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Review article

Beyond the genome—Towards an epigenetic understanding of handedness ontogenesis

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ABSTRACT

Hemispheric asymmetries represent one of the major organizational principles in vertebrate neurobiology, but their molecular determinants are not well understood. For handedness, the most widely investigated form of hemispheric asymmetries in humans, single gene explanations have been the most popular ontogenetic model in the past. However, molecular genetic studies revealed only few specific genes that explain a small fraction of the phenotypic variance. In contrast, family studies indicated heritability of up to 0.66. It has been suggested that the lack of recognizable genetic heritability is partly accounted for by heritable epigenetic mechanisms. Based on recent neuroscientific findings highlighting the importance of epigenetic mechanisms for brain function and disease, we review recent findings describing non-genetic influences on handedness from conception to childhood. We aim to advance the idea that epigenetic regulation might be the mediating mechanism between environment and phenotype. Recent findings on molecular epigenetic mechanisms indicate that particular asymmetries in DNA methylation might affect asymmetric gene expression in the central nervous system that in turn mediates handedness. We propose that an integration of genes and environment is essential to fully comprehend the ontogenesis of handedness and other hemispheric asymmetries.

Contents

Abbreviations: ADHD, attention deficit hyperactivity disorder; *APOE*, apolipoprotein E gene; *AR*, androgen receptor gene; *bdnf*, brain derived neurotrophic factor; CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; *COMT*, catechol-*O*-methyltransferase gene; *CYP2E1*, cytochrome P450 2E1 gene; DES, diethylstilbestrol; *FKBP5*, FK506 binding protein 5 gene; *GR*, glucocorticoid receptor gene; *IGF1R*, Insulin-like growth factor 1 receptor gene; Lefty, left-right determination factor; *LRRTM1*, leucine rich repeat transmembrane neuronal 1; miRNAs, microRNAs; MRI, magnetic resonance imaging; NLH, natural left-handers; Nodal, nodal growth differentiation factor; NRH, natural right-handers; *OXTR*, oxytocin receptor gene; *PCSK6*, proprotein convertase subtilisin/kexin type 6; PLH, pathological left-handedness; PRH, pathological right-handedness; *PRKCZ*, protein kinase C zeta gene; SES, socioeconomic status; *SETDB2*, SET domain bifurcated 2; SNP, single nucleotide polymorphism; *VIT*, vitrin gene.

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1. Introduction

One of the essential organizational principles of invertebrate (Frasnelli et al., 2012) and vertebrate (Ströckens et al., 2013b) neurobiology is asymmetric organization of functional or structural properties within the central nervous system. Hemispheric asymmetry is an important feature of brain organization in many species, ranging from invertebrates like *Caenorhabditis elegans* (Downes et al., 2012; Hobert, 2014) and *Drosophila melanogaster* (Pascual et al., 2004) to vertebrates like zebrafish (Roussigne et al., 2012), rodents (Sullivan, 2004), non-human primates (Hopkins et al., 2017, 2015) and humans (Renteria, 2012). A strong population asymmetry with 90% being more skillful in using the right hand for complex tasks makes handedness the strongest and most investigated form of human motor asymmetries. Strength and direction of handedness have often been associated with mental disorders (Ocklenburg et al., 2015b; Paracchini et al., 2016; Sommer et al., 2001) and are used as a proxy for hemispheric asymmetries (Ooki, 2014). Based on these findings, it comes to no surprise that neuroscientists have been trying to understand the molecular determinants of handedness for decades.

1.1. (The missing) heritability of handedness

Large-scale twin studies have estimated heritabilities of around 0.25 for handedness. An analysis of handedness data from 20,000 twins found that additive genetic effects explain about 25% of the variance in handedness (Medland et al., 2006), which was confirmed in a sample of more than 50,000 twins and their siblings (Medland et al., 2009). Taking into account that left-handers might have been trained to modify their hand-preference, Vuoksimaa et al. (2009) obtained comparative results, i.e. 26% of variance in handedness are explained by genetic effects. However, an overestimation of heritabilities in twin studies compared to family studies may be associated with larger environmental overlap in twins or epistatic effects (Feldman and Otto, 1997). Hence, the estimate of about one quarter of the variance in handedness attributed to additive genetic effects should be interpreted as an upper bound.

