Journal of Affective Disorders 294 (2021) 200–209

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Handedness and depression: A meta-analysis across 87 studies

Julian Packheiser[a,*,#], Judith Schmitz[b,*], Clara C. Stein[c], Lena Sophie Pfeifer[d], Gesa Berretz[c], Marietta Papadatou-Pastou[e,f], Jutta Peterburs[g], Sebastian Ocklenburg[c]

[a] Social Brain Lab, Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, the Netherlands
[b] School of Medicine, University of St Andrews, St Andrews, UK
[c] Institute of Cognitive Neuroscience, Biopsychology, Department of Psychology, Ruhr University Bochum, Bochum, Germany
[d] Institute of Cognitive Neuroscience, Cognitive Psychology, Department of Psychology, Ruhr University Bochum, Bochum, Germany
[e] School of Education, Department of Primary Education, National and Kapodistrian University of Athens, Athens, Greece
[f] Biomedical Research Foundation, Academy of Athens, Athens, Greece
[g] Institute for Systems Medicine, Department of Medicine, MSH Medical School Hamburg, Hamburg, Germany

ARTICLE INFO

Keywords:
Mental disorders
Asymmetry
Handedness
Depression
Meta-analysis
Brain development

ABSTRACT

Alterations in functional brain lateralization, often indicated by an increased prevalence of left- and/or mixed-handedness, have been demonstrated in several psychiatric and neurodevelopmental disorders like schizophrenia or autism spectrum disorder. For depression, however, this relationship is largely unclear. While a few studies found evidence that handedness and depression are associated, both the effect size and the direction of this association remain elusive. Here, we collected data from 87 studies totaling 35,501 individuals to provide a precise estimate of differences in left-, mixed- and non-right-handedness between depressed and healthy samples and computed odds ratios (ORs) between these groups. Here, an OR > 1 signifies higher rates of atypical handedness in depressed compared to healthy samples. We found no differences in left- (OR = 1.04, 95% CI = [0.95, 1.15], p = .384), mixed- (OR = 1.64, 95% CI = [0.98, 2.74], p = .060) or non-right-handedness (OR = 1.05, 95% CI = [0.96, 1.15], p = .309) between the two groups. We could thus find no link between handedness and depression on the meta-analytical level.

1. Introduction

Many forms of human behavior are characterized by side biases, for example a preference for using one limb or sensory organ over the other (Pearson and Hodgetts, 2004; Ocklenburg and Güntürkün, 2017). Side biases can be found in several motor actions, such as hand (Papadatou-Pastou et al., 2020), foot (Packheiser et al., 2020), or eye use (Brown and Taylor, 1988), but also many other actions, such as social touch or turning behavior (Mohr et al., 2003; Ocklenburg et al., 2018). Of these, the most researched side bias is handedness (Güntürkün et al., 2020). Approximately 10.6% of the population favor using the left hand and 9.3% favor no hand for everyday tasks indicating a strong right-sided population bias in hand preference (Papadatou-Pastou et al., 2020). Individuals who are either left- or mixed-handed are therefore considered atypical in their hand preference.

Since behavior is generated in the brain, lateral behavioral biases are inevitably linked to functional hemispheric asymmetries. In motor or premotor cortices, movements with the preferred/dominant hand are usually accompanied by strong activations of the contralateral hemisphere whereas movements of the non-dominant hand demonstrate more bilateral activation patterns (Grabowska et al., 2012; Packheiser et al., 2020; Schmitz et al., 2019; van den Berg et al., 2011). Atypical cerebral motor lateralization would therefore be constituted if individuals demonstrate stronger right-hemispheric activation if the left hand is used and a rather bilateral activation pattern if the right hand is used. Apart from motor lateralization, language processing is also strongly lateralized in humans on the population level (Hirnstein et al., 2014). Here, the left hemisphere is dominant in language processing and speech production in the large majority of individuals (Friederici, 2011). Thus, individuals with bilateral or right-hemispheric language lateralization demonstrate atypical language lateralization.

Both atypical handedness and atypical language lateralization have been associated with increased rates of mental and neurodevelopmental disorders (Hugdahl and Davidson, 2004). Patients with schizophrenia

Corresponding author.
E-mail address: j.packheiser@nin.knaw.nl (J. Packheiser).
* equal contribution

https://doi.org/10.1016/j.jad.2021.07.052
Received 4 March 2021; Received in revised form 7 May 2021; Accepted 10 July 2021
Available online 16 July 2021
0165-0327/

for example demonstrate less left-hemispheric language lateralization compared to controls (Bleich-Cohen et al., 2009; Sommer et al., 2001; Weiss et al., 2006). Differences between patients with schizophrenia and healthy controls are not limited to functional hemispheric asymmetries but can also be seen structurally in decreased lateralization of the planum temporale (PT) which plays a major role in language processing (Sommer et al., 2001). Individuals with schizophrenia also display elevated rates of atypical hand preference (Dragovic and Hammond, 2005; Sommer et al., 2001). In individuals with dyslexia, reduced structural PT asymmetries and hypoactivation in the left-hemispheric language network (Altarelli et al., 2014; Norton et al., 2015) as well as increased rates of non-right-handedness have been detected (Eglinton and Annett, 1994). A similar picture also emerges in individuals with autism spectrum disorders (ASD) as they demonstrate an average rightward asymmetry of the PT (Gage et al., 2009), altered white matter asymmetries that are associated with deficits in language processing (Lo et al., 2011), and higher prevalence of atypical handedness (Markou et al., 2017).

Compared to other disorders, less is known about the association of depression with atypical lateralization despite depression being one of the most prevalent mental disorders worldwide with more than 264 million individuals affected (World Health Organization, WHO). Depression is a multifaceted disorder with several different subdiagnoses that differ for example in symptoms, severity or duration (Benazzi, 2006). It has also been described as the leading cause for disability in the world (WHO, 2020). Regarding lateralization, the strongest evidence of changes in patients suffering from depression comes from studies investigating EEG alpha asymmetries (for review, see Bruder et al., 2017). A meta-analysis investigating alpha asymmetries in depression found a moderate effect of frontal alpha power asymmetries between patient and control groups (Thibodeau et al., 2006). Since frontal alpha asymmetries are strongly linked to deficits in emotional regulation (Reznik and Allen, 2018), this finding could indicate a deficiency in emotional regulation in depressed patients. Given these changes in EEG alpha asymmetries, there seems to be some evidence in favor of the hypothesis that depression and atypical lateralization are associated.

Only a few studies have investigated an association with language lateralization, and their results are inconclusive. Wale and Carr (1990), for example, studied language lateralization in individuals suffering from Major Depressive Disorder (MDD) and controls in a dichotic listening task. They found decreased left-hemispheric lateralization in depressed individuals compared to controls indicating more symmetrical language processing in MDD. In contrast, Bruder et al. (1989) and Hugdahl et al. (2003) found that individuals suffering from melancholic depression and MDD, respectively, do not display any difference from healthy controls in dichotic listening tasks.

With regard to handedness, several studies have found a significant association between hand preference and depression. Bruder et al. (1989) found an increased prevalence of left-handedness in 65 individuals with melancholic depression compared to 30 controls. A systematic investigation of left-handedness and attention deficit hyperactivity disorder (ADHD) revealed no direct association in 140 ADHD and 120 control children, but found that non-right-handedness increased the risk for MDD and reduced psychosocial functioning in children with ADHD (Beiderman et al., 1994). In 137 non-diagnosed college students with high scores in the Beck Depression Inventory (BDI), Overby III (1994) found elevated rates of left-handedness compared to a control sample consisting of 963 students with low BDI scores. This increase was, however, only detected in females. Interestingly, Elias et al. (2001) designed a similar study in a total sample of 541 undergraduate students, finding an increased rate of left-handedness specifically in depressed males compared to male controls. In contrast, Moscovitch et al. (1981) found decreased rates of left-handedness in individuals suffering from MDD compared to healthy controls. Most recently, Logue et al. (2015) studied 692 children and found a 53% increased risk of suffering from depression in left-handed children.

Overall, most small to medium scale studies indicate that depression and handedness are associated, with the majority of studies showcasing an increased rate of left-handedness in depressed individuals. To provide more substantial and well-powered insight into this matter, Denny (2009) evaluated a large population survey on the association between depression and atypical handedness in a sample of 27,482 individuals from twelve European countries. He found that in males who experienced depressive symptoms for at least two weeks according to the Euro-D questionnaire (Castro-Costa et al., 2008; Prince et al., 1999), the risk of depression was significantly increased in left-handed (25%) compared to right-handed individuals (19%). For females, a non-significant increase from 33% (left-handers) to 36% (right-handers) was observed.

As evident from the literature, most of the studies that specifically investigated the relation between handedness and depression support the notion that these variables are associated with one another. However, the results are inconclusive as the aforementioned studies strongly differ in their reported effect sizes, their effect direction and possible sex differences. Due to the low power of each study (with the exception of the study by Denny (2009)) and to the heterogeneity of sampling and experimental procedures as well as in the measurements for handedness and depression that were used, individual studies can hardly be representative for the relationship between these variables. Recently, it was argued that the skewedness of individual studies is especially true for laterality research because lateralized phenotypes are heavily skewed in the population (Tran et al., 2014). Therefore, very large sample sizes are required to represent each phenotype sufficiently (Ocklenburg et al., 2020). Importantly, these issues can be resolved via the application of meta-analyses as they are (1) more resistant to sampling errors, (2) allow for the identification of publication/small study biases and (3) enable the investigation of moderating factors that could potentially influence the association between handedness and depression.

