment, with 38% of mothers and 39% of fathers reporting having completed tertiary education (slightly higher than the national German average of 32%; OECD, 2019).~~ Prior to the study, parents gave their informed consent, and children were allowed to stop participating at any point during the study. The study was conducted in accordance with the declaration of Helsinki.

To determine whether children were at risk of developing MLD, we used a standardized math ability score (see below for a description of the calculation of this score). Based on this standardized math ability score, children were then classified as at risk or not at risk for developing MLD. We classified those children that were at least 1 SD under the mean performance of their age group as being at risk. The at risk group consisted of 19 children (10 males, mean age = 5.43 yts., SD = 0.79; 9 females, mean age = 5.15 months, SD = 0.75), and the not at risk group consisted of 134 children (67 males, mean age = 5.52 months, SD = 0.68; 63 females, mean age = 5.41 months, SD = 0.75). Groups were matched for age, $t(151) = .96$, $p = .337$, and sex, $\chi^2(1) = .01$, $p = .926$, but not for Backward visual working memory Span, $t(151) = 4.13$, $p < .001$, and conceptual thinking, $t(151) = 3.31$, $p < .01$.

4.1.2. Material

4.1.2.1. Measures of handedness

Because handedness in young children is often not yet fully developed (Scharoun & Bryden, 2014), handedness was measured via two different measures.

Hand preference: First, children's preferred writing hand was recorded twice: Once when they attempted to write their first name and once when they performed a line tracing task. The performance scores of these tasks were not relevant to the current research question and are not reported here.

Degree of hand skill: In order to receive a continuous measure of children's handedness, we also measured children's tapping speed with the left and right hand. Children performed a tapping task for 10 seconds once with their right and once with their left index finger on a touchscreen using the app 'Tap Test Pro' for Android (Hesesport, 2015). This app records the number of taps performed on the screen with the index finger and only starts recording once the first tap is made. From this task, we calculated children's relative degree of hand skill similar to the Relative Hand Skill ('PegQ') reported by Brandler et al. (2013). The formula used for this calculation was 2(R-L)/(R+L), and resulted in a measure of the degree of hand skill in which positive values indicated a faster right hand and negative values indicated a faster left hand performance.

4.1.2.2. Measures of precursor numerical abilities

The three numerical ability measures used in this study were chosen based on their predictive value for future mathematical development, as well as on previous reports of these abilities being impaired in children with MLD. According to longitudinal studies, precursor numerical abilities can reliably predict both future mathematical development as well as the development of MLD in elementary school (Geary, Bailey, Littlefield, Wood, Hoard, & Nugent, 2009; Stock, Desoete, &

Roebers, 2010). Among other abilities, kindergarten children's procedural and conceptual counting skills were found to be predictive of their later MLD diagnosis (Stock, Desoete, & Roebers, 2010), with the understanding of ordinality and cardinality playing a particularly important role in long-term mathematical development (Chu, vanMarle, & Geary, 2015; Lyons, Price, Vaessen, Blomert, & Ansari, 2011). Therefore, ordinal counting and cardinal magnitude understanding were tested via finger-based tasks. Additionally, as most children with MLD display problems with arithmetic operations (e.g., Butterworth, 2001), a subtest from a dyscalculia test battery (German Version of the TEDI-MATH, Kaufmann et al., 2009) was used to test children's early calculation skills.

Finger counting: To assess children's finger counting ability, children were asked to count aloud while using their fingers. This task tested whether children were capable of assigning each finger the correct counting word and using the counting sequence correctly. All numbers from 1 to 10 were tested in a mixed order to keep children from simply adding another finger for each subsequent number. For each correctly counted-to number, children were awarded one point. For the analysis, the sum of correctly counted-to numbers was used as the dependent variable, with a maximum score of 10.

Showing numbers with fingers: As for the finger counting test, children were asked to show the experimenter a number using their fingers. This task required children to instantaneously show a number with their fingers instead of counting up to it, and therefore tested their cardinal understanding of numbers. Again, all numbers from 1 to 10 were tested in a mixed order. For each correctly shown number of fingers, children received a point, again resulting in a maximum score of 10.

Arithmetic operations: Children's calculation abilities were tested using the *Arithmetic Operations with Object Depictions* subtest from the German version of the standardized test battery TEDI-MATH (Kaufmann et al., 2009). For this test, children are presented with pictures of, for example, six balloons, of which four are red and two are blue. They are then verbally presented with an addition or subtraction problem, for example: "How many are 4 balloons plus 2 balloons?". While reading the problem, the experimenter points to the respective blue and red balloons to help the child with the decision. Children are presented with three addition and three subtraction problems and are allowed to solve them in any way they choose. Each correctly solved problem was rewarded with one point, resulting in a maximum of 6 points.

4.1.2.3. Control variables

Cognitive abilities: To control for children's domain general cognitive abilities, we used the conceptual thinking subtest of the KABC-II (Kaufman & Kaufman, 2015). This subtest measures a child's ability to reason about classifications of things and objects in a nonverbal format. Children are presented with four or five pictures and have to decide which one of the pictures does not fit with the set (e.g., three red umbrellas and one yellow umbrella). Children give their response by pointing at the chosen picture and are awarded one point per correct response. In total, the subtest consists of 28 items, but testing stops when a child answers four out of five consecutive items incorrectly. The sum score was entered as a covariate in the analysis.

Visual working memory: Children's visual working memory was assessed via a backward Corsi block-tapping task, in which children had to memorize and replicate a visually presented sequence in the reverse order. The task was conducted using a wooden board with nine wooden cubes (3cm x 3cm x 3cm) glued onto it in a non-geometrical pattern (replicated after the layout presented in Kessels et al., 2000). First, the experimenter tapped the cubes in a certain order at a speed of approximately one cube per second. The child was instructed to wait until after the experimenter was finished, and then tap the cubes in the reversed order. Two items were presented per span length, with difficulty starting at two blocks and increasing up to seven blocks. If the child successfully replicated at least one of the two items of a given length, testing continued with the length increasing by one. As soon as two items of the same length were replicated incorrectly, testing was stopped. The longest successfully replicated span – not the number of correctly remembered items – was used in the analysis as the child's visual working memory span.

4.1.3. Procedure

Children were tested individually by student research assistants in separate rooms in their respective kindergartens. Each child was tested on two separate days to avoid overexertion. No testing session took longer than 40 minutes. The study was presented as a story about an otter that wanted to find out what the children had already learned. At the end of the study, children received a keychain depicting the otter as a reward for helping the otter learn. Because it is as of yet unclear at which age handedness has predictive value for children's mathematical performance, this study was conducted before the start of formal schooling to assess whether children at risk of developing MLD would show differences in the distribution of their handedness.

4.1.4. Statistical analysis

All analyses were performed using SPSS v. 25 (IBM Corporation, 2017). Prior to the statistical analysis, all measures were *z*-standardized. For mathematical abilities, a composite score was calculated by first brining all measures to the same scale so that all of them were weighted equally and then a sum score was created. This sum score was then standardized for younger children and older children (median split) separately to account for the large age span in our sample. Three analyses were performed: First, the distributions of left- and right-handers over the two MLD groups were compared via a Chi-square test. We then calculated a *t*-test to compare children at risk with children not at risk for developing MLD on their degree of hand skill. Then, we calculated a Pearson correlation coefficient between degree of hand skill and mathematical abilities.

4.2. Results

Only 5 children wrote with their left hand, and one child switched hands in between the two hand preference assignments (writing hand and hand used for line tracing; inconsistent handedness) and was excluded from further analysis comparing left- and right-handed children. Because of the small overall number of left-handed children, analyses were not conducted separately for male and female participants. There was evidence of a difference in the degree of hand skill between left- (M = -.05) and right-handed children (M = .23), t(150) = 2.05, p = .042.

The numbers of male and female participants in the MLD and handedness groups are presented in Table 5. Descriptive statistics are presented in Table 6.

Please insert Tables 5 & 6 about here

Considering the distribution of participants across MLD and hand preference groups, the chi square statistic revealed no evidence of associations between hand preference and MLD status, χ^2 (1) = 3.575, p = .059. There was also no evidence of a difference between the two groups with regard to degree of hand skill, $t(151) = -.40$, $p = .692$. Degree of hand skill was not correlated with the math ability score, $r = .012$, $p = .883$.

4.3. Discussion

The results of Study 3 indicate that in early childhood, before the onset of formal schooling, handedness does not seem to play a major role in children's numerical abilities. Children who were classified as being at risk for developing MLD did not show a different degree of handedness than children not at risk for developing MLD. Also, the degree of hand skill measure reported here was not associated with children's numerical performance.

Three possible explanations can account for these findings: The first is that handedness does not play a role in the early developmental stages of numerical abilities, and that instead, cognitive abilities and numerical precursor abilities are more relevant. The second explanation could be that the degree of hand skill measure calculated from the tapping task does not provide a sensitive enough measurement of children's handedness, at least not in our sample. The third one could be that the size of the sample was too small to capture any handedness effects and it further included only five left-handed writers. Future studies could therefore make use of different, maybe less speed-based and more accuracy-based measurements of handedness in larger samples.

5. Study 4: Meta-analysis

5.1. Method

Two sets of analyses took place 1) meta-analysis set 1 included meta-analyses of studies that provided handedness data on individuals with MLD as well as TA individuals acting as controls, 2) meta-analysis set 2 included meta-analyses of studies that reported data on the handedness prevalence in individuals with MLD (irrespective of the presence of a control group).