Family studies have proposed even higher heritability estimates for handedness of up to 0.66 (Risch and Pringle, 1985). For instance, the probability to be left-handed increases with the number of left-handed parents, which is consistent with a genetic influence on handedness ontogenesis. Whereas children having two right-handed parents have a chance of 9% to be left-handed, the chance rises to 19% in case one parent is left-handed and up to 26% in case both parents are left-handed (McManus and Bryden, 1992). Moreover, the strength of lateralization of biological parents is predictive for the offspring's handedness. In contrast, stepparents' strength of lateralization is unrelated to their children's handedness (Hicks and Kinsbourne, 1976). Similar findings have been reported for biologically related and adoptive families (Carter-Saltzman, 1980). A small, but statistically significant elevation of concordance in monozygotic (MZ) compared to dizygotic (DZ) twins (McManus and Bryden, 1992; Sicotte et al., 1999) is also consistent with a genetic basis of handedness ontogenesis.

However, after sequencing the human genome made large-scale molecular studies on handedness possible in the early 2000s, no genome-wide association study (GWAS) found any single nucleotide polymorphism (SNP) reaching genome-wide significance (Armour et al., 2014; Eriksson et al., 2010). Candidate gene studies revealed several genes related to handedness, including the androgen receptor gene *AR* (Arning et al., 2015; Hampson and Sankar, 2012; Medland et al., 2005), apolipoprotein E gene *APOE* (Bloss et al., 2010; Hubacek et al., 2013; Piper et al., 2013), catechol-*O*-methyltransferase gene *COMT* (Savitz et al., 2007), leucine rich repeat transmembrane neuronal 1 *LRRTM1* (Francks et al., 2007), proprotein convertase subtilisin/kexin type 6 *PCSK6* (Arning et al., 2013; Brandler et al., 2013; Robinson et al., 2016; Scerri et al., 2011), and SET domain bifurcated 2 *SETDB2* (Ocklenburg et al., 2015a). This is in contrast to early single gene explanations for handedness (Annett, 1998; McManus, 1985). A recent linkage study conducted in a Dutch population isolate (Somers et al., 2015b) and whole exome sequencing in a Pakistani consanguineous family (Kavakliogl u et al., 2016) also indicated absence of a single gene determining handedness. Overall, handedness is likely to be a complex trait with multiple genes exerting small influences on the phenotype (Ocklenburg et al., 2014). However, the amount of phenotypic variance that can be explained by variation in these genes typically is very small.

The divergence between heritability estimates from family studies and results obtained from molecular studies has been referred to as the missing heritability problem (Maher, 2008). Interestingly, heritable epigenetic mechanisms have been proposed as potentially accounting for a part of the missing heritability in complex phenotypes (Eichler et al., 2010). The term epigenetics refers to a number of modifications that affect gene expression without altering the nucleotide sequence (Jaenisch and Bird, 2003). Epigenetic modifications can result from either DNA sequence variation or environmental factors (Kilpinen and Dermitzakis, 2012) and regulate gene expression for cell determination and differentiation (Tammen et al., 2013). Epigenetic inheritance refers to a transmission of phenotypic variation to subsequent generations independently of DNA variations (Jablonka and Raz, 2009) and seems to be ubiquitous in eukaryotes, although

its precise mechanisms, its consistency and requirements remain unclear (Heard and Martienssen, 2014; Jablonka and Raz, 2009).

How can epigenetic mechanisms become a source of the missing heritability? As recently suggested, classic family studies are mainly based on a definition of genetics that can also include heritable epigenetic effects, such as transmission over generations contributing to a certain phenotype. This phenomenon may be based on DNA variation, but is equally true for heritable epigenetic effects. However, since GWASs are designed to reveal information on DNA variation only, family studies obtain a higher estimate of heritability than GWASs if heritable epigenetic mechanisms are not correlated with DNA variations (Bourrat et al., 2017). Therefore, besides including rare genetic variants or increasing sample sizes in GWASs, the investigation of heritable epigenetic mechanisms might also contribute to finding the missing heritability in handedness (see Fig. 1). Beyond these factors, experimental errors or developmental noise might also contribute to phenotypic variance.