The aim of the present study was to conduct a large-scale meta-analysis on the relationship between handedness and depression in order to identify possible differences in atypical handedness between patient and control samples. To this end, we investigated clinical samples and their respective control groups (if available) with regard to their handedness. We included not only studies that specifically investigated handedness in depressed individuals and healthy controls (as they were rather rare), but also studies that merely reported handedness as a demographic variable. Patient-to-control odds ratios (ORs) of atypical handedness were classified using multiple classification schemes from a conservative left-mixed-right-handedness criterion to a more liberal non-right-handedness criterion. Moderator analyses were conducted investigating (1) sex ratio, (2) age, (3) handedness classification, and (4) publication year to assess possible interaction effects with sample type.

2. Materials and methods

For consistency purposes, we will label all groups that were determined as the depression group in the respective study as patient groups, regardless of whether or not a clinical diagnosis was made.

2.1. Study selection

The electronic databases PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (https://www.webofknowledge.com), and Google Scholar (https://scholar.google.de/) were searched for the terms "depression", "major depression", "unipolar depression", "bipolar depression" and "mood disorder" combined with the terms "handedness" or "hand preference". Next, reference lists of eligible studies were inspected for relevant publications. E-mail requests were sent to corresponding authors if the study clearly stated that data on handedness and depression had been collected but did not report them in a way that allowed for data extraction (e.g., data only presented in graphs). Study selection was conducted by CCS and JS and concluded in August 2020. Details about the study selection are shown in Fig. 1. Data extraction was conducted by CCS, LP, and evaluated by JP. Interrater reliability was at 91.8%. Disagreements were resolved by discussion. Study selection was in agreement with the PRISMA guidelines on reporting items for systematic reviews (Moher et al., 2009).

2.2. Inclusion and exclusion criteria

This study used the following criteria to determine in- or exclusion of datasets:

(1) Participants: participants of all ages were included into the meta-analysis. Datasets were classified as child cohorts if the participants' age ranged between 0 and 17 years and classified as adult cohorts if the participants' ages were 18 years or above. If the cohort consisted both of children and adults ($k = 8$ studies), they

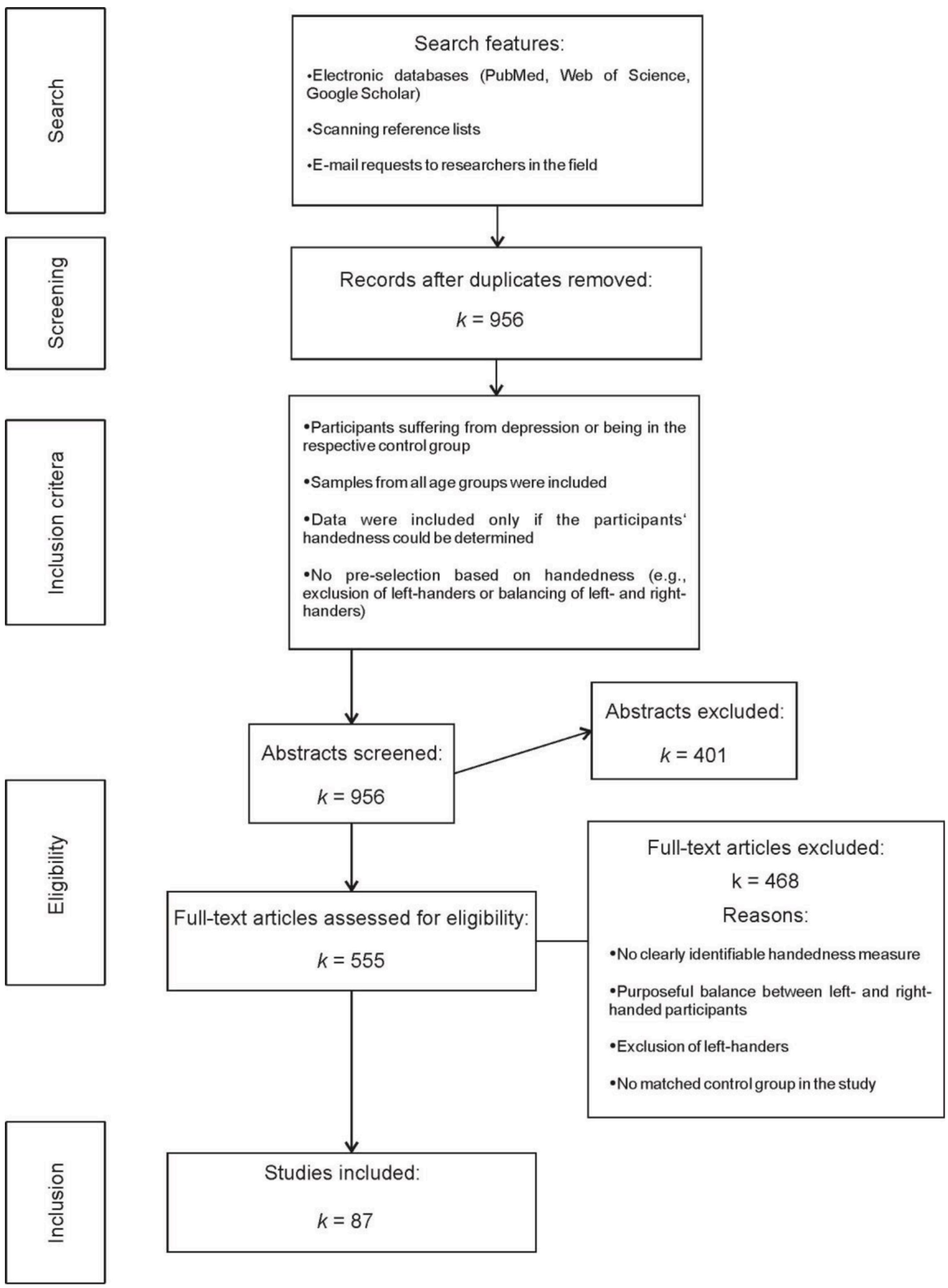

Fig. 1. Flow diagram of the search and inclusion criteria. The procedures were followed in accordance with the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009). A complete list of all included studies and additional study information can be found in Supplementary Table 1.

were excluded from the moderator analysis comparing child and adult cohorts (see below).
(2) Studies had to report at least one patient group and a corresponding control group.
(3) Publication language: articles included in the present meta-analysis had to be written either in English, German, Greek or French (all articles finally included in the study were written in English however).
(4) Handedness report: studies were included if handedness prevalence was clearly stated or could be recovered by contacting the authors. Studies reporting only lateralization quotients or p-values were excluded.
(5) Pre-selection based on handedness: studies were excluded if the sample was pre-selected to solely contain left- or right-handed individuals or if the sample purposefully balanced the number of left- and right-handed participants.

A total of $k = 87$ studies were eligible for statistical analysis after applying the inclusion and exclusion criteria. All included articles could be found on Google Scholar, 17 duplicates were found on PubMed and no included studies were found on Web of Science.

2.3. Statistical analysis

Meta-analysis was performed using the R package metafor (Viechtbauer, 2010). Random effect models were used as they acknowledge differences in research designs and data collection approaches. The following protocol was followed in the analyses:

(1) For each study, we derived patient-to-control odds ratios (ORs) for left-, mixed- and non-right-handedness. ORs indicate whether or not there is a difference between two groups, with a value of 1 representing no difference. In this case, ORs > 1 indicated a higher prevalence of atypical handedness in patient groups compared to controls. Meta-analysis was performed on the ORs using random effect models.
(2) Each grouping (left-, mixed- and non-right-handedness) was tested for homogeneity using the homogeneity statistic Q, and the I2 index reflecting the variance explained by heterogeneity across studies. The I2 index levels can be described as low, moderate, and high, when close to 25%, 50%, and 75%, respectively (Higgins et al., 2003). Additionally, the Tau2 index was computed to specify if there was variance between studies.
(3) The funnel plot (funnel() function) was visually inspected to identify small study bias. Furthermore, we used Egger's regression test (regtest() function) to provide a quantitative estimate of the asymmetry of the funnel plot. Finally, the trim and fill method (trimfill() function) (Duval and Tweedie, 2000) was used to make the funnel plot symmetrical by omitting and/or adding hypothetical data points due to an asymmetrical distribution.
(4) Moderator analyses were conducted for all moderator variables using the Non-Right/Right classification from all included studies. The Non-Right/Right classification was chosen to maximize the sample size as it was the most inclusive classification system.

2.4. Moderator analyses

(1) Sex ratio: Sex effects are well established in handedness research with males showing increased rates of left-handedness compared to females (Papadatou-Pastou et al., 2008). These effects were investigated through the ratio of males to females in the study as a proxy. Almost no study reported handedness broken down by sex precluding a direct comparison of males and females.
(2) Age: We included the moderators "mean age", "age group" (< 18, 18 – 30, 31 – 50, 51 – 70, > 70; based on mean age) and "children vs. adults" (< 18 vs. > 18; based on mean age) since handedness has been associated with age (Papadatou-Pastou et al., 2020).
(3) Handedness classification: We included three classification systems (Left-Mixed-Right (L-M-R), Left-Right (L-R), and Non-Right/Right (NR-R)) to identify the effect of a conservative or liberal classification of handedness.
(4) Year of publication: Higher prevalences of left-handedness have been shown in more recent studies compared to very early studies (Papadatou-Pastou et al., 2020). We therefore included year of publication as a moderator.
(5) Patient studies vs. cohort studies: We additionally tested whether ORs differ between studies conducted in clinically diagnosed patients and cohort studies, performed in student or general population samples (e.g., Denny (2009)).