5.1.1 Locating studies

The studies that were entered into the meta-analyses were located via the online databases Pubmed MEDLINE, PsychINFO, HEALLink, Scopus and National Documentation Centre using the search terms (handedness OR “hand preference” OR “hand skill”) AND (dyscalculia OR math*). All fields were searched for the target words with no time restriction. The cited literature of all articles that were eligible for inclusion was scanned as well. In addition, e-mail requests for unpublished data were sent to the authors of the included articles (when e-mail addresses could be retrieved), in order to ensure that no study was left out of the meta-analyses. The number of the abstracts screened was 376 (299 articles were excluded at this stage). The number of full text articles assessed for eligibility was 77. Nineteen studies were included in the meta-analysis, in addition to the three studies reported in the present article. Details about the method of literature search and study selection are shown in Figure 2. Data extraction was performed by MPP and DP (intercoder agreement 97%). Any inconsistencies were resolved through discussion. Data collection ended in April 2020. The meta-analyses were conducted following the guidelines of the PRISMA statement (Moher et al., 2009).

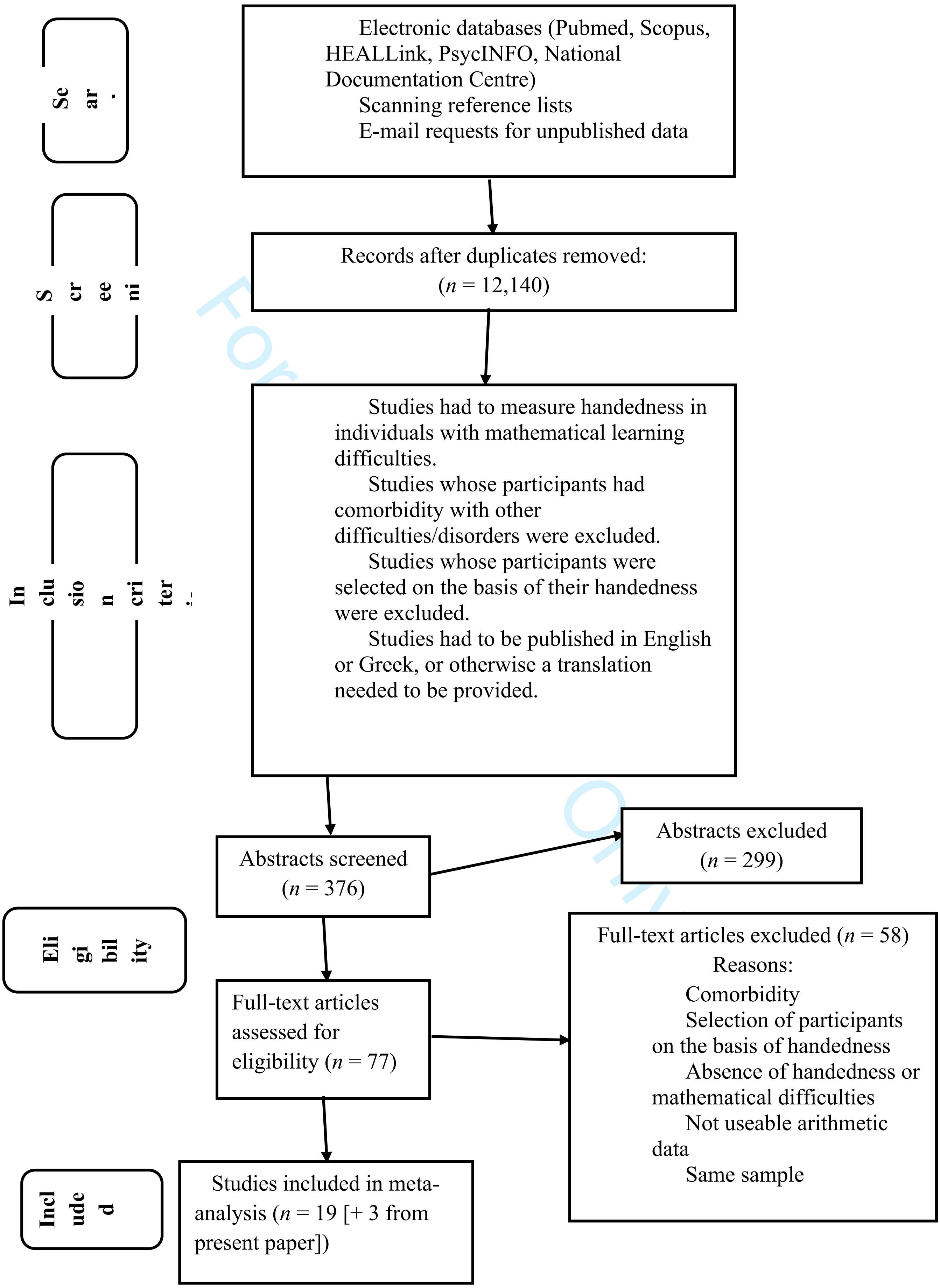
Se ar
Electronic databases (Pubmed, Scopus, HEALLink, PsycINFO, National Documentation Centre)
Scanning reference lists
E-mail requests for unpublished data
S cr ee ni
Records after duplicates removed: (n = 12,140)
In clu sio n cri ter
Studies had to measure handedness in individuals with mathematical learning difficulties.
Studies whose participants had comorbidity with other difficulties/disorders were excluded.
Studies whose participants were selected on the basis of their handedness were excluded.
Studies had to be published in English or Greek, or otherwise a translation needed to be provided.
Abstracts screened (n = 376)
Abstracts excluded (n = 299)
Eli gi bil ity
Full-text articles assessed for eligibility (n = 77)
Full-text articles excluded (n = 58)
Reasons:
Comorbidity
Selection of participants on the basis of handedness
Absence of handedness or mathematical difficulties
Not useable arithmetic data
Same sample
Incl ude d
Studies included in meta-analysis (n = 19 [+ 3 from present paper])

Figure 2. Flow diagram for the search and inclusion criteria for studies in the meta-analysis. The figure was created according to the guidelines of the PRISMA statement (Moher, et al., 2009).

5.1.2. Study selection

The following criteria were set for inclusion of a study in the meta-analyses:

Participants: To be considered for inclusion, studies had to measure handedness in participants who were assigned to a MLD group after their mathematical ability was objectively measured (terms used in the included studies were developmental dyscalculia, MLD, low mathematic score, arithmetic deficiency, mathematically impaired, low mathematical ability, but as stated earlier the term MLD is here used inclusively). In the cases where the presence of MLD was self-reported, studies were excluded (e.g., Hoffmann, Mussolin, Martin, & Schiltz, 2014; Rodriguez et al., 2010).

Absence of comorbidity: Studies including participants with MLD that also presented with aphasia (e.g., Semenza et al., 2006), posterior cortical atrophy (e.g., Miller et al., 2018), acute vestibular neuritis (e.g., Moser, Vibert, Caversaccio & Mast, 2017a), peripheral vestibular deficits (e.g., Moser et al., 2017b), developmental language disorder (e.g., Verly et al., 2018), or dyslexia (e.g., Koerte et al., 2016) were excluded. The study of Shalev et al. (1995) was included, although 13 out of the 25 dyscalculic children had a diagnosis of ADHD, but only the data from participants without the disorder were used. Rubinsten and Henik (2006) used both a group of participants with dyscalculia and a group with dyslexia in which case only the data of the former group were used. Similarly, when studies included groups of individuals with comorbidity or other disorders (e.g., reading deficiency or dual deficiency;

Greiffenstein & Baker, 2002), or groups of individuals with high scores in mathematics (e.g., Kovas et al., 2009; Whittington & Richards, 1991) only the data on individuals with MLD were included in the meta-analyses.

No selection of participants on the basis of their handedness: Studies that either encouraged or discouraged right- or left-handers participate or it was not clear from description of the methods whether participants were right-handed on purpose or by chance were excluded (e.g., Gómez-Velázquez et al., 2017; González-Garrido et al., 2018; Grabner et al., 2009; Stanescu-Cosson et al., 2000; Strang & Rourke, 1983). Those studies were excluded following a conservative approach. Furthermore, in the case of brain imaging studies, where participants are typically selected for right-handedness, unless this choice was directly reported, the authors of the original studies were contacted and after confirmation studies were excluded (Kucian et al., 2006; Kucian, Loenneker, Martin, & von Aster, 2011b; Rotzer et al., 2008) or included (Price et al., 2007).

Publication language: Reports written in English and Greek were included. The only exception was the study of Jovanović et al. (2014), which the author kindly translated for us.

A few studies did include participants with MLD and also provided information about their handedness, but the arithmetic data was not useable (e.g., Ashkenazi et al., 2012; Ayyildiz et al., 2019; Cohen, Gliksman, & Henik, 2019; Huber, Nuerk, Reips, & Soltanlou, 2017; Mazzocco & Thompson, 2005; Rosenberg, 1989; Salvador et al., 2019; Shalev, Manor, & Gross-Tsur, 1997; Whittington & Richards, 1991). In addition, case studies were not included (e.g., DeVisscher & Noël, 2013; Hsieh et al.,2017; Iuculano & Cohen Kadosh, 2014; Martins et al.,1999; von Aster, 2000). When two studies used the same sample of individuals we kept only one (e.g., Kucian et al., 2011a; Michels, O'Gorman, & Kucian, 2018; Lafay, Macoir, & St-Pierre, 2018; Lafay, St-Pierre, & Macoir, 2017). The McCaskey (2018a) dataset included all the participants from the longitudinal study reported in McCaskey et al. (2018) and most of the participants of McCaskey, Von Aster, O' Gorman Tuura and Kucian (2017). The McCaskey (2018b) dataset included only the participants that were additionally measured for the magnitude study reported in McCaskey et al. (2017), ensuring no participants' data were entered into the meta-analysis twice. Finally, in the Spellacy and Peter (1978) study, the two groups of participants with MLD were merged for the purposes of this analysis.

5.1.3. Moderators

The possible moderating effect of a number of variables previously employed in meta-analyses on handedness in individuals with special educational needs (i.e.,ASD; Markou et al., 2017; deafness; Papadatou-Pastou & Safar, 2016; intellectual disability; Papadatou-Pastou & Tomprou, 2015) was examined in the second set of meta-analysis where heterogeneity was found to be significant. There were sufficient data (at least three data points per level of a categorical moderator variable) to include the following variables as potential moderators:

Year of publication. The year of publication was entered numerically for each study. Year of publication of each study has been previously used as a proxy for secular change (e.g., Markou et al., 2017; Ntolka & Papadatou-Pastou, 2017; Papadatou et al., 2008).