1.2. Epigenetic mechanisms in neuroscience

In recent years several types of epigenetic mechanisms have been studied. The most investigated epigenetic mechanism is DNA methylation, which involves adding a methyl ($—CH_3$) group to CpG sites usually resulting in decreased or prevented transcription and consequently gene expression. DNA methylation has been shown to have wide implications on brain structure and function (Nikolova and Hariri, 2015). Recent research indicates that DNA methylation is not only relevant for the formation of psychiatric diseases, but also for the development of many basic functions within the human central nervous system (for example learning and memory, stress, psychiatric disorders, for reviews see Day et al., 2015; Nikolova and Hariri, 2015; Roth, 2012). Approximately 147 DNA base pairs are wrapped around an octamer of proteins called histones to form the nucleosome. Gene transcription is also altered by post-translational histone modifications via histone acetylation, methylation, and phosphorylation (Rothbart and Strahl, 2014). These processes contribute to neurogenesis and neural plasticity throughout development (Contestabile and Sintoni, 2013). Post-transcriptionally, gene expression is further regulated by 21–25 nucleotide, non-coding RNAs called miRNAs. In mammals, miRNAs primarily provoke destabilization of target mRNAs (Guo et al., 2010). It is estimated that 30% of all genes are subject to this kind of regulation (Lewis et al., 2003), which has strong impact on embryonic development, cell differentiation and proliferation (Takasaki, 2015).

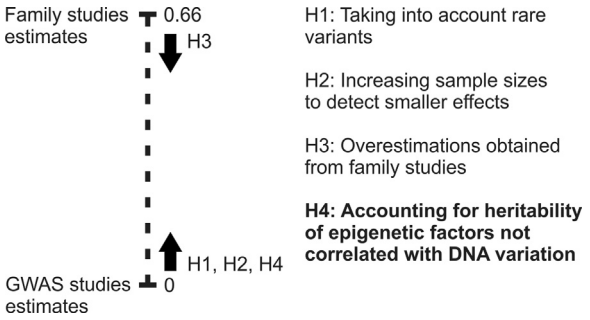

Fig. 1. The major hypotheses (H1, H2, H3, and H4) for finding the missing heritability in handedness. H1 and H2 apply to methodological improvements in future GWASs. H3 refers to a lower actual heritability of handedness than estimated in recent family studies. H4 refers to heritable epigenetic mechanisms accounting for high heritability estimates in family studies that are not captured by GWASs. Figure inspired by Bourrat et al. (2017).

Over the course of the last few years, an epigenetic revolution took place in neuroscience. Epigenetic regulation plays an important role in the pathogenesis and retention of neurodevelopmental (Abdolmaleky et al., 2015; Kubota et al., 2014) and mental disorders like schizophrenia and depression (Cariaga-Martinez et al., 2016; Dalton et al., 2014). Integrating epigenetics set the milestone that helped to disentangle the complexity of these disorders (Stuffrein-Roberts et al., 2008) and lead to much better understanding of risk factors and biomarkers in clinical research (Molfese, 2011).

In line with this research, our review is aimed at elucidating the molecular mechanisms through which environmental factors might influence handedness. It has been proposed that complex phenotypes like handedness are never fully explained by DNA variation and that non-genetic – potentially epigenetic – factors contribute to their development (Kilpinen and Dermitzakis, 2012). We propose that epigenetic regulation might be the mediating mechanism between environment and phenotype and therefore possibly account for a part of the large heritability estimates found in family studies. The review continues with a summary of the relevance of human handedness and its relation to pathologies. We will further review recent findings describing environmental influences on handedness from conception to childhood. Furthermore, this review aims to advance the idea that the molecular basis for lateralization extends beyond the actual DNA sequence. We will discuss potential molecular mechanisms and further present an outlook on the integration of genes and environment that is essential to fully comprehend the ontogenesis of handedness.

1.3. Implications of handedness in neurodevelopmental and psychiatric disorders

A variety of neuropsychiatric and developmental disorders has been linked to a higher frequency of left- and mixed-handedness. Especially the early work of Geschwind and Behan (1982) revealed associations between strong left-handedness and increased incidence of developmental disorders, especially dyslexia and stuttering. However, there has been no empirical confirmation of a relationship between dyslexia or reading disability and left- or non-right-handedness ever since (Gaillard and Satz, 1989; Gilger et al., 1992; Satz and Soper, 1986). Likewise, no significant differences in stuttering were found between left- and right-handers (Salihović and Sinanović, 2000; van Strien et al., 1987; Webster and Poulos, 1987). However, subjects with persistent stuttering have been found to display less pronounced structural asymmetries regarding prefrontal and occipital lobe volumes (Foundas et al., 2003) and atypical gray and white matter asymmetries in language-related brain areas (Foundas et al., 2004; Jancke et al., 2004). Overall, there seems to be some evidence for a relationship between stuttering and reduced hemispheric asymmetries (Kushner, 2012).