We did not include known moderators of handedness such as ancestry or cultural background as the large majority of studies were conducted in Western societies with European ancestry. Moreover, we did not include specific diagnoses as moderator, as the majority of studies included patients diagnosed with Major Depression.

2.5. Data availability

All data and analysis codes are made available in the OSF project "Meta-analysis on handedness and depression" under the link: https://osf.io/sx2ew/.

3. Results

We first tested whether there was a difference in left-, mixed-, or non-right-handedness between patient and control samples, i.e., whether ORs were different from 1. The overall sample included $k = 87$ studies totaling $n = 35{,}501$ individuals ($n_{\text{depression}} = 9{,}801$; $n_{\text{control}} = 25{,}700$). Study details are presented in Supplementary Table 1.

Meta-analysis 1: Left-handedness. Among the 87 studies, $k = 59$ reported data on left-handedness, totaling $n = 33{,}092$ individuals ($n_{\text{depression}} = 8{,}814$; $n_{\text{control}} = 24{,}278$). The left-handedness OR was estimated to be 1.04 (95% CI = [0.95, 1.15], $z = 0.87$, $p = .383$, Figure S1). There was no evidence for heterogeneity among the studies ($Q(58) = 35.85$, $p = .990$, $I^2 = 0.00\%$, Tau$^2 = 0.00$). Neither Egger's regression test for funnel plot asymmetry ($z = -1.30$, $p = .195$) nor visual inspection of the funnel plot (Fig. 2A) revealed any evidence for small study bias. However, according to the trim and fill test, eight studies (SE = 5.02) would need to be imputed to the right of the mean for the funnel plot to be symmetrical. The resulting adjusted OR was 1.06 (95% CI = [0.96, 1.17], $z = 1.22$, $p = .221$), also suggesting absence of small study bias.

Meta-analysis 2: Mixed-handedness. Only $k = 12$ studies reported data on mixed-handedness, totaling $n = 1{,}838$ individuals ($n_{\text{depression}} = 428$; $n_{\text{control}} = 1{,}410$). The mixed-handedness OR was estimated to be 1.64 (95% CI = [0.98, 2.74], $z = 1.88$, $p = .060$, Figure S2). There was no evidence for heterogeneity among the studies ($Q(11) = 6.71$, $p = .822$, $I^2 = 0.00\%$, Tau$^2 = 0.00$). Neither Egger's regression test for funnel plot asymmetry ($z = -0.93$, $p = .350$) nor visual inspection of the funnel plot (Fig. 2B) revealed any evidence for small study bias. However, according to the trim and fill test, three studies (SE = 2.36) would need to be imputed to the right of the mean for the funnel plot to be symmetrical. The resulting adjusted OR was 1.90 (95% CI = [1.16, 3.12], $z = 2.54$, $p = .011$).

Meta-analysis 3: Non-right-handedness. In total, $k = 82$ studies reported data on non-right-handedness, totaling $n = 35{,}095$ individuals ($n_{\text{depression}} = 9{,}581$; $n_{\text{control}} = 25{,}514$). The non-right-handedness OR was estimated to be 1.05 (95% CI = [0.96, 1.15], $z = 1.02$, $p = .309$, Figure S3). There was no evidence for heterogeneity among the studies ($Q(81) = 54.12$, $p = .991$, $I^2 = 0.00\%$, Tau$^2 = 0.00$). Neither Egger's regression test for funnel plot asymmetry ($z = -1.43$, $p = .152$) nor visual inspection of the funnel plot (Fig. 2C) revealed any evidence for small

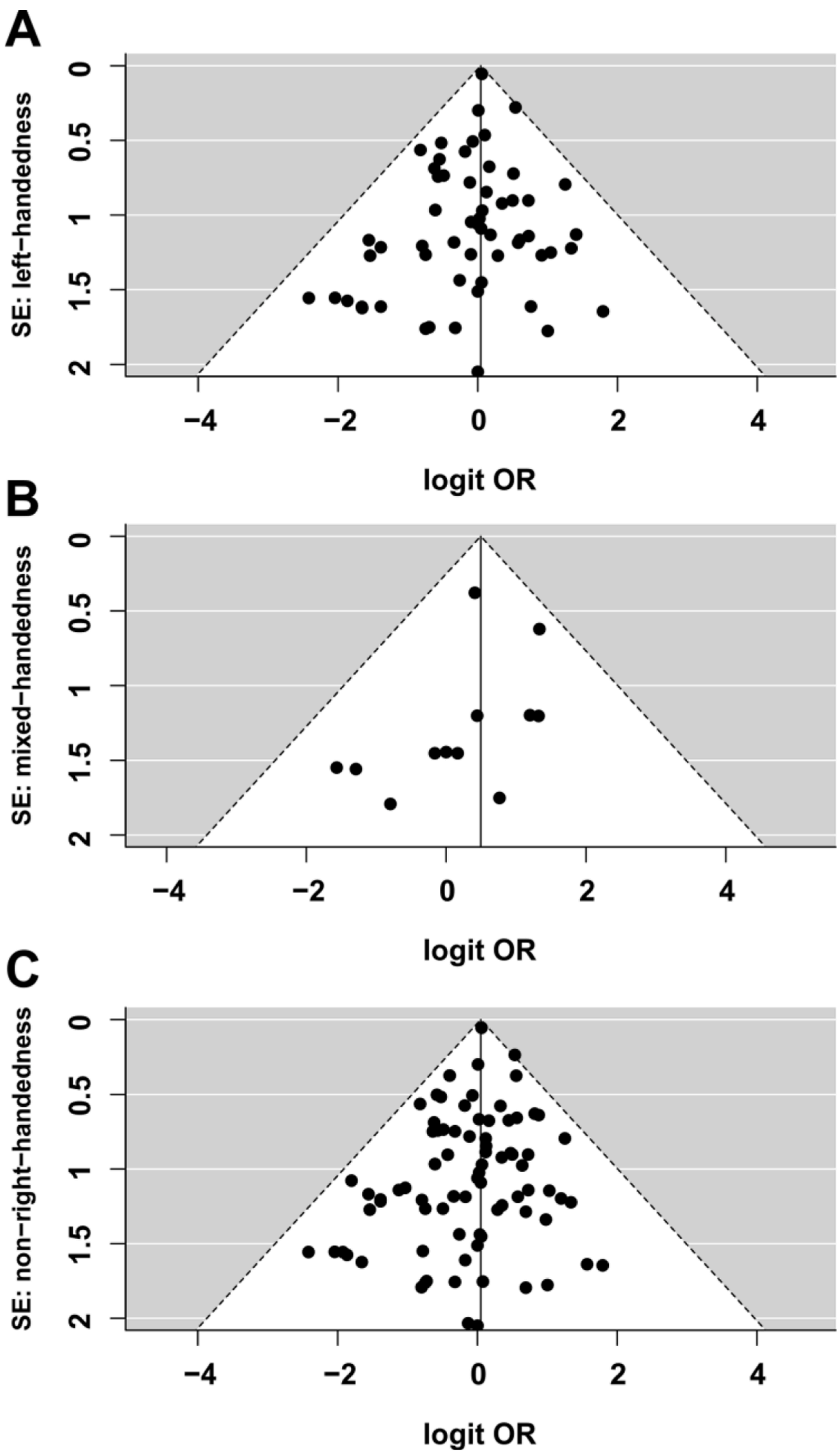

Fig. 2. Funnel plots of standard errors on logit OR. No asymmetries in the funnel plots could be detected for (A) left-handedness, (B) mixed-handedness and (C) non-right-handedness, indicating that there was no small study bias.

study bias. However, according to the trim and fill test, 11 studies (SE = 5.90) would need to be imputed to the right of the mean for the funnel plot to be symmetrical. The resulting adjusted OR was 1.07 (95% CI = [0.98, 1.17], $z = 1.53$, $p = .125$), again suggesting absence of small study bias.

With an overall sample size of n = 27,482 participants ($n_{\text{depressed}}$ = 6,549, n_{control} = 20,933), the study by Denny (2009) contributed the most participants to the overall sample. In accordance with Richards et al. (2021), we reran meta-analyses 1 and 3 (as Denny (2009) did not provide data on mixed-handedness) excluding this study. The left-handedness OR was estimated to be 0.98 (95% CI = [0.79, 1.21], z = -0.18, $p = .857$) and the non-right-handedness OR was estimated to be

1.05 (95% CI = [0.96, 1.15], $z = 1.02$, $p = .991$), suggesting that the study results obtained by Denny (2009) did not substantially affect the overall result pattern.

3.1. Moderator variable analysis

We performed moderator analyses in the Non-Right/Right classification as this was the most inclusive ($k = 82$ studies overall).

3.2. Sex ratio

Sex ratio was extracted from $k = 81$ studies. There was no evidence for a moderating effect of sex ratio on non-right-handedness OR ($Q(1) = 0.92$, $p = .337$).

3.3. Mean age

Mean age was extracted from $k = 66$ studies. There was no evidence for a moderating effect of mean age on non-right-handedness OR ($Q(1) = 0.002$, $p = .964$).