Location of the study. Two groups were formed, studies that took place in Europe (n = 14) and studies that took place outside of Europe (n = 8). The countries included in the second group came from Asia (Israel) (n = 3), America (n = 4), and

Australia (*n* = 1). The creation of the non-Europe group was deemed necessary because of the low number of studies in each of the included locations.

Sex ratio. Possible sex differences in the handedness prevalence in MLD could not be directly investigated, because no published study broke down the results by sex. The sex ratio of participants was therefore used and entered numerically as the percentage of female participants. It should be noted that one study did not report the sex distribution of its samples (Price et al., 2007) and could not be entered into the sex ratio analysis.

Mean age of MLD. The mean age of the participants was entered numerically as mean age in years in order to ensure consistency between the studies. When only the age range was available, we used the midpoint of the range (e.g., in Jastrzebski, Crewther, & Crewther, 2015, the age range reported was 19-33 years and the midpoint used in our analysis was 26 years). Two studies did not report the age of their samples (Jovanović et al., 2014; Price et al., 2007) and could not be entered into the mean age analysis.

Age group (adults/children). Age was also employed as a categorical variable using the categories children or adults.

Classification of handedness. The classification of handedness in the studies that were included in the meta-analysis followed either a binary classification with two handedness classes (right- or left-handed; RH-LH; right- or non-right-handed; RH-nonRH; dextral or non-dextral; D-ND) or a classification with three handedness classes (right-, left-handed or ambidextrous; right-; strong left-, strong right-handers, or remainder). The studies were coded for classification of handedness using two different groupings: (a) studies with two handedness classes and (b) studies with three handedness classes.

Measurement of handedness -instrument. The studies were coded in two groups: a) studies that used the Edinburgh Handedness Inventory (Oldfield, 1971) and b) studies that used other instruments for measuring handedness or did not report on how handedness was measured.

Measurement MLD -instrument. The studies were coded in two groups: a) studies that used the ZAREKI-R and b) studies that used other forms of assessment.

Some further variables with a possible moderating effect were not examined due to missing or unusable data, namely the main purpose of the study, familial MLD, whether handedness was collected by self-report measures or observation, IQ, and the ethnicity of the participants. Only one study mentioned data about familial MLD (Shalev et al., 1995). In addition, only one of the studies indicated the report of handedness (i.e., self-report; Jovanovic et al., 2014). In the case of the ethnicity of the participants, only two studies reported it. In the first, the ethnicity of the final sample - it included two more subgroups- was 51.1% white/Caucasian, 21.3% Hispanic, 6.4% African American, 6.4% Asian, 8.5% other, and 6.4% elected not to report (Skeide et al., 2018). In the second one, all participants were French-speaking and selected from French schools in Quebec City, Canada (Lafay et al., 2017).

5.1.4 Statistical analysis

Data analysis was performed using R Studio v.3 (R Core Team, 2018) using the packages robumeta and meta. Two separate meta-analysis sets were conducted following the steps listed below (following Markou et al., 2017; Papadatou-Pastou & Safar, 2016; Papadatou-Pastou & Tomprou, 2015):

Step 1. Effect size calculation. An effect size together with its 95% confidence interval was calculated for each data set independently. Two effect sizes were used: (a) for meta-analysis set 1, the ratio of atypical handedness odds (OR) between individuals with MLD and TA individuals, and (b) for meta-analysis set 2 the handedness rate for individuals with MLD. In the case of the odds ratio, a value of 1.0 corresponds to the null hypothesis of no differences in handedness between individuals with MLD and TA individuals, whereas values greater than 1.0 indicate a larger proportion of atypical handedness among individuals with MLD.

Step 2. Heterogeneity tests and possible overall effect re-estimation using random effects. Three tests of homogeneity were used, namely the Q statistic, the Tau^2 statistic and the I^2 index. Of note, I^2 index levels of 25%, 50%, and 75% are considered as low, moderate, and high, respectively (Higgins, Thompson, Deeks, & Altman, 2003).

Step 3. Overall effect estimation using random-effects. The overall effect was calculated as a weighted average of the effects sizes across all data sets. In the case of meta-analysis set 1, the overall estimate can also be presented as a simple proportion using the formula MLD = TA x OR/[1 + TA(OR - 1)], where MLD and TA are the probabilities of atypical handedness in individuals with MLD and TA populations, respectively. Simple proportions are easier to grasp intuitively, hence this transformation was also reported.

Step 4. Small study bias analysis. Small studies might be only published when reporting the desired effect, hence they might contribute to publication bias, which can distort the overall effect. The presence of small study bias was tested using the funnel plot graphical test and Egger's t statistical test. Duval and Tweedie's (2000) trim and fill method of correcting bias was also used. Publication bias was only assessed in the first set of meta-analyses, on the odds ratio of handedness between MLD and TA, as in the second set of meta-analyses, the prevalence of handedness in MLD the event rate (the effect size of interest) cannot be subject to publication bias (no comparisons are being made, hence no expected finding). Still, in the first set of meta-analysis, no published studies aimed specifically at investigating handedness odds between MLD and TA, thus publication bias is reported here with caution.

Step 5. Moderator variables analysis. In the case of meta-analysis set 2, significant heterogeneity between studies was found to exist, making it necessary to search for the presence of moderators. Meta-regression using the method of moments was used in order to test for the moderating effect of the interval moderator variables (i.e., year of publication, sex ratio, and mean age), with evaluation in terms of the I^2 statistic. In the case of categorical moderator variables (i.e., classification of handedness, location, measurement of handedness, measurement of MLD, and age group) the average effect sizes in the different subgroups that form the levels of the moderator were compared again by means of the I^2 statistic.

Each set of meta-analyses included three different comparisons: (i) left-handedness, (ii) non-right-handedness, and (iii) mixed-handedness. In the left-handedness comparison, left-handers were either (i) the participants classified as left-handers in the binary classifications (RH-LH, RH-nonRH, or D-ND) or (ii) the participants at the left extreme of three-way classifications (right-, left- handed or ambidextrous; strong left-, strong right-handers or remainder). In the non-right-handedness comparison, non-right-handers were (i) the participants classified as left-handers, non-right-handers, non-dextral in the studies using binary classifications as well as (ii) the participants that were classified as left-handers and as ambidextrous or remainders in studies employing three-way classifications. Forest plots were used as a graphical display of the findings.

5.2. Results

A total of 22 studies were included in the analysis adding up to n = 3,667 participants (n = 1,017 individuals with MLD, n = 2,650 TA individuals). The details of all studies used can be found in Table 7.

Please Insert Table 7 about here

5.2.1. Meta-analysis set 1: MLD-to-TA handedness odds ratios

Overall effect estimate (left-handedness): This comparison included k = 13 datasets adding up to n = 2,622 individuals (n = 741 individuals with MLD, n = 1,881 TD individuals). The studies of Price et al. (2007), Skeide et al. (2018), and McCaskey (2018b) had zero left-handers in both the MLD and the TA groups, which cannot be translated into a ratio. There was no evidence of heterogeneity among the data sets, Q (12) = 7.56, p = .81, Tau^2 = .00, with no inconsistency between studies, I^2= .00%, indicating that no variables moderate the MLD-to-TA left-handedness odds ratio. A random effects model was employed, which gave a pooled odds ratio (OR) = 1.06, 95% confidence interval (CI) = .79, 1.42, Z = .42, p = .67 (see Figure 3). Therefore, there is no statistical evidence for differences between MLD and TA individuals in terms of left-handedness. The analysis was repeated after removing the largest study representing 68.1% of participants (Study 2, n = 1893) and no evidence of a difference was similarly found (OR = 1.59, 95% confidence interval (CI) = .95, 2.68, Z = 1.77, p = .07). We refrain from interpreting the last p-value as weak evidence for a difference, as three studies showing no differences but reporting zero left-handers for both groups were not included in the analysis, as mentioned above (McCaskey, 2018b; Price et al., 2007; Skeide et al., 2018). Egger's t provided evidence for small study bias, $t(11)$, = 3.44, p = .006. Visual inspection of the funnel plot graphical test marginally suggests that the left side of the funnel (representing lower odds of non-right-handedness for the MLD individuals) might be slightly underrepresented (see .3). Using Duval and Tweedie's trim and fill method for bias correction for the fixed effects model six datasets were "filled" to the left of mean, representing no differences between MLD and TA individuals, and the adjusted overall estimate was 0.97, 95% CI .73, 1.28.