3.4. Age group

Age group was extracted from $k = 77$ studies (< 18: 7 studies, 18 – 30: 10 studies, 31 – 50: 45 studies, 51 – 70: 11 studies, > 70: 4 studies). There was no evidence for a moderating effect of age group on non-right-handedness OR ($Q(4) = 3.82$, $p = .431$).

3.5. Children vs. adults

Children vs. adults was extracted from $k = 79$ studies (children: 7 studies, adults: 72 studies). There was no evidence for a moderating effect on non-right-handedness OR ($Q(1) = 0.92$, $p = .339$).

3.6. Handedness classification

Handedness classification was extracted from $k = 78$ studies (L-M-R: 10 studies, L-R: 42 studies, R-NR: 26 studies). There was a trend towards a moderating effect on non-right-handedness OR ($Q(2) = 5.07$, $p = .079$). Compared to the L-M-R classification (OR = 1.51, 95% CI = [1.08, 2.12], $z = 2.39$, $p < .05$), the non-right-handedness OR was reduced in the L-R classification (OR = 1.02, 95% CI = [0.92, 1.13], $z_{diff} = -2.18$, $p_{diff} < .05$). In the R-NR classification, the OR did not significantly differ from the L-M-R classification (OR = 0.96, 95% CI = [0.69, 1.31], $z_{diff} = -1.93$, $p_{diff} = .053$).

3.7. Year of publication

Year of publication was extracted from $k = 82$ studies. There was no evidence for a moderating effect of publication year on non-right-handedness OR ($Q(1) = 2.53$, $p = .112$).

3.8. Patient studies vs. cohort studies

This moderator was extracted from $k = 74$ studies ($k = 6$ cohort studies and $k = 68$ patient studies). There was no evidence for a moderating effect of patient studies vs cohort studies on non-right-handedness OR ($Q(1) = 1.60$, $p = .206$).

4. Discussion

In the present study, we investigated the relationship between depression and handedness on a meta-analytical level as these variables have been associated in previous research, but only within the scope of individual studies. To assess possible differences in the prevalence of atypical handedness between depression and healthy samples, we determined ORs between groups diagnosed with depression and their respective control groups. We found no evidence of increased left-, mixed-, or non-right-handedness in individuals with depression compared to healthy controls. Furthermore, there was no evidence for a moderating effect of any variable on patient-to-control ORs.

In contrast to previous studies on the association between depression and handedness (e.g., Elias et al., 2001; Overby III, 1994), we did not find increased rates of left- or mixed-handedness in depressed compared to control samples. This finding is especially striking given its contrast to the study conducted by Denny (2009) who investigated a large sample of 27,482 individuals and found a small effect of increased risk for depression in left-handed individuals. The discrepancy in the results highlights the importance of conducting meta-analyses in addition to large-scale data collections. A potential reason explaining the difference between our and Denny's findings could relate to sampling biases. Denny (2009) solely studied non-clinically diagnosed individuals, similar to most other studies reporting effects on the distribution of altered handedness in depression (Elias et al., 2001; Overby III, 1994). In these studies, questionnaires were used to determine whether an individual was classified as depressed or non-depressed, but no proper clinical assessment was conducted. Since other individual studies found decreased rates of left-handedness in patients compared to controls (Moscovitch et al., 1981), the heterogeneity of results in the literature can be potentially explained by underpowered studies and/or sampling errors. We should note that there was a trend in the mixed-handedness analysis that even reached significance when hypothetical studies were imputed. This result could indicate that future research might discover a significant link between increased rates of mixed-handedness and depression. However, even if this association becomes robust in future research, it is likely of a very small effect size.

Our null finding about the association between handedness and depression fits well into recent large-scale investigations on the link between functional and structural brain asymmetries and depression. A meta-analysis in 1883 patients and 2161 controls investigated frontal alpha power asymmetries as a diagnostic marker and found that this functional asymmetry was of no diagnostic value (van der Vinne et al., 2017). For structural asymmetries, de Kovel et al. (2019) investigated both subcortical volume and cortical thickness as well as surface area in a sample of 2540 individuals with MDD and 4230 healthy controls. Not a single effect for any evaluated parameter exceeded a threshold of Cohen's d > 0.1 which would be equal to at least a small effect (Cohen, 2013). Thus, any possible association of depression with brain asymmetries seems to be exceedingly small, if existent at all.

Since we could not demonstrate a relationship between depression and atypical handedness, the question remains why there is evidence that other disorders such as dyslexia (Vlachos et al., 2013), autism spectrum disorders (Markou et al., 2017) and schizophrenia (Sommer et al., 2001) show altered levels of left- and/or mixed-handedness. While most findings on depression point towards no association with language lateralization (Bruder et al., 1989; Hugdahl et al., 2003), changes in language lateralization seem to be present in all of these disorders (Heim et al., 2004; Ocklenburg et al., 2013; Pearson and Hodgetts, 2004) even though the literature has also pointed otherwise in the case of schizophrenia (Sommer et al., 2001). Interestingly, Papadatou-Pastou and Sáfár (2016) found that increased rates of atypical handedness in deaf individuals were present when handedness was measured using manipulative actions but not when it was measured using sign actions. Moreover, the authors suggested that deaf individuals who acquired language (either sign or spoken) at a later age are those who present with increased rates of atypical handedness. A possible reason could be that increased rates of left- and/or mixed-handedness seem to be specifically associated with conditions related to impaired language-related abilities (Papadatou-Pastou et al., 2019). This is in line with the finding that higher genetic risk for ADHD and genetic liability towards lower intelligence and educational years have been associated with reduced language-related skills (Verhoef et al., 2019) and left-handedness, while there is no association between handedness and genetic factors involved in bipolar disorder (Schmitz et al., 2021). The null result in depression disorders for altered distributions of atypical handedness could thus be related to depression not affecting language acquisition and/or language lateralization. It should be noted however that handedness and language lateralization have recently been demonstrated to be less associated than previously thought (Packheiser et al., 2020) calling into question whether there is a strong association between language lateralization and handedness.

The present study is subject to limitations that should be addressed. First, our study specifically measured only hand preference and not hand skill because hand preference was the only reported variable in almost all studies. These two concepts have however been suggested to be lateralized independently (Triggs et al., 2000) despite them being moderately to strongly correlated (Todor and Doane, 1977). Future studies will need to investigate differences in lateralization of hand skill in patients compared to healthy controls. Second, a major factor that is indicated in the literature is the role of sex in handedness (Papadatou-Pastou et al., 2008). In this study, we used sex ratios as moderators as almost no study broke down handedness in depressed and healthy individuals by sex. Thus, a direct comparison between males and females could only be approximated. We urge researchers for that reason to upload raw data sets in Open Science formats to allow for a more fine-grained evaluation of their data. Finally, the large majority of our studies comprised patients diagnosed with Major Depression with only a small subset of patients suffering from for example bipolar disorders preventing a meaningful analysis of diagnosis as moderator. The possibility therefore remains that our null findings are specific for Major Depression. Similarly, while we recorded comorbidities, they were too diverse for meaningful moderator analysis. Since many psychiatric and neurodevelopmental disorders are associated with atypical brain asymmetries, it cannot be excluded that some of these comorbidities slightly influenced the results.

In conclusion, we found no effect that atypical handedness is increased in individuals who suffer from depression compared to healthy controls. Considering that large-scale meta-analyses found no structural and functional alterations in hemispheric asymmetries in depressed individuals, this result is well in line with recent discoveries about the impact of depression on brain lateralization or vice versa. In the future, it would be interesting to specifically investigate the association between language lateralization and depression in larger samples to further determine if there is no link between depression and atypical lateralization patterns.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

The authors want to express their gratitude to Kevin Denny, Lauren J. Harris, Jason Almerigi, Peter Gallagher and Bethany Little for their positive responses to data requests.

Funding

JP is funded by the Deutsche Forschungsgemeinschaft (DFG) Research Training Group “Situated Cognition” (GRK 2185/1). JS is funded by the DFG (Grant number 418445085). GB is funded by the DFG (OC 127/9-1).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.07.052.

References

Altarelli, I., Leroy, F., Monzalvo, K., Fluss, J., Billard, C., Dehaene-Lambertz, G., Ramus, F., 2014. Planum temporale asymmetry in developmental dyslexia: Revisiting an old question. Hum. Brain Mapp. 35 (12), 5717–5735.
Beiderman, J., Lapey, K.A., Milberger, S., Faraone, S.V., Reed, E.D., Seidman, L.J., 1994. Motor preference, major depression and psychosocial dysfunction among children with attention deficit hyperactivity disorder. J. Psychiatr. Res. 28 (2), 171–184.
Benazzi, F., 2006. Various forms of depression. Dialog. Clin. Neurosci. 8 (2), 151.
Bleich-Cohen, M., Hendler, T., Kotler, M., Strous, R.D., 2009. Reduced language lateralization in first-episode schizophrenia: an fMRI index of functional asymmetry. Psychiatry Res. 171 (2), 82–93.
Brown, E.R., Taylor, P., 1988. Handedness, footedness, and eyedness. Percept. Mot. Skills 66 (1), 183–186.
Bruder, G.E., Quitkin, F.M., Stewart, J.W., Martin, C., Voglmaier, M.M., Harrison, W.M., 1989. Cerebral laterality and depression: differences in perceptual asymmetry among diagnostic subtypes. J. Abnorm. Psychol. 98 (2), 177.
Bruder, G.E., Stewart, J.W., McGrath, P.J., 2017. Right brain, left brain in depressive disorders: Clinical and theoretical implications of behavioral, electrophysiological and neuroimaging findings. Neurosci. Biobehav. Rev. 78, 178–191. https://doi.org/10.1016/j.neubiorev.2017.04.021.
Castro-Costa, E., Dewey, M., Stewart, R., Banerjee, S., Huppert, F., Mendonca-Lima, C., Ritchie, K., 2008. Ascertaining late-life depressive symptoms in Europe: An evaluation of the survey version of the EURO-D scale in 10 nations. The SHARE project. Int. J. Methods Psychiatr. Res. 17 (1), 12–29.
Cohen, J., 2013. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hoboken: Taylor and Francis. Retrieved from. http://gbv.eblib.com/patron/FullRecord.aspx?p=1192162.
Denny, K., 2009. Handedness and depression: evidence from a large population survey. Laterality 14 (3), 246–255.
Dragovic, M., Hammond, G., 2005. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatr. Scand. 111 (6), 410–419.
Duval, S., Tweedie, R., 2000. Trim and fill: a simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56 (2), 455–463.
Eglinton, E., Annett, M., 1994. Handedness and dyslexia: a meta-analysis. Percept. Mot. Skills 79 (3_suppl), 1611–1616.
Elias, L.J., Saucier, D.M., Guylee, M.J., 2001. Handedness and depression in university students: a sex by handedness interaction. Brain Cogn. 46 (1-2), 125–129.
Friederici, A.D., 2011. The brain basis of language processing: from structure to function. Physiol. Rev. 91 (4), 1357–1392.
Gage, N.M., Juranek, J., Filipek, P.A., Osann, K., Flodman, P., Isenberg, A.L., Spence, M. A., 2009. Rightward hemispheric asymmetries in auditory language cortex in children with autistic disorder: an MRI investigation. J. Neurodev. Disord. 1 (3), 205–214.
Grabowska, A., Gut, M., Binder, M., Forsberg, L., Rymarczyk, K., Urbanik, A., 2012. Switching handedness: fMRI study of hand motor control in right-handers, left-handers and converted left-handers. Acta Neurobiol. Exp. 72 (4), 439–451.
Güntürkün, O., Ströckens, F., Ocklenburg, S., 2020. Brain lateralization: a comparative perspective. Physiol. Rev. 100 (3), 1019–1063.
Heim, S., Kissler, J., Elbert, T., Rockstroh, B., 2004. Cerebral lateralization in schizophrenia and dyslexia: Neuromagnetic responses to auditory stimuli. Neuropsychologia 42 (5), 692–697. https://doi.org/10.1016/j.neuropsychologia.2003.09.007.
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327 (7414), 557–560.
Hirnstein, M., Hugdahl, K., Hausmann, M., 2014. How brain asymmetry relates to performance–a large-scale dichotic listening study. Front. Psychol. 4, 997.
Hugdahl, K., Davidson, R.J., 2004. The Asymmetrical Brain. MIT press.
Hugdahl, K., Lund, A., Asbjørnsen, A., Egeland, J., Landrø, N.I., Roness, A., Sundet, K., 2003. Attentional and executive dysfunctions in schizophrenia and depression: evidence from dichotic listening performance. Biol. Psychiatry 53 (7), 609–616.
de Kovel, C.G.F., Aftanas, L., Aleman, A., Alexander-Bloch, A.F., Baune, B.T., Brack, I., Francks, C., 2019. No alterations of brain structural asymmetry in major depressive disorder: an ENIGMA consortium analysis. Am. J. Psychiatry 176 (12), 1039–1049. https://doi.org/10.1176/appi.ajp.2019.18101144.
. . . Lo, Y.-C., Soong, W.-T., Gau, S.S.-F., Wu, Y.-Y., Lai, M.-C., Yeh, F.-C., Tseng, W.-Y.I., 2011. The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion spectrum imaging tractography Psychiatry Res. 192 (1), 60–66.
Logue, D.D., Logue, R.T., Kaufmann, W.E., Belcher, H.M.E., 2015. Psychiatric disorders and left-handedness in children living in an urban environment. Laterality 20 (2), 249–256.
Markou, P., Ahtam, B., Papadatou-Pastou, M., 2017. Elevated levels of atypical handedness in autism: meta-analyses. Neuropsychol. Rev. 27 (3), 258–283.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097.
Mohr, C., Landis, T., Bracha, H.S., Brugger, P., 2003. Opposite turning behavior in right-handers and non-right-handers suggests a link between handedness and cerebral dopamine asymmetries. Behav. Neurosci. 117 (6), 1448.
Moscovitch, M., Strauss, E., Olds, J., 1981. Handedness and dichotic listening performance in patients with unipolar endogenous depression who received ECT. Am. J. Psychiatry 138 (7), 988–990. https://doi.org/10.1176/ajp.138.7.988.
Norton, E.S., Beach, S.D., Gabrieli, J.D.E., 2015. Neurobiology of dyslexia. Curr. Opin. Neurobiol. 30, 73–78.

Ocklenburg, S., Berretz, G., Packheiser, J., Friedrich, P., 2020. Laterality 2020: entering the next decade. Laterality 1–33.
Ocklenburg, S., Güntürkün, O., 2017. The Lateralized Brain: the Neuroscience and Evolution of Hemispheric Asymmetries. Academic Press.
Ocklenburg, S., Packheiser, J., Schmitz, J., Rook, N., Güntürkün, O., Peterburs, J., Grimshaw, G.M., 2018. Hugs and kisses–The role of motor preferences and emotional lateralization for hemispheric asymmetries in human social touch. Neurosci. Biobehav. Rev. 95, 353–360.
Ocklenburg, S., Westerhausen, R., Hirnstein, M., Hugdahl, K., 2013. Auditory hallucinations and reduced language lateralization in schizophrenia: a meta-analysis of dichotic listening studies. J. Int. Neuropsychol. Soc. 19 (4), 410–418. https://doi.org/10.1017/s1355617712001476.
Overby III, L.A, 1994. The relationship of handedness to depression in male and female college students. Person. Individ. Differ. 16 (4), 537–541.
Packheiser, J., Schmitz, S., Arning, L., Beste, C., Güntürkün, O., Ocklenburg, S., 2020. A large-scale estimate on the relationship between language and motor lateralization. Sci. Rep. 10 (1), 1–10. https://doi.org/10.1038/s41598-020-70057-3.
Packheiser, J., Schmitz, J., Berretz, G., Carey, D.P., Paracchini, S., Papadatou-Pastou, M., Ocklenburg, S., 2020. Four meta-analyses across 164 studies on atypical footedness prevalence and its relation to handedness. Sci. Rep. 10 (1), 14501. https://doi.org/10.1038/s41598-020-71478-w.
Packheiser, J., Schmitz, J., Pan, Y., El Basbasse, Y., Friedrich, P., Güntürkün, O., Ocklenburg, S., 2020. Using mobile EEG to investigate alpha and beta asymmetries during hand and foot use. Front. Neurosci. 14, 109. https://doi.org/10.3389/fnins.2020.00109.
Papadatou-Pastou, M., Martin, M., Munafò, M.R., Jones, G.V., 2008. Sex differences in left-handedness: a meta-analysis of 144 studies. Psychol. Bull. 134 (5), 677–699. https://doi.org/10.1037/a0012814.
Papadatou-Pastou, M., Ntolka, E., Schmitz, J., Martin, M., Munafò, M.R., Ocklenburg, S., Paracchini, S., 2020. Human handedness: a meta-analysis. Psychol. Bull.
Papadatou-Pastou, M., Panagiotidou, D. A., Abbondanza, F., Fischer, U., Paracchini, S., & Karagiannakis, G. (2019). *Hand Preference and Mathematical Learning Difficulties: New Data from Greece, the United Kingdom, and Germany and Two Meta-Analyses of the Literature.* 10.31234/osf.io/pc6zh.
Papadatou-Pastou, M., Sáfár, A., 2016. Handedness prevalence in the deaf: meta-analyses. Neurosci. Biobehav. Rev. 60, 98–114. https://doi.org/10.1016/j.neubiorev.2015.11.013.
Pearson, A., Hodgetts, S., 2004. Cerebral lateralization in schizophrenia and dyslexia: neuromagnetic responses to auditory stimuli. Neuropsychologia 42 (5), 692–697. https://doi.org/10.1016/j.neuropsychologia.2003.09.007.
Prince, M.J., Beekman, A.T.F., Deeg, D.J.H., Fuhrer, R., Kivela, S.-L., Lawlor, B.A., van Oyen, H., 1999. Depression symptoms in late life assessed using the EURO–D scale. Br. J. Psychiatry 174 (4), 339–345.
Reznik, S.J., Allen, J.J.B., 2018. Frontal asymmetry as a mediator and moderator of emotion: an updated review. Psychophysiology 55 (1), e12965.
Richards, G., Medland, S.E., Beaton, A.A., 2021. Digit ratio (2D: 4D) and handedness: a meta-analysis of the available literature. Laterality 1–64.
Schmitz, J., Packheiser, J., Birnkraut, T., Hinz, N.-A., Friedrich, P., Güntürkün, O., Ocklenburg, S., 2019. The neurophysiological correlates of handedness: insights from the lateralized readiness potential. Behav. Brain Res. 364, 114–122.
Schmitz, J., Zheng, M., Lui, K.F.H., McBride, C., Ho, C.S.H., Paracchini, S., 2021. Quantitative Multidimensional Phenotypes Improve Genetic Analysis Of Laterality Traits. bioRxiv.
Sommer, I., Ramsey, N., Kahn, R., Aleman, A., Bouma, A., 2001. Handedness, language lateralisation and anatomical asymmetry in schizophrenia: meta-analysis. Br. J. Psychiatry 178, 344–351. https://doi.org/10.1192/bjp.178.4.344.
Sommer, I.E.C., Ramsey, N.F., Kahn, R.S., 2001. Language lateralization in schizophrenia, an fMRI study. Schizophr. Res. 52 (1-2), 57–67.
Thibodeau, R., Jorgensen, R.S., Kim, S., 2006. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. J. Abnorm. Psychol. 115 (4), 715.
Todor, J.I., Doane, T., 1977. Handedness classification: preference versus proficiency. Percept. Mot. Skills 45 (3), 1041–1042. https://doi.org/10.2466/pms.1977.45.3f.1041. Pt 2.
Triggs, W.J., Calvanio, R., Levine, M., Heaton, R.K., Heilman, K.M., 2000. Predicting hand preference with performance on motor tasks. Cortex 36 (5), 679–689. https://doi.org/10.1016/S0010-9452(08)70545-8.
Van den Berg, Femke E, Swinnen, S.P., Wenderoth, N., 2011. Involvement of the primary motor cortex in controlling movements executed with the ipsilateral hand differs between left-and right-handers. J. Cogn. Neurosci. 23 (11), 3456–3469.
Van der Vinne, N., Vollebregt, M.A., van Putten, M.J.A.M., Arns, M., 2017. Frontal alpha asymmetry as a diagnostic marker in depression: fact or fiction? A meta-analysis. NeuroImage. Clin. 16, 79–87. https://doi.org/10.1016/j.nicl.2017.07.006.
... Verhoef, E., Demontis, D., Burgess, S., Shapland, C.Y., Dale, P.S., Okbay, A., St Pourcain, B., 2019. Disentangling polygenic associations between attention-deficit/hyperactivity disorder, educational attainment, literacy and language Transl. Psychiatry 9 (1), 1–12.
Viechtbauer, W., 2010. Conducting meta-analyses in R with the metafor Package. J. Statist. Softw. 36 (3) https://doi.org/10.18637/jss.v036.i03.
Vlachos, F., Andreou, E., Delliou, A., Agapitou, P., 2013. Dyslexia and hand preference in secondary school students. Psychol. Neurosci. 6 (1), 67–72. https://doi.org/10.3922/j.psns.2013.1.10.
Wale, J., Carr, V., 1990. Differences in dichotic listening asymmetries in depression according to symptomatology. J. Affect. Disord. 18 (1), 1–9.
Weiss, E.M., Hofer, A., Golaszewski, S., Siedentopf, C., Felber, S., Fleischhacker, W.W., 2006. Language lateralization in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. Psychiatry Res. 146 (2), 185–190.