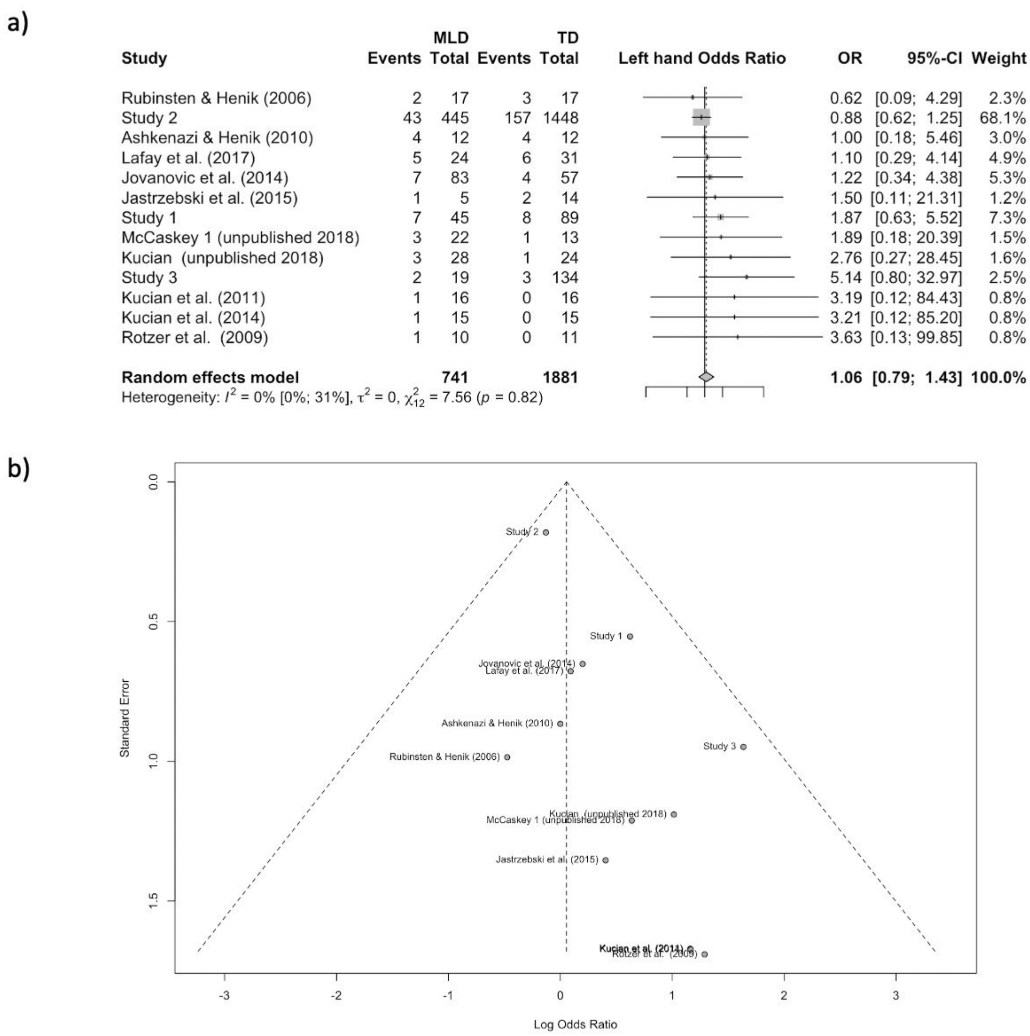

Figure 3. a) Forest plot for the left-handedness comparison. In the plot the 95% confidence interval for each study is represented by a horizontal line and the point

estimate is represented by a vertical line. The confidence intervals for totals are represented by a diamond shape at the bottom of the plot. b) Funnel plot of standard error on log odds ratio, for the left-handedness comparison.

Overall effect estimate (non-right-handedness): This comparison included k = 14 studies adding up to n = 2,646 individuals (n = 747 individuals with MLD, n = 1899 TD individuals). Price et al. (2007) and Skeide et al. (2018) reported zero non-right-handers for both MLD and TA individuals and were not included. There was no evidence of heterogeneity among the datasets, Q (13) = 10.59, p = .65, Tau^2 = .00, with no inconsistency between studies, I^2= .00%, indicating that no variables moderate the MLD-to-TA non-right-handedness odds ratio. A random effects model was employed, which gave a pooled odds ratio (OR) = 1.04, 95% confidence interval (CI) = .79, 1.37, Z = .31, p = .75 (see Figure 4). Therefore, there is no statistical evidence for differences between MLD and TA individuals in terms of non-right-handedness. The analysis was repeated after removing the largest study representing 64.4% of participants (Study 2, n = 1907) and no evidence of a difference was similarly found (OR = 1.42, 95% confidence interval (CI) = .89, 2.260, Z = 1.45, p = .13). Egger's t showed no evidence of small study bias, t(12), = 2.07, p = .06. However, visual inspection of the funnel plot graphical test marginally suggests that the left side of the funnel (representing lower odds of non-right-handedness for the MLD individuals) might be slightly underrepresented (see Figure 6). Using Duval and Tweedie's trim and fill method for bias correction for the random effects model three datasets were "filled" to the left of mean, representing no differences between MLD and TD individuals, and the adjusted overall estimate was 0.97, 95% CI .69, 1.36.

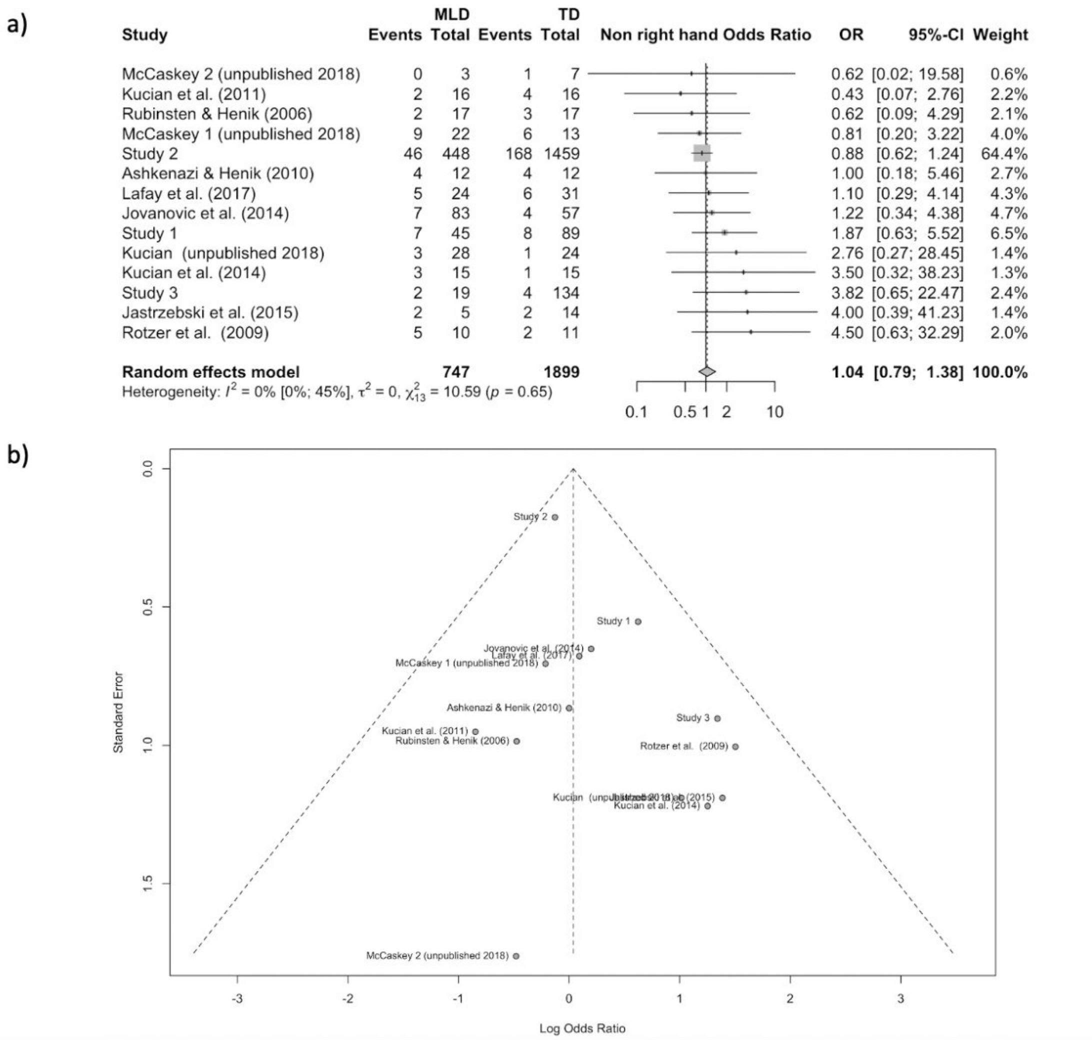

Figure 4. a) Forest plot of the non-right-handedness comparison. b) Funnel plot of standard error on log odds ratio, for the non-right-handedness comparison.

Overall effect estimate (mixed-handedness): This comparison included $k = 9$ studies adding up to $n = 2,372$ individuals ($n = 603$ individuals with MLD, $n = 1,769$ TD individuals). The studies of Ashkenazi and Henik (2010), Jovanović et al. (2014), Price et al. (2007), and Rubinsten and Henik (2006) could not be included, as they reported zero mixed-handers for both MLD and TA individuals, which cannot be translated into a ratio. There was no evidence of heterogeneity among the datasets, $Q(8) = 5.82$, $p = .66$, Tau^2 = .00, with no inconsistency between studies, I^2= .00%, indicating that no variables moderate the MLD-to-TA mixed-handedness odds ratio.

A random effects model was employed, which gave a pooled odds ratio (OR) = 1.2, 95% confidence interval (CI) = .67, 2.174, $Z = .63$, $p = .52$ (see Figure 6). Therefore, there is no statistical evidence of differences between MLD and TA individuals in terms of mixed-handedness. The analysis was repeated after removing the largest study representing 79.62% of participants (Study 2, $n = 1905$) and no evidence of a difference was similarly found (OR = 1.241, 95% confidence interval (CI) = .66, 2.35, $Z = .68$, $p = .49$). Egger's t showed no evidence of small study bias, $t(7)$, t = .05, $p = .93$. Visual inspection of the funnel plot graphical test did not suggest any asymmetries (see Figure 5), but using Duval and Tweedie's trim and fill method for bias correction for the fixed effects model one dataset was "filled" to the left of mean, representing no differences between MLD and TD individuals, and the adjusted overall estimate was 1.21, 95% CI .68, 2.18.