Further reading

Bench, C.J., Friston, K.J., Brown, R.G., Frackowiak, R.S., Dolan, R.J., 1993. Regional cerebral blood flow in depression measured by positron emission tomography: the relationship with clinical dimensions. Psychol. Med. 23 (3), 579–590. https://doi.org/10.1017/S0033291700025368.
Paradiso, S., Hermann, B.P., Blumer, D., Davies, K., Robinson, R.G., 2001. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J. Neurol. Neurosurg. Psychiatry 70 (2), 180–185. https://doi.org/10.1136/jnnp.70.2.180.
Peluso, É.D.T.P., Blay, S.L., 2009. Public stigma in relation to individuals with depression. J. Affect. Disord. 115 (1-2), 201–206. https://doi.org/10.1016/j.jad.2008.08.013.
Pillay, S.S., Renshawa, P.F., Bonelloa, C.M., Lafer, B., Fava, M., Yurgelun-Todd, D., 1998. A quantitative magnetic resonance imaging study of caudate and lenticular nucleus gray matter volume in primary unipolar major depression: relationship to treatment response and clinical severity. Psychiatry Res. 84 (2-3), 61–74.
Pine, D.S., Kentgen, L.M., Bruder, G.E., Leite, P., Bearman, K., Ma, Y., Klein, R.G., 2000. Cerebral laterality in adolescent major depression. Psychiatry Res. 93 (2), 135–144.
Postolache, T.T., Doty, R.L., Wehr, T.A., Jimma, L.A., Han, L., Turner, E.H., Matthews, J. R., Neumeister, A., No, C., Kroger, H., Bruder, G.E., Rosenthal, N.E, 1999. Monorhinal odor identification and depression scores in patients with seasonal affective disorder. J. Affect. Disord. 56 (1), 27–35. https://doi.org/10.1016/S0165-0327(99)00027-0.
Riordan, H.J., Flashman, L.A., Saykin, A.J., Frutiger, S.A., Carroll, K.E., Huey, L., 1999. Neuropsychological correlates of methylphenidate treatment in adult ADHD with and without depression. Arch. Clin. Neuropsychol. 14 (2), 217–233. https://doi.org/10.1016/S0887-6177(98)00015-8.
Bernier, D., Bartha, R., Devarajan, S., MacMaster, F.P., Schmidt, M.H., Rusak, B., 2009. Effects of overnight sleep restriction on brain chemistry and mood in women with unipolar depression and healthy controls. J. Psychiatry Neurosci. 34 (5), 352–360.
Ruchsow, M., Groen, G., Kiefer, M., Beschoner, P., Hermle, L., Ebert, D., Falkenstein, M., 2008. Electrophysiological evidence for reduced inhibitory control in depressed patients in partial remission: a Go/Nogo study. Int. J. Psychophysiol. 68 (3), 209–218. https://doi.org/10.1016/j.ijpsycho.2008.01.010.
Schecklmann, M., Dresler, T., Beck, S., Jay, J.T., Febres, R., Haeusler, J., Fallgatter, A.J., 2011. Reduced prefrontal oxygenation during object and spatial visual working memory in unpolar and bipolar depression. Psychiatry Res. 194 (3), 378–384. https://doi.org/10.1016/j.pscychresns.2011.01.016.
Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Dudas, R.B., Murray, G.K., 2016. Abnormal frontostriatal activity during unexpected reward receipt in depression and schizophrenia: relationship to anhedonia. Neuropsychopharmacology 41 (8), 2001–2010. https://doi.org/10.1038/npp.2015.370.
Starkstein, S.E., Mayberg, H.S., Leiguarda, R., Preziosi, T.J., Robinson, R.G., 1992. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 55 (5), 377–382. https://doi.org/10.1136/jnnp.55.5.377.
Suzuki, H., Botteron, K.N., Luby, J.L., Belden, A.C., Gaffrey, M.S., Babb, C.M., Barch, D. M., 2013. Structural-functional correlations between hippocampal volume and cortico-limbic emotional responses in depressed children. Cogn. Affect. Behav. Neurosci. 13 (1), 135–151. https://doi.org/10.3758/s13415-012-0121-y.
Trichard, C., Martinot, J.L., Alagille, M., Masure, M.C., Hardy, P., Ginestet, D., Féline, A., 1995. Time course of prefrontal lobe dysfunction in severely depressed in-patients: a longitudinal neuropsychological study. Psychol. Med. 25 (1), 79–85. https://doi.org/10.1017/s0033291700028105.
. . . Van Eijndhoven, P., van Wingen, G., van Oijen, K., Rijpkema, M., Goraj, B., Jan Verkes, R., Tendolkar, I, 2009. Amygdala volume marks the acute state in the early course of depression Biol. Psychiatry 65 (9), 812–818. https://doi.org/10.1016/j.biopsych.2008.10.027.
Van Wingen, G.A., van Eijndhoven, P., Cremers, H.R., Tendolkar, I., Verkes, R.J., Buitelaar, J.K., Fernández, G., 2010. Neural state and trait bases of mood-incongruent memory formation and retrieval in first-episode major depression. J. Psychiatr. Res. 44 (8), 527–534. https://doi.org/10.1016/j.jpsychires.2009.11.009.
Vasavada, M.M., Leaver, A.M., Njau, S., Joshi, S.H., Ercoli, L., Hellemann, G., Espinoza, R., 2017. Short- and long-term cognitive outcomes in patients with major depression treated with electroconvulsive therapy. J. ECT 33 (4), 278–285. https://doi.org/10.1097/YCT.0000000000000426.
Videbech, P., Ravnkilde, B., Gammelgaard, L., Egander, A., Clemmensen, K., Rasmussen, N.A., Rosenberg, R., 2004. The Danish PET/depression project: performance on Stroop's test linked to white matter lesions in the brain. Psychiatry Res. 130 (2), 117–130. https://doi.org/10.1016/j.pscychresns.2003.10.002.
Vuga, M., Fox, N.A., Cohn, J.F., George, C.J., Levenstein, R.M., Kovacs, M., 2006. Long-term stability of frontal electroencephalographic asymmetry in adults with a history of depression and controls. Int. J. Psychophysiol. 59 (2), 107–115. https://doi.org/10.1016/j.ijpsycho.2005.02.008.
. . . Vythilingam, M., Heim, C., Newport, J., Miller, A.H., Anderson, E., Bronen, R., Bremner, J.D., 2002. Childhood trauma associated with smaller hippocampal volume in women with major depression Am. J. Psychiatry 159 (12), 2072–2080. https://doi.org/10.1176/appi.ajp.159.12.2072.
. . . Whalley, H.C., Sussmann, J.E., Romaniuk, L., Stewart, T., Kielty, S., Lawrie, S.M., McIntosh, A.M., 2015. Dysfunction of emotional brain systems in individuals at high risk of mood disorder with depression and predictive features prior to illness Psychol. Med. 45 (6), 1207–1218. https://doi.org/10.1017/S0033291714002256.
Whalley, H.C., Sussmann, J.E., Romaniuk, L., Stewart, T., Papmeyer, M., Sprooten, E., McIntosh, A.M., 2013. Prediction of depression in individuals at high familial risk of

mood disorders using functional magnetic resonance imaging. PLoS One 8 (3), e57357. https://doi.org/10.1371/journal.pone.0057357.