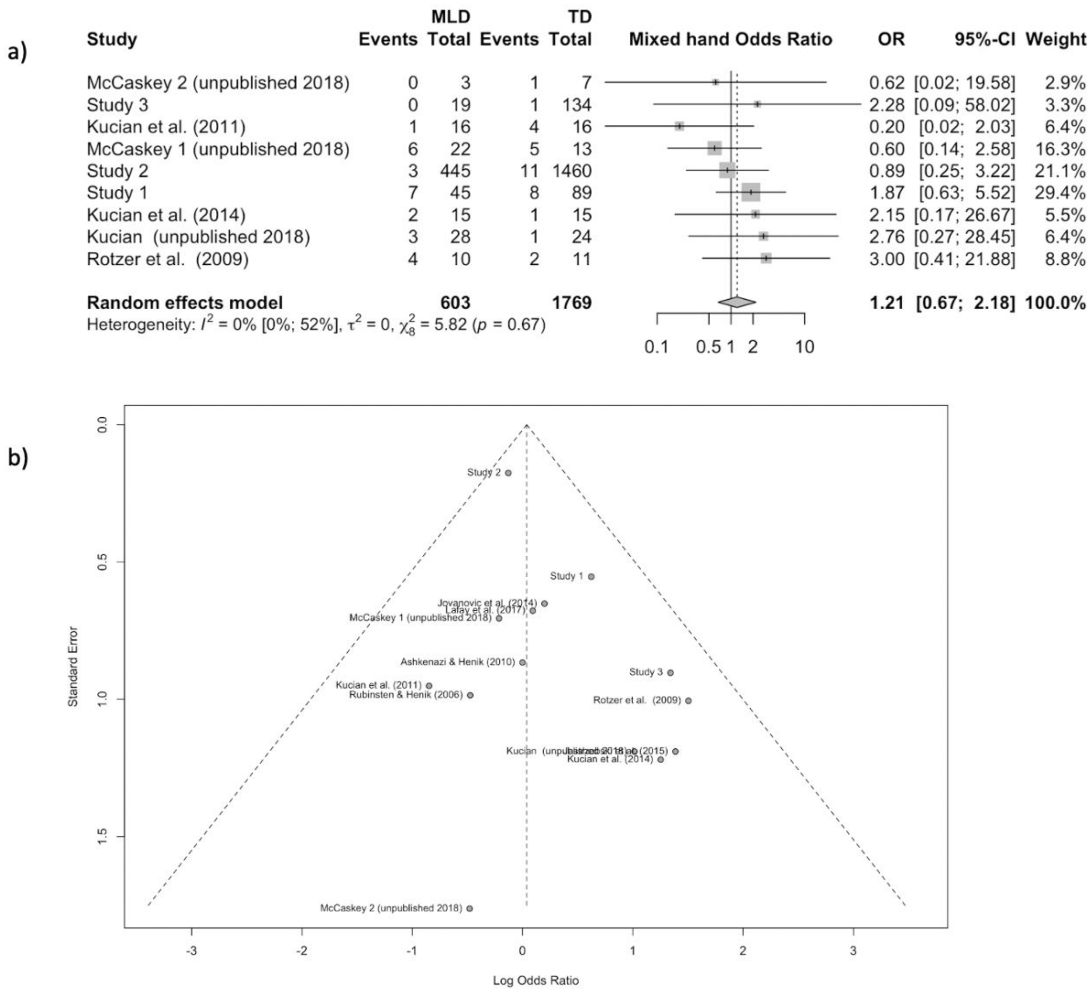

Figure 5. a) Forest plot of the mixed-handedness comparison. b) Funnel plot of standard error on log odds ratio, for the mixed-handedness comparison.

5.2.2. Meta-analysis set 2: Handedness prevalence in individuals with MLD

Overall effect estimate (left-handedness). A total of k = 22 data sets were included in the analysis, totaling n = 1,017 individuals with MLD. There was evidence of moderate-to-high heterogeneity among studies, I^2= 67.8%, $Q(21)$ = 65.8, $p < .001$, Tau^2 = .49, indicating the presence of moderator variables. A random effects model was employed, which gave a weighted average of left-handedness prevalence across all data sets of 19.8.%, 95% confidence interval (CI) = 12.8%, 26.9%, $p <$ .001) (see Figure 6). In other words, the range of the left-handedness prevalence in the distribution of populations studied is 12.8% to 26.9%. Egger's t showed no evidence of small study bias, *t*(20), t = 0.8647, p = 0.3975.

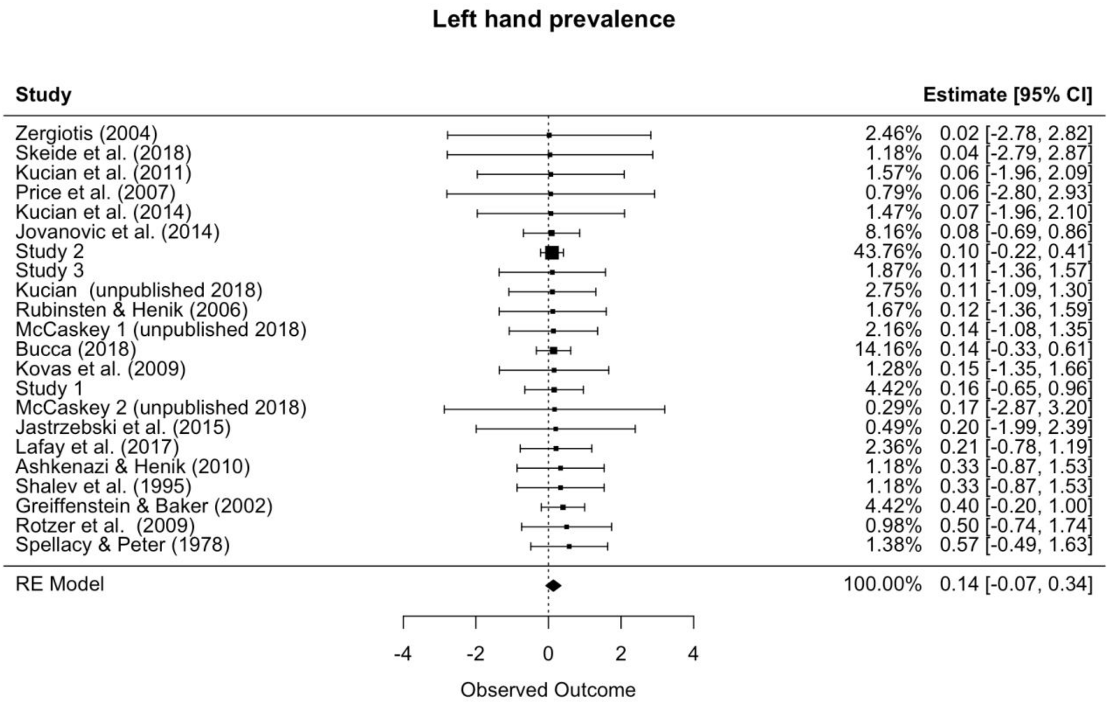

Figure 6. Forest plot for the left-handedness event rate. Estimate effects sizes are estimated as the logit of event rates.

Overall effect estimate (non-right-handedness). A total of $k = 22$ data sets were included in the analysis, totaling $n = 1{,}020$ individuals with MLD. There was evidence of high heterogeneity among the datasets, $I^2 = 66.9\%$, $Q(21) = 69.5$, $p < .001$, Tau^2 = .41, indicating the presence of moderator variables. A random effects model was employed, which gave a weighted average of non-right-handedness prevalence across all data sets of 23.4% with a 95% confidence interval (CI) = 16.7%, 30.1%, , $p < .001$ (see Figure 7). In other words, the range of the non-right-handedness prevalence in the distribution of populations studied is 16.7% to 30.1%. Egger's t showed no evidence of small study bias, t(20), t =1.6026, $p = 0.1247$

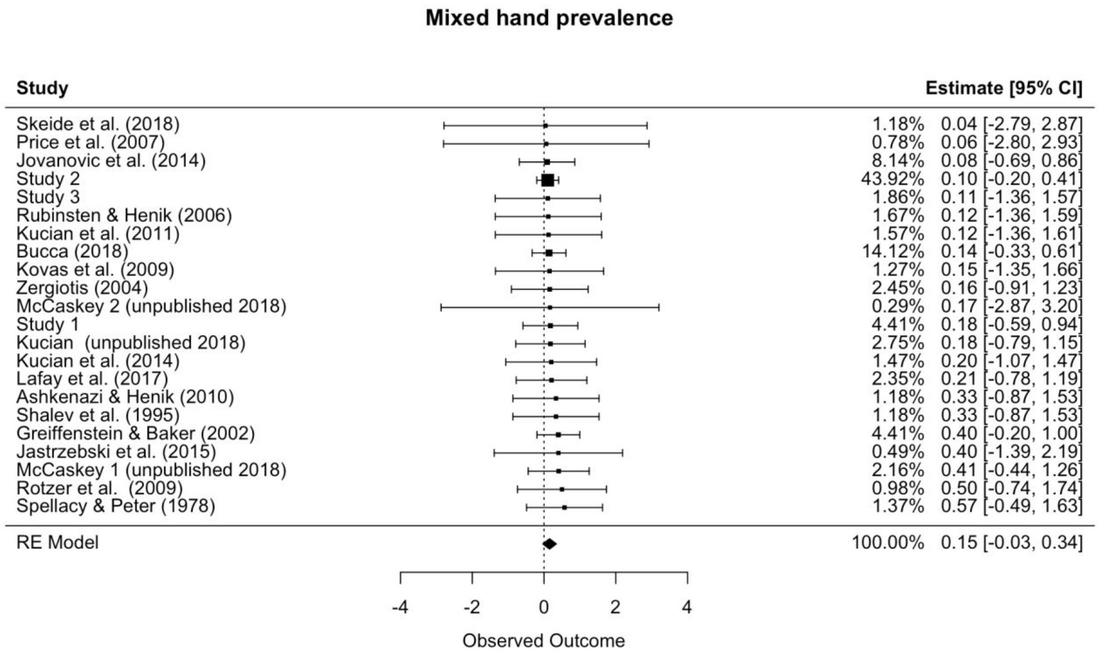

Figure 7. Forest plot for the non-right-handedness event rate. Estimate effects sizes are estimated as the logit of event rates