Wu, M., Andreescu, C., Butters, M.A., Tamburo, R., Reynolds, C.F., Aizenstein, H., 2011. Default-mode network connectivity and white matter burden in late-life depression. Psychiatry Res. 194 (1), 39–46. https://doi.org/10.1016/j.pscychresns.2011.04.003.

Bruder, Gerard E., Fong, Regan, Tenke, Craig E., Leite, Paul, Towey, James P., Stewart, Jonathan E., McGrath, Patrick J., Quitkin, F.M, 1997. Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. Biol. Psychiatry 41 (9), 939–948. https://doi.org/10.1016/S0006-3223(96)00260-0.

Burdick, K.E., Gunawardane, N., Goldberg, J.F., Halperin, J.M., Garno, J.L., Malhotra, A. K., 2009. Attention and psychomotor functioning in bipolar depression. Psychiatry Res. 166 (2-3), 192–200. https://doi.org/10.1016/j.psychres.2008.03.006.

Caetano, S.C., Fonseca, M., Hatch, J.P., Olvera, R.L., Nicoletti, M., Hunter, K., Soares, J. C., 2007. Medial temporal lobe abnormalities in pediatric unipolar depression. Neurosci. Lett. 427 (3), 142–147. https://doi.org/10.1016/j.neulet.2007.06.014.

Arnold, J.F., Zwiers, M.P., Fitzgerald, D.A., van Eijndhoven, P., Becker, E.S., Rinck, M., Tendolkar, I., 2012. Fronto-limbic microstructure and structural connectivity in remission from major depression. Psychiatry Res. 204 (1), 40–48. https://doi.org/10.1016/j.pscychresns.2012.07.010.

Cavézian, C., Danckert, J., Lerond, J., Daléry, J., d'Amato, T., Saoud, M., 2007. Visual-perceptual abilities in healthy controls, depressed patients, and schizophrenia patients. Brain Cogn. 64 (3), 257–264. https://doi.org/10.1016/j.bandc.2007.03.008.

Cooney, R.E., Joormann, J., Eugène, F., Dennis, E.L., Gotlib, I.H., 2010. Neural correlates of rumination in depression. Cogn. Affect. Behav. Neurosci. 10 (4), 470–478. https://doi.org/10.3758/CABN.10.4.470.

Cullen, K.R., Westlund, M.K., Klimes-Dougan, B., Mueller, B.A., Houri, A., Eberly, L.E., Lim, K.O., 2014. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry 71 (10), 1138–1147. https://doi.org/10.1001/jamapsychiatry.2014.1087.

Dalby, R.B., Frandsen, J., Chakravarty, M.M., Ahdidan, J., Sørensen, L., Rosenberg, R., Ostergaard, L., 2010. Depression severity is correlated to the integrity of white matter fiber tracts in late-onset major depression. Psychiatry Res. 184 (1), 38–48. https://doi.org/10.1016/j.pscychresns.2010.06.008.

Debener, Stefan, Beauducel, André, Nessler, Doreen, Brocke, Burkhard, Heilemann, Hubert, Kayser, J, 2000. Is resting anterior EEG alpha asymmetry a trait marker for depression? Findings for healthy adults and clinically depressed patients. Neuropsychobiology 41 (1), 31–37. https://doi.org/10.1159/000026630.

Deligiannidis, K.M., Sikoglu, E.M., Shaffer, S.A., Frederick, B., Svenson, A.E., Kopoyan, A., Moore, C.M., 2013. Gabaergic neuroactive steroids and resting-state functional connectivity in postpartum depression: A preliminary study. J. Psychiatr. Res. 47 (6), 816–828. https://doi.org/10.1016/j.jpsychires.2013.02.010.

de Delvenne, V., Goldman, S., Maertelaer, V., Wikler, D., Damhaut, P., Lotstra, F., 1997. Brain glucose metabolism in anorexia nervosa and affective disorders: influence of weight loss or depressive symptomatology. Psychiatry Res. 74 (2), 83–92.

Desmond, D.W., Remien, R.H., Moroney, J.T., Stern, Y., Sano, M., Williams, J.B.W., 2003. Ischemic stroke and depression. J. Int. Neuropsychol. Soc. 9 (3), 429–439. https://doi.org/10.1017/s1355617703930086.

Arrondo, G., Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Murray, G.K., 2015. Reduction in ventral striatal activity when anticipating a reward in depression and schizophrenia: a replicated cross-diagnostic finding. Front. Psychol. 6, 1280. https://doi.org/10.3389/fpsyg.2015.01280.

D'Haenen, Hugo, Bossuyt, Axel, Mertens, John, Bossuyt-Piron, Caroline, Gijsemans, Mireille, Kaufman, L, 1992. SPECT imaging of serotonin$_2$ receptors in depression. Psychiatry Res. 45 (4), 227–237. https://doi.org/10.1016/0925-4927(92)90018-Y.

Douglas, K.M., Porter, R.J., Knight, R.G., Maruff, P., 2011. Neuropsychological changes and treatment response in severe depression. Br. J. Psychiatry 198 (2), 115–122. https://doi.org/10.1192/bjp.bp.110.080713.

Elderkin-Thompson, V., Kumar, A., Mintz, J., Boone, K., Bahng, E., Lavretsky, H., 2004. Executive dysfunction and visuospatial ability among depressed elders in a community setting. Arch. Clin. Neuropsychol. 19 (5), 597–611. https://doi.org/10.1016/j.acn.2003.08.009.

Elderkin-Thompson, V., Mintz, J., Haroon, E., Lavretsky, H., Kumar, A., 2006. Executive dysfunction and memory in older patients with major and minor depression. Arch. Clin. Neuropsychol. 21 (7), 669–676. https://doi.org/10.1016/j.acn.2006.05.011.

Elderkin-Thompson, V., Moody, T., Knowlton, B., Hellemann, G., Kumar, A., 2011. Explicit and implicit memory in late-life depression. Am. J. Geriatr. Psychiatry 19 (4), 249–255. https://doi.org/10.1097/JGP.0b013e3181e89a5b.

Elderkin-Thomson, V., Kumar, A., Bilker, W., Dunkin, J., Mintz, J., Moberg, P., Gur, R., 2003. Neuropsychological deficits among patients with late-onset minor and major depression. Arch. Clin. Neuropsychol. 18 (5), 529–549. https://doi.org/10.1016/S0887-6177(03)00022-2.

Bailey, N.W., Segrave, R.A., Hoy, K.E., Maller, J.J., Fitzgerald, P.B., 2014. Impaired upper alpha synchronisation during working memory retention in depression and depression following traumatic brain injury. Biol. Psychol. 99, 115–124. https://doi.org/10.1016/j.biopsycho.2014.03.008.

Epstein, J., Perez, D.L., Ervin, K., Pan, H., Kocsis, J.H., Butler, T., Silbersweig, D.A., 2011. Failure to segregate emotional processing from cognitive and sensorimotor processing in major depression. Psychiatry Res. 193 (3), 144–150. https://doi.org/10.1016/j.pscychresns.2011.01.012.

Eyre, H.A., Yang, H., Leaver, A.M., van Dyk, K., Siddarth, P., Cyr, N.S., Lavretsky, H., 2016. Altered resting-state functional connectivity in late-life depression: a cross-sectional study. J. Affect. Disord. 189, 126–133. https://doi.org/10.1016/j.jad.2015.09.011.

Frodl, T., Reinhold, E., Koutsouleris, N., Reiser, M., Meisenzahl, E.M., 2010. Interaction of childhood stress with hippocampus and prefrontal cortex volume reduction in major depression. J. Psychiatr. Res. 44 (13), 799–807. https://doi.org/10.1016/j.jpsychires.2010.01.006.

Frodl, T.S., Koutsouleris, N., Bottlender, R., Born, C., Jäger, M., Scupin, I., Reiser, M., Möller, H.-J., Meisenzahl, E.M, 2008. Depression-related variation in brain morphology over 3 years: effects of Stress? Arch. Gen. Psychiatry 65 (10), 1156–1165. https://doi.org/10.1001/archpsyc.65.10.1156.

Gaffrey, M.S., Luby, J.L., Botteron, K., Repovš, G., Barch, D.M., 2012. Default mode network connectivity in children with a history of preschool onset depression. J. Child Psychol. Psychiatry, Allied Discip. 53 (9), 964–972. https://doi.org/10.1111/j.1469-7610.2012.02552.x.