Overall effect estimate (mixed-handedness). A total of $k = 11$ data sets were included in the analysis, totaling $n = 711$ individuals with MLD. There was evidence of high heterogeneity among the datasets, $I^2 = 77.96\%$, $Q(10) = 46.24$, $p < .001$, Tau^2 = 1.68, indicating the presence of moderator variables. A random effects model was employed, which gave a weighted average of mixed-handedness prevalence across all data sets of 15% with a 95% confidence interval (CI) = 6.2%, 23.8%, $p = .003$ (see Figure 8). In other words, the range of the mixed-handedness prevalence in the distribution of populations studied is 6.23% to 23.8%. Egger's t showed no evidence of small study bias, t(9) , t = -0.9398, $p = 0.3719$

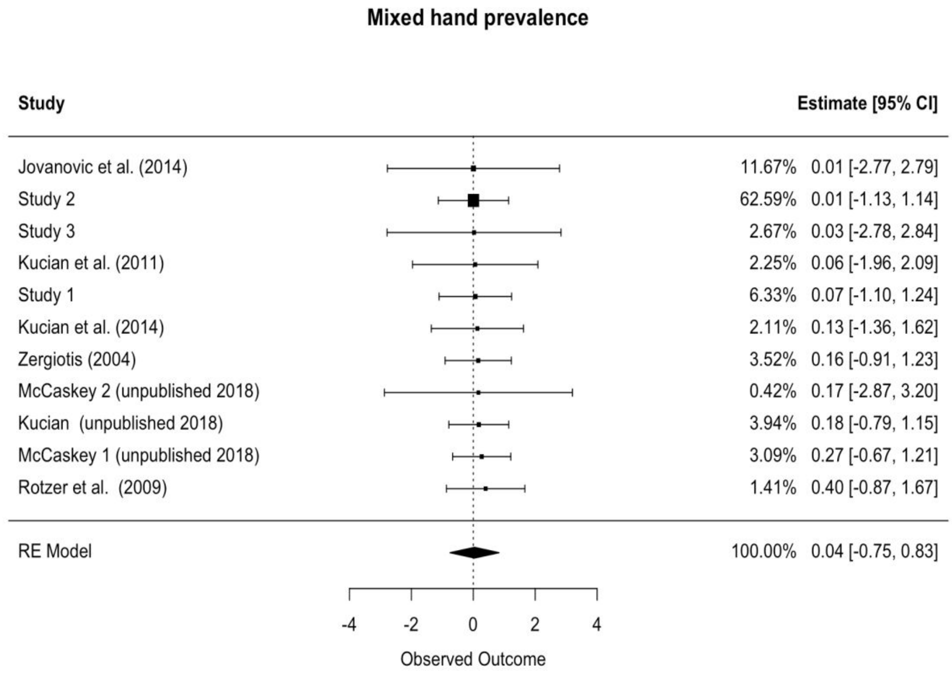

Figure 8. Forest plot for the mixed-handedness event rate. Estimate effects sizes are estimated as the logit of event rates.

Moderating variables analysis. Because of the heterogeneity detected among studies in meta-analyses set 2, the moderating effects of the previously indicated variables were tested within the left-handedness and the non-right-handedness comparisons. The mixed-handedness comparisons did not include enough data sets to allow for moderating variables analysis. Below the results of the left-handedness comparison are presented. Only when the non-right-handedness comparison gave different statistical evidence are the results for this comparison reported.

Publication year. The three new studies reported in the present paper were included using 2019 as the year of publication. Meta-regression of the year of publication of the studies revealed clear evidence of a linear trend in left-handedness (I2= 62.8%, p < .001). The best-fitting linear relation between event rate and year being event rate) = -1.09 (*year*) +2217.41, reflecting a decrease in the estimated rate of left-handedness in MLD individuals between 1978 and 2019.

Location of the study. Location was found to have a clear moderating effect on left-handedness prevalence, I2= 76.60 %, p = 0.01. The best-fitting linear relation between event rate and year being event rate = 16.8 (location) + 14.2. It was found that individuals with MLD have a left-handedness prevalence of 14.2% (95% CI 7.49%, 20.9%) and of 29.8% (95% CI, 16.2%, 42.3%) when residing in a country in Europe (14 studies) and in a non-European country (America, Asia, Australia; 8 studies), respectively. Small levels of heterogeneity were found both within studies conducted in Europe, p < 0.01, I2 = 69. 04% , and small to moderate heterogeneity within studies performed in non-European countries, , p < 0.01, I2 = 83.90%

Sex ratio. Meta-regression was performed and it was found that the percentage of females in the study sample did not affect the pooled effect estimate of the meta-analysis I2= 0 %, p = 0.22

Mean age. Meta-regression of the mean age did not provide evidence as to whether mean age moderates left-handedness rates in MLD (p = .21). In the case of non-right-handedness there was only weak evidence of a moderating effect of mean age, p = .08, I2= 88.15%.

Age group (children/adults). The prevalence of left-handedness was found to be 18.5% (95% CI, 10.2%, 26.9%) and 27.9% (95% CI, 6.58%, 49.3%)in children (18 studies) and adults (4 studies), respectively. No evidence for a moderating effect of age group was found, p = .18. Heterogeneity was further examined within the two age groups, which revealed moderate to high heterogeneity within studies that used children as participants, I2= 86.61% , as well as within studies that used adult participants, I2= 78.71%, Of note, the fact that only four studies had adult samples, calls for caution when interpreting this comparison.

Classification of handedness. The prevalence of left-handedness was found to be 27.7% (95% CI, 16%, 39.5%) and 14% (95% CI, 5.42%, 22.6%)) in two-way (9 studies) and three-way (12 studies) classifications, respectively. There was clear evidence of a moderating effect of classification, $p = .04$. Heterogeneity was further examined within the two classifications, which revealed high heterogeneity within two-way classification, I2= 91.04% and moderate to high heterogeneity within the three-way classification, I2= 73.39% In the case of non-right-handedness evidence this analysis was not applicable.

Measurement of handedness -instrument. The prevalence of left-handedness was found to be 17.5% (95% CI, 2.41%, 32.7%) when handedness was assessed with the Edinburgh Handedness Inventory (7 studies) and 20.6% (95% CI, 11.8%, 29.5%) when handedness was measured with another instrument, or no instrument was reported (15 studies). No evidence for a moderating effect of the instrument was found, $p = .93$. Heterogeneity was further examined and revealed high heterogeneity within the studies that used other instruments than the Edinburgh Handedness Inventory, $I^2 = 73.39\%$, and high heterogeneity within the studies that had used the Edinburgh Handedness Inventory, $I^2 = 91.04\%$.

Measurement of MLD -instrument. The prevalence of left-handedness was found to be 18.7% (95% CI, 3.57%, 33.8%) when mathematical ability was assessed with the Zareki-R (7 studies) and 20.2% (95% CI, 11.3%, 29.2%) when mathematical ability was measured with another instrument or no instrument was reported. No evidence of a moderating effect of the instrument was found $p = .62$. Heterogeneity was further examined and revealed high heterogeneity within the studies that used other instruments than the Zareki-R, $I^2 = 79.51\%$, and high to moderate heterogeneity within the studies that had used the Zareki-R, $Q(6) = 9.72$, $p = .14$, $I^2 = 91.12\%$.

5.3. Discussion

Within Study 4, two separate sets of meta-analyses were carried out, including 22 studies that evaluated the handedness prevalence of 3,667 participants, of whom 1,017 were diagnosed with MLD and 2,650 were TA individuals. The first set of meta-analyses included studies that assessed handedness in both MLD and TA. The second set of meta-analyses included studies that reported the handedness prevalence of individuals with MLD irrespective of the presence of a control group.

Meta-analysis set 1 failed to find any statistically evidence for a difference in atypical handedness odds between individuals with MLD and TA individuals for all three comparisons (left-, non-right-, and mixed-handedness). No heterogeneity was further found within any of the three comparisons. Significant small study bias was detected only for the left-handedness comparison using statistical Egger's Test. However, for all three comparisons the Duval and Tweedie's trim and fill method identified studies missing from the left side of the plot indicating less atypical handedness in MLD compared to TD individuals.

According to meta-analysis set 2, the left-handers prevalence rate among individuals with MLD ranges from 12.8 % to 26.9%, the prevalence rate of non-right-handedness from 16.7% to 30.1%, and the prevalence rate of mixed handedness from 6.2% to 23.8%, with the best point estimates being 19.8%, 23.4%, and 15%, respectively. These ranges are quite large and when it comes to left-handedness they do not include the 10.6% (95%CI 9.71%, 11.50%) estimate of the left-handedness prevalence in the general population that was calculated by a recent large-scale meta-analysis (Papadatou-Pastou et al., 2020). Similarly, the non-right and mixed-handedness estimates are higher than those estimated for the general population by Papadatou-Pastou et al. (2020) (non-right-handedness: 18.10%, 95% CI [13.9%, 22.30%], mixed-handedness: 9.33%, 95% CI [6.67%, 12.00%], but they do overlap in these cases.Therefore, meta-analysis set 2 does provide some evidence of elevated levels of atypical handedness in individuals with MLD, but the absence of a control group remains a limitation of this analysis.

Heterogeneity was found to be significant within all three comparisons of meta-analysis 2 (left-, non-right, and mixed-handedness), indicating the presence of moderating variables. Therefore, the possible moderating effect of year of publication, location of the study, sex ratio, mean age, age group (adults vs. children), classification of handedness, instrument used measure handedness, and instrument used to diagnose MLD was investigated within the left- and non-right-handedness comparisons (the mixed-handedness comparison did not include enough studies for such a comparison to take place). For the year of publication, the location of the study and the classification of handedness there was statistical evidence of a moderating effect on the prevalence of left-handedness among MLD individuals, with older studies, studies located in non-European countries, and studies using the right vs. left classification reporting a higher prevalence of left-handedness. The non-EU group consisted of only eight studies in countries with predominantly Caucasian populations, which should in theory be comparable with the EU samples. Thus, interpretation of this finding should be done with caution.

None of the other variables were found to exert a moderating effect on the handedness prevalence in MLD. This could be taken as indicating true absence of a moderating effect or due to the lack of sufficient data. Some studies did not report information on all the moderating variables, resulting in fewer studies included in the moderator variables analysis compared to the overall effect analysis. Another reason could be the low power of meta-analysis when it comes to detecting moderating effects (Hunter & Schmidt, 1990). It is indeed the case that only large moderating effects can be detected within a meta-analysis, as the number of studies included and not the number of participants is what determines the power to detect such effects.

Limitations of the present study include the fact that all studies measured hand preference, with no information being given on hand skill. Hand skill is an important parameter for the evaluation of the function of central nervous system (Gundogan, Kiziltan, Aydin, & Ogus, 2016). Although hand preference is considered as a primary manifestation of handedness compared to hand skill (McManus, Murray, Doyle, & Baron-Cohen, 1992), hand preference and hand skill are two distinct concepts and there is evidence that they are independently lateralized (Triggs, Calvanio, Levine, Heaton, & Heilman, 2000. Moreover, all studies treated handedness as a categorical variable, with only one study providing information on the degree of handedness (McCaskey, 2017). Degree of handedness may be the more appropriate indicator of cerebral organization and of behavior than the direction of handedness (Prichard, Propper, & Christman, 2013). The researchers argue that previous research has failed to identify individual differences in handedness effects on behavior as they used the direction to define it so that they did not detect the differences associated with degree. The distinction between direction and degree of handedness is further important, as functional magnetic imaging studies have shown that these two aspects are independent and encoded separately in the brain (Dassonville et al., 1997). Had hand skill and degree of handedness data been included in the present meta-analysis, it could be the case that the finding would have been different. Another limitation is that only a handful of studies used adult participants (Ashkenazi & Henik, 2010a; Greiffenstein & Baker, 2002; Jastrzebski et al., 2015; Rubinsten & Henik, 2006), with their average age not exceeding thirty years. Thus, further developmental effects could not have been investigated. Moreover, not all variables with a possible moderating effect were examined due to missing or unusable data, namely the main purpose of the study, familial MLD, whether handedness was collected by self-report measures or not, participants' IQ and the ethnicity of the participants. When conducting Study 4, we could not use the continuous score of mathematical performance of the participants as a moderator variable, as only the seven studies using the Zareki test reported such scores (Kucian et al., 2011; Kucian et al., 2014; Kucian, unpublished 2018; Lafay et al., 2017; McCaskey 1, unpublished 2018; McCaskey 2, unpublished 2018; Rotzer et al., 2009). Only McCaskey (2018b) used an adolescent sample, therefore this could not be used as a separate age category and was not included in the age category analysis.

6. Overall Discussion

The present study investigated atypical handedness (i.e., left-, non-right-, and mixed-handedness) in individuals with MLD and reports both new data from three different countries, as well as two sets of meta-analyses. Despite evidence in the published literature of elevated levels of atypical handedness in general population samples with low mathematical abilities (e.g., Johnston et al., 2013) and in individuals with neurodevelopmental disorders (e.g., Markou et al., 2017), this is the first study to specifically investigate the relationship between handedness and MLD.

Study 1 did not find evidence of a difference in atypical handedness between MLD and TA individuals, when handedness direction was taken under consideration (i.e., when comparing left- and right-handers), except for weak evidence of a difference when only writing hand was used as the handedness criterion (merging those that used their left hand with those who reported using both hands, $p = .049$). Of note, Papadatou-Pastou, Martin, and Munafò (2013) using a sample balanced for handedness and sex found that the mismatch between writing and hand preference inventories was 0.4% for right-handers, but 13.5% for left-handers. Study 1 further showed that hand preference scores were correlated with mathematical achievement scores ($p < 0.001$), which was stronger in the MLD group ($p = .001$) than the TA group ($p = .04$). Study 2, which used writing hand as the handedness criterion, similarly found no evidence of a difference in left-handedness between MLD and TA individuals. Study 3 further found no differences between MLD and TA individuals neither when direction of hand preference was employed, nor when degree of hand skill task was employed.

These findings point to the direction of no relationship between handedness and MLD, even if Study 1 provides some weak evidence of such a relationship. This picture is representative of the handedness literature, where different studies, especially if they measure and operationalize handedness using different measures and classifications, provide different findings. In a recent meta-analysis on the prevalence of handedness Papadatou-Pastou et al. (2020) urge researchers to define universal criteria for measuring hand preference, a message we would like to reinforce here. Specifically, we ask for short questionnaires, the reporting both writing hand and Edinburgh Handedness Inventory scores, and the reporting of at least two classifications, for example R-L and R-M-L, as well as making raw data publically available in open-access repositories. It is moreover suggested that future studies include information on hand skill and degree of handedness. Additionally, the data should be broken down by ~~age and~~ gender, in order for this relationships to be investigated as well. Publishing registered reports before embarking on data collection is also recommended, as this practice can act as a safeguard against publication bias as well as against a host of other replication-related issues, such as *p*-

hacking. It is encouraging that such efforts are already taking place within the field of handedness (e.g., Pritchard, Malone, Burgoyne, Burgoyne, Heron-Delaney, & Bishop, 2019). In addition to these good handedness practices, the literature would also benefit from a clear and consistent definition of MLD, leading to a better identification of individuals who present with them and a better matching of control individuals.

When combining the evidence of the three studies reported here for the first time with already published data, no evidence of a difference in the odds ratio of atypical handedness between MLD and TA participants was found (all $p < .05$). When synthesizing the data of studies that measured handedness in MLD without the presence of a control group, then the observed levels of atypical handedness were elevated compared to general population estimates (Papadatou-Pastou et al., 2020). However, the very absence of a control group does not allow for this evidence to be reliable, as the elevated levels of atypical handedness found could be due to a number of factors. For example studies might have implicitly recruited more individuals of atypical handedness or might have used more lax criteria for defining handedness groups. Of note, in the first set of meta-analyses, which used the odds ratio as the effect size, the base rate of atypical handedness of each study could not affect the estimated ratio between MLD and TA participants.

Overall, the evidence weights to the direction of atypical handedness levels not being different between MLD and TA individuals, at least when direction of hand preference is taken into account. Our findings challenge the link between handedness and mathematical ability supported by studies measuring low mathematical abilities in general population samples (e.g., Johnston et al., 2009).

The meta-analyses are limited by the fact that they included studies that measured only hand preference and not hand skill, the other manifestation of handedness. Moreover, primary studies grouped participants according to the direction of the participants' preference, hence no data on the degree of handedness was included in the meta-analysis. However, not being able to use hand skill and/or hand preference data is a common issue when conducting meta-analyses of handedness studies (e.g., Papadatou-Pastou, 2018). Of note, we were not able to exclude preterm individuals, as it has been shown that preterm birth is associated with higher levels of non-right handedness (Domellöf, Johansson, & Rönnqvist, 2011).

Higher prevalence rates of atypical hand preference have been found in populations with other special education needs, such as dyslexia (Vlachos et al., 2013), deafness (Papadatou-Pastou & Sáfár, 2016), and the low functioning end of the autism spectrum disorder (Markou et al., 2017). Dyslexia, deafness, and autism are conditions associated with poor outcomes on language-related abilities. When it comes to deafness, Papadatou-Pastou and Sáfár (2016) suggest that elevated levels of atypical handedness are found only in those deaf individuals who acquired language, be it either sign language or spoken language, at a later age. It is therefore here argued that elevated levels of atypical handedness are not a general characteristic of individuals with special educational needs, but rather specifically related to those conditions that affect language. Of note, no hand preference differences were found between children who stutter and children who do not stutter (Mohamadi & Papadatou-Pastou, 2019), but stuttering is not a condition that affects language at a cognitive level, rather than articulation. Another possible explanation is that the handedness effect on MLD was too subtle to be detected in the present sample, given that some of the included studies had small sample sizes and that heterogeneity was detected in the second set of meta-analyses (albeit not in the first set). Moreover, direction of hand preference might not be a sensitive enough measure of handedness and other handedness measures, such as hand skill or degree of hand preference, might be more appropriate. Nicholls, Chapman, Loetscher, and Grimshaw (2010) similarly argue that when it comes to the effects of handedness on cognitive ability these are subtle and identifiable in large scale studies with sensitive measures of hand performance.

In summary, we here report new data from three countries (Studies 1-3) and two sets of meta-analysis on the question of handedness in MLD (Study 4). The evidence points to the direction of no differences in atypical handedness levels in individuals with MLD compared to TA individuals, at least when the direction of hand preference is used as the handedness measure. We argue that the increased rates of atypical handedness that have been reported in recent meta-analyses on the relationship of handedness and language-related conditions cannot be extended to cognitive traits in general.

Conflict of interest

No conflict of interest to declare.

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Data availability statement

Datasets and analysis codes have been uploaded in the Open Science Framework repository (https://osf.io/wqf7j/).

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Table 1.

Hands preferred for the four actions by males and females in the two groups for Study 1.

		Learning Difficulties in Mathematics			**Typically Achieving**		
		Right	Both	Left	Right	Both	Left
Males	Writing hand	16 (84.2%)	-	3 (15.8%)	39 (92.9%)	-	3 (7.1%)
	Drawing hand	15 (78.9%)	2 (10.5%)	2 (10.5%)	36 (85.7%)	4 (9.5%)	2 (4.8%)
	Throwing hand	12 (63.2%)	5 (26.3%)	2 (10.5%)	18 (42.9%)	19 (45.2%)	5 (11.9%)
	Hand using computer mouse	16 (84.2%)	2 (10.5%)	1 (5.3%)	38 (90.5%)	4 (9.5%)	0 (0%)
Females	Writing hand	21 (80.8%)	1 (3.8%)	4 (15.4%)	44 (93.6%)	-	3 (6.4%)
	Drawing hand	19 (73.1%)	3 (11.5%)	4 (15.4%)	39 (83%)	5 (10.6%)	3 (6.4%)
	Throwing hand	9 (34.6%)	16 (61.5%)	1 (11.5%)	20 (42.6%)	24 (51%)	3 (6.4%)
	Hand using computer mouse	20 (76.9%)	4 (15.4%)	2 (7.7%)	36 (76.6%)	8 (17%)	3 (6.4%)
Total	Writing hand	37 (82.2)	1 (2.2%)	7 (15.5%)	83 (93.3%)	-	6 (6.7%)
	Drawing hand	34 (75.6%)	5 (11.1%)	6 (13.3%)	75 (84.3%)	9 (10.1%)	5 (5.6%)
	Throwing hand	21 (46.7%)	21 (46.7%)	3 (6.7%)	38 (42.7%)	43 (48.3%)	8 (9%)
	Hand using computer mouse	36 (80%)	6 (13.3%)	3 (6.7%)	74 (83.3%)	12 (13.5%)	3 (3.4%)

Table 2

Handedness groupings of the participants in the two groups, broken down by sex.