Gaffrey, M.S., Luby, J.L., Repovš, G., Belden, A.C., Botteron, K.N., Luking, K.R., Barch, D. M., 2010. Subgenual cingulate connectivity in children with a history of preschool-depression. Neuroreport 21 (18), 1182–1188. https://doi.org/10.1097/WNR.0b013e32834127eb.

Garrett, A., Kelly, R., Gomez, R., Keller, J., Schatzberg, A.F., Reiss, A.L., 2011. Aberrant brain activation during a working memory task in psychotic major depression. Am. J. Psychiatry 168 (2), 173–182. https://doi.org/10.1176/appi.ajp.2010.09121718.

Ge, R., Blumberger, D.M., Downar, J., Daskalakis, Z.J., Dipinto, A.A., Tham, J.C.W., Vila-Rodriguez, F., 2017. Abnormal functional connectivity within resting-state networks is related to rTMS-based therapy effects of treatment resistant depression: A pilot study. J. Affect. Disord. 218, 75–81. https://doi.org/10.1016/j.jad.2017.04.060.

Barch, D.M., Sheline, Y.I., Csernansky, J.G., Snyder, A.Z., 2003. Working memory and prefrontal cortex dysfunction: specificity to schizophrenia compared with major depression. Biol. Psychiatry 53 (5), 376–384. https://doi.org/10.1016/S0006-3223(02)01674-8.

Gyagenda, J.O., Ddumba, E., Odokonyero, R., Kaddumukasa, M., Sajatovic, M., Smyth, K., Katabira, E., 2015. Post-stroke depression among stroke survivors attending two hospitals in Kampala Uganda. Afr. Health Sci. 15 (4), 1220–1231. https://doi.org/10.4314/ahs.v15i4.22.

Hahn, A., Haeusler, D., Kraus, C., Höflich, A.S., Kranz, G.S., Baldinger, P., Lanzenberger, R., 2014. Attenuated serotonin transporter association between dorsal raphe and ventral striatum in major depression. Hum. Brain Mapp. 35 (8), 3857–3866. https://doi.org/10.1002/hbm.22442.

Hastings, R.S., Parsey, R.V., Oquendo, M.A., Arango, V., Mann, J.J., 2004. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. Neuropsychopharmacology 29 (5), 952–959. https://doi.org/10.1038/sj.npp.1300371.

Holsen, L.M., Lancaster, K., Klibanski, A., Whitfield-Gabrieli, S., Cherkerzian, S., Buka, S., Goldstein, J.M., 2013. Hpa-axis hormone modulation of stress response circuitry activity in women with remitted major depression. Neuroscience 250, 733–742. https://doi.org/10.1016/j.neuroscience.2013.07.042.

Bauer, M., London, E.D., Rasgon, N., Berman, S.M., Frye, M.A., Altshuler, L.L., Whybrow, P.C., 2005. Supraphysiological doses of levothyroxine alter regional cerebral metabolism and improve mood in bipolar depression. Mol. Psychiatry 10 (5), 456–469. https://doi.org/10.1038/sj.mp.4001647.

Jaworska, N., Blier, P., Fusee, W., Knott, V., 2012. A Power, α asymmetry and anterior cingulate cortex activity in depressed males and females. J. Psychiatr. Res. 46 (11), 1483–1491. https://doi.org/10.1016/j.jpsychires.2012.08.003.

Johnston, B.A., Steele, J.D., Tolomeo, S., Christmas, D., Matthews, K., 2015. Structural MRI-based predictions in patients with treatment-refractory depression (TRD). PLoS One 10 (7), e0132958. https://doi.org/10.1371/journal.pone.0132958.

Joshi, S.H., Espinoza, R.T., Pirnia, T., Shi, J., Wang, Y., Ayers, B., Narr, K.L., 2016. Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. Biol. Psychiatry 79 (4), 282–292. https://doi.org/10.1016/j.biopsych.2015.02.029.

... Kelley, R., Garrett, A., Cohen, J., Gomez, R., Lembke, A., Keller, J., Schatzberg, A., 2013. Altered brain function underlying verbal memory encoding and retrieval in psychotic major depression Psychiatry Res. 211 (2), 119–126.

Kerestes, R., Ladouceur, C.D., Meda, S., Nathan, P.J., Blumberg, H.P., Maloney, K., Phillips, M.L., 2012. Abnormal prefrontal activity subserving attentional control of emotion in remitted depressed patients during a working memory task with emotional distracters. Psychol. Med. 42 (1), 29–40. https://doi.org/10.1017/S0033291711001097.

Kettle, J.W.L., O'Brien-Simpson, L., Allen, N.B., 2008. Impaired theory of mind in first-episode schizophrenia: Comparison with community, university and depressed controls. Schizophr. Res. 99 (1-3), 96–102. https://doi.org/10.1016/j.schres.2007.11.011.

Kishi, Yasuhiro, Robinson, Robert G, Kosier, J.T, 1996. The validity of observed depression as a criteria for mood disorders in patients with acute stroke. J. Affect. Disord. 40 (1-2), 53–60.

Klimkeit, E.I., Tonge, B., Bradshaw, J.L., Melvin, G.A., Gould, K., 2011. Neuropsychological deficits in adolescent unipolar depression. Arch. Clin. Neuropsychol. 26 (7), 662–676. https://doi.org/10.1093/arclin/acr051.

Koolschijn, P.C.M.P., van Haren, N.E.M., Schnack, H.G., Janssen, J., Hulshoff Pol, H.E., Kahn, R.S., 2010. Cortical thickness and voxel-based morphometry in depressed elderly. Eur. Neuropsychopharmacol. 20 (6), 398–404. https://doi.org/10.1016/j.euroneuro.2010.02.010.

Bearden, C.E., Glahn, D.C., Monkul, E.S., Barrett, J., Najt, P., Villarreal, V., Soares, J.C., 2006. Patterns of memory impairment in bipolar disorder and unipolar major depression. Psychiatry Res. 142 (2-3), 139–150. https://doi.org/10.1016/j.psychres.2005.08.010.

Leon, M.J., La Regina, M.E., Ferris, S.H., Gentes, C.I., Miller, J.D., 1986. Reduced incidence of left-handedness in clinically diagnosed dementia of the Alzheimer type. Neurobiol. Aging 7 (3), 161–164. https://doi.org/10.1016/0197-4580(86)90037-0.

Li, Y., Cao, D., Wei, L., Tang, Y., Wang, J., 2015. Abnormal functional connectivity of EEG gamma band in patients with depression during emotional face processing. Clin. Neurophysiol. 126 (11), 2078–2089. https://doi.org/10.1016/j.clinph.2014.12.026.

Linden, D.E.J., Habes, I., Johnston, S.J., Linden, S., Tatineni, R., Subramanian, L., Goebel, R., 2012. Real-time self-regulation of emotion networks in patients with depression. PLoS One 7 (6), e38115. https://doi.org/10.1371/journal.pone.0038115.

Marrus, N., Belden, A., Nishino, T., Handler, T., Ratnanather, J.T., Miller, M., Botteron, K., 2015. Ventromedial prefrontal cortex thinning in preschool-onset depression. J. Affect. Disord. 180, 79–86. https://doi.org/10.1016/j.jad.2015.03.033.

Meisenzahl, E.M., Seifert, D., Bottlender, R., Teipel, S., Zetzsche, T., Jäger, M., Frodl, T., 2010. Differences in hippocampal volume between major depression and schizophrenia: a comparative neuroimaging study. Eur. Arch. Psychiatry Clin. Neurosci. 260 (2), 127–137. https://doi.org/10.1007/s00406-009-0023-3.

Miller, Anita, Fox, Nathan A., Cohn, Jeffrey F., Forbes, Erika E., Sherrill, Joel T., Kovacs, M., 2002. Regional patterns of brain activity in adults with a history of childhood-onset depression: gender differences and clinical variability. Am. J. Psychiatry 159 (6), 934–940. https://doi.org/10.1176/appi.ajp.159.6.934.

Msetfi, R.M., Murphy, R.A., Kornbrot, D.E., 2012. The effect of mild depression on time discrimination. Q. J. Exp. Psychol. 65 (4), 632–645. https://doi.org/10.1080/17470218.2011.608908.

Njau, S., Joshi, S.H., Espinoza, R., Leaver, A.M., Vasavada, M., Marquina, A., Narr, K.L., 2017. Neurochemical correlates of rapid treatment response to electroconvulsive therapy in patients with major depression. J. Psychiatry Neurosci. 42 (1), 6–16. https://doi.org/10.1503/jpn.150177.

O'Brien, J.T., Gallagher, P., Stow, D., Hammerla, N., Ploetz, T., Firbank, M., Olivier, P., 2016. A study of wrist-worn activity measurement as a potential real-world biomarker for late-life depression. Psychol. Med. 47 (1), 93–102. https://doi.org/10.1017/s0033291716002166.

Pannekoek, J.N., van der Werff, S.J.A., van Tol, M.J., Veltman, D.J., Aleman, A., Zitman, F.G., van der Wee, N.J.A., 2015. Investigating distinct and common abnormalities of resting-state functional connectivity in depression, anxiety, and their comorbid states. Eur. Neuropsychopharmacol. 25 (11), 1933–1942. https://doi.org/10.1016/j.euroneuro.2015.08.002.

von Weatherill, R., Almerigi, J., Levendosky, A., Bogat, G.A., Eye, A., Harris, L.J., 2021. Is maternal depression related to side of infant holding?. Int. J. Behav. Dev.