(RH= Right-handed, LH = Left-handed, MH = Mixed-handed) for Study 1

		Mathematical Difficulties			**Typically Achieving**		
		Males	**Females**	**Total**	**Males**	**Females**	**Total**
Right vs. Left Classification	**RH**	16 (42.11%)	22 (57.89 %)	38	39 (48.15%)	42 (51.85%)	81
	LH	3 (42.96%)	4 (57.14%)	7	3 (37.5%)	5 (62.5%)	8
Right - Mixed - Left Classification	**RH**	16 (43.24%)	21 (56.76%)	37	36 (47.37%)	40 (52.63%)	76
	MH	1 (33.33%)	2 (66.6%)	3	4 (44.44%)	5 (55.56%)	9
	LH	2 (40%)	3 (60%)	5	2 (50%)	2 (50%)	4
Degree of handedness (mean ± SD)		1.32 ± 2.36	1.77 ± 2.12	1.58 ± 2.21	1.12 ± 1.55	1.30 ± 1.55	1.21 ± 1.54

Table 3

Handedness data for the MLD and TA groups, broken down by sex for Study 2

	Mathematical Learning Difficulties			**Typically Achieving**		
	Right	**Left**	**Total**	**Right**	**Left**	**Total**
Male	165 (89.67%)	19 (10.33%)	184	512 (86.78%)	78 (13.22%)	590
Female	237 (90.80%)	24 (9.20%)	261	779 (90.79)	79 (9.21%)	858
Total	402 (90.33%)	43 (9.66%)	**445**	1291 (89.16%)	157 (10.84%)	**1448**

Table 4

Comparison of handedness and sex in individuals with severe and less severe mathematical difficulties for Study 2.

MA < -1.75 SD	**Right**	**Left**	**Total**
Male	67 (89.33%)	8 (10.67%)	75
Female	71 (87.65%)	10 (12.35%)	81
Total	138 (88.46%)	18 (11.54%)	**156**

Table 5

Handedness groupings of the participants in the two groups, broken down by sex for Study 3

	Not at risk of MLD				**At risk of MLD**			
	Right-handed	**Left-handed**	**Incon-sistent**	**Total**	**Right-handed**	**Left-handed**	**Incon-sistent**	**Total**
Male	67 (97.10%)	1 (1.45%)	1 (1.45%)	69	9 (90%)	1 (10%)	0 (0%)	10
Female	63 (96.92%)	2 (3.08%)	0 (0%)	65	8 (88.89%)	1 (11.11%)	0 (0%)	9
Total	130 (97.01%)	3 (2.24%)	1 (0.75%)	134	17 (89.47%)	2 (10.53%)	0 (0%)	19

Table 6

Descriptive statistics for children's age, degree of hand skill, control variables, and math ability score grouped by risk of MLD and handedness for Study 3

	Not at risk of MLD		At risk of MLD	
	Right- handed	**Left-handed**	**Right- handed**	**Left- handed**
Age in months	65.82	59.33	62.82	69.50
Degree of hand skill	.23	-.14	.27	.07
Visual working memory span	3.33	2.33	1.59	2.50
Cognitive abilities	13.78	12.67	9.71	17.00
Math ability score	85.87	69.67	38.71	54.50

Table 7

Details of studies included in the meta-analyses. MLD = individuals with mathematical learning difficulties, TA = typically achieving individuals

Study	N (total)	N (MLD)	N (TA)	Mean Age MLD (years)	Mean Age TA (years)	Measure of Handedness	Classification of Handedness	Diagnosis of MLD	Handedness MLD Right / Left/Mixed/ Non-right	Handedness TA Right / Left/Mixed/ Non-right	Notes
Study 1 (2019)	134	45	89	9.79	9.75	4-item inventory	Right-handed, Left-handed, Mixed	Mathematical Learning Difficulties (MLD)	37/5/3/8	76/4/9/13	-
Study 2 (2019)	2,109	445	1,664	11.14	11.27	Self-reported writing hand	Right-handed, Left-handed, Inconsistent	Mathematical Learning Difficulties (MLD)	391/45/3/48	1291/157/12/169	-
Study 3 (2019)	153	19	134	5.5	5.27	Observation of writing hand & tapping speed	Right-handed, Left-handed, Inconsistent	Mathematical Learning Difficulties (MLD)	12/2/0/2	130/3/1/4	-
Ashkenazi, & Henik (2010)	24	12	12	24	24.3	-	Right-handed, Left-handed	Developmental	8/4/-/-	8/4/-/-	-

								Dyscalculia -DD			
Bucca (2018)	144	144	-	-	-	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed	Dyscalculia	124/20/-/-	-	There are four other groups different from TA.
Greiffenstein, & Baker (2002)	45	45	-	28.57	-	-	Right-handed, Non-right-handed	Arithmetic Deficiency-AD	27/-/-/18	-	There are two more groups of participants: reading deficiency (RD) and dual deficiency (RAD). All participants were drawn from a sample of 267 adults referred for neuropsychological testing for work-adjustment difficulties.
Jastrzebski, Crewther, & Crewther (2015)	19	5	14	19-33	24	-	-	Mathematically impaired	4/1/-/-	12/2/-/-	All participants are females.

Jovanović, Purić, & Ignjatović-Ristić (2014)	140	83	57	-	-	Observation of 12 tasks of dominant laterality of upper extremities	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	76/7/-/-	53/4/-/-	-
Kovas, Giampietro, Viding, Brammer, Barker, ... & Plomin (2009)	13	13	-	10	-	-	Right-handed, Left-handed	Low mathematical ability	11/2/-/-	-	There is one more group of participants with high mathematical ability
Kucian (unpublished 2018)	52	28	24	12.06	11.19	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	23/3/2/-	19/1/4/-	-
Kucian,Ashkenazi, Hänggi, Rotzer, Jäncke, Martin, & von Aster (2014)	30	15	15 (8 + 7)*	10	10.1	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	12/1/2/-	14/0/1/-	Seven TA children were recruited from two other studies running at the Center for MR Research of the University Children's

											Hospital Zurich.
Kucian, Grond, Rotzer, Henzi, Schönmann, Plangger,. …. & von Aster (2011a)	32	16	16	9.5	9.5	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	14/1/1/-	12/0/4/-	-
Lafay et al. (2017)	61	24	37	9.01	8.94	Not reported	Right-handed, Left-handed	Mathematics Difficulties (MD) Developmental Dyscalculia (DD)	19/5/-/5	31/6/-/6	-
McCaskey 1 (unpublished 2018)	35	22	13	9.67	9.42	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	13/3/6/9	7/1/5/6	Includes all the participants from the longitudinal study McCaskey et al. (2018). Most of those individuals

										also participated in McCaskey et al. (2017).
McCaskey 2 (unpublished 2018)	10	3	7	15.13	13.5	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidextrous	Developmental Dyscalculia -DD	3/-/-/-	6/-/1/1	Includes only participants that were additionally measured for the magnitude study McCaskey et al. (2017).
Price, Holloway, Räsänen, Vesterinen, & Ansari (2007)	16	8	8	-	-	-	-	Developmental Dyscalculia -DD	8/-/-/-	8/-/-/-	-
Rotzer, Loenneker, Kucian, Martin, Klaver, & Von Aster (2009)	21	10	11	10.4	10.2	Edinburgh Handedness Inventory (Oldfield, 1971)	Right-handed, Left-handed, Ambidexter	Developmental Dyscalculia -DD	5/1/4/-	9/0/2/-	-

Rubinsten, & Henik (2006)	34	17	17	23.9	22.1	-	Right-handed, Left-handed	Developmental Dyscalculia -DD	15/2/-/-	14/3/-/-	There is one more group of participants with the diagnosis of dyslexia
Shalev, Manor, Amir, Wertman-Elad, & Gross-Tsur (1995)	12	12	-	11.5	-	-	Right-handed, Left-handed	Developmental Dyscalculia -DD	8/4/-/-		Total number of participants is 25. We include only participants with dyscalculia without ADHD
Skeide et al. (2018)	24	12	12	8.88	8.7	Not reported	Right-handed, Left-handed	Low mathematical ability (LM)	12/0/-/0	12/0/-/0	There are three other groups different from TA.
Spellacy, & Peter (1978)	14	14	-	10.15	-	Lateral dominance examination (Spreen & Gaddes, 1969).	Dextral/D-Non Dextral/ND	Developmental Dyscalculia -DD	6/-/-/8	-	The DD participants are separated in two groups: good reading (G) and pour reading (P) group, which

											were merged for the purposes of the present analysis.
Zergiotis (2004)	25	25	-	8.7	-	Athena Test	Right-handed, Left-handed, Ambidextrous	Mathematical Learning Difficulties -MLD	21/-/4/-	-	There is a TA group of 96 participants, but there is not information about their handedness.
Shalev, Manor, Amir, Wertman-Elad, & Gross-Tsur (1995)	12	12	-	11.5	-	-	Right-handed, Left-handed	Developmental Dyscalculia -DD	8/4/-/-		Total number of participants is 25. We include only participants with dyscalculia without ADHD