Autism spectrum disorders (ASD) have also been associated with a stronger tendency towards left-handedness (Colby and Parkison, 1977; Preslar et al., 2014; Rysstad and Pedersen, 2016). Reduced cerebral specialization (Forrester et al., 2014) and left hemisphere impairment (Perkins et al., 2014) have been discussed as its underlying mechanisms. Moreover, genotypes of *PCSK6*, a gene involved in handedness formation, also showed significant associations with total autism score in a student sample (Robinson et al., 2016).

Left-handedness and ambidexterity have been reported to occur in up to 60% of individuals affected by attention deficit hyperactivity disorder (ADHD) (Shaw and Brown, 1991; Yamamoto and Hatta, 1982), although there are also conflicting results

(Ghanizadeh, 2013). A systematic investigation of left-handedness and ADHD revealed no direct association, but found that non-right-handedness elevates the risk for major depression and reduced psychosocial functioning in ADHD children (Biederman et al., 1994). Moreover, ADHD might not only be related to non-right-handedness alone, but anomalous lateralization overall (Reid and Norvilitis, 2000). Brandler and Paracchini (2014) proposed a genetic link between handedness and neurodevelopmental disorders that is based on biological mechanisms responsible for the left-right asymmetry of the human body, with cilia formation playing a critical role.

Left-handedness has been associated with depression in adults (Denny, 2009; Elias et al., 2001; Overby, 1994) as well as children (Logue et al., 2015). Moreover, there is some evidence for a higher incidence of left-handedness in bipolar disorder than in healthy controls (Nowakowska et al., 2008; van Dyck et al., 2012), although there are also studies that challenge this association (Savitz et al., 2007; Webb et al., 2013). Left-handedness has been associated with higher levels of anxiety (Hicks and Pellegrini, 1978; Logue et al., 2015; Orme, 1970), while other authors only found higher state scores of anxiety in left-handers (Wright and Hardie, 2012). Wienrich et al. (1982) proposed that people on the extreme ends of the handedness continuum show a higher level of anxiety – regardless of handedness direction. Moreover, it has been proposed that higher anxiety scores appear only in inconsistent compared to consistent left-handers (Hardie et al., 2016; Lyle et al., 2013).

There is strong evidence for an association of non-right-handedness and schizophrenia. For example, Webb et al. (2013) found a 40% prevalence of left-handedness in patients suffering from schizoaffective disorder or schizophrenia. Likewise, the chance of being prescribed antipsychotics was increased by 53% in left-handed compared to right-handed hospitalized children (Logue et al., 2015). This overrepresentation of left-handers among schizophrenia patients has been confirmed by two meta-analyses (Dragovic and Hammond, 2005; Sommer et al., 2001). Moreover, the consistency of results has led to the assumption of atypical lateralization as the central neurological background of schizophrenia (Oertel-Knochel and Linden, 2011) and to the postulation that schizophrenia is caused by decreased lateralization (Crow, 1997). Systematic confounding variables like gender or biases in the assessment of handedness were ruled out by another meta-analysis by Hirnstein and Hugdahl (2014), who proposed a genetic link between handedness, brain lateralization and schizophrenia. Risk alleles for schizophrenia have also been proposed as relevant for the ontogenesis of handedness in clinical and nonclinical populations (Francks et al., 2007; Leach et al., 2014; Ludwig et al., 2009) and partial pleiotropy has been postulated in a review by Ocklenburg et al. (2015b). A relation between schizotypal personality and mixed-handedness has also been confirmed in nonclinical samples (Chapman et al., 2011; Somers et al., 2009; Tsuang et al., 2013).

Different forms of addiction have been associated with atypical lateralization and non-right-handedness. Left-handedness has been linked to alcohol (Denny, 2011; Mandal et al., 2000; Sperling et al., 2000) and drug addiction (Yüksel et al., 2012). These results are consistent with the finding that left-handers exhibit greater brain activity in response to drugs affecting the central nervous system, i.e. antipsychotics, sedatives and hypnotics (Irwin, 1985).

The previously discussed studies indicate that handedness in general might be used as an effective endophenotype for schizophrenia (Allen et al., 2009) and might potentially shed light on the underlying pathophysiology of many associated disorders (Ooki, 2014), which makes its ontogenesis a highly interesting feature for further investigation.

1.4. The idea of pathological left-handedness

Over the past decades, a pathological cause has often been attributed to left-handedness. The concept of pathological left-handedness introduced by Satz (1972) is based on the observation that there is a probability of 17% of left-handedness in retarded groups. The author explains his concept based on 1000 hypothetical individuals with an 8% chance of natural left-handedness (80 natural left-handers (NLH) and 920 natural right-handers (NRH)), who are subject to random left- or right-sided brain lesion. The model implies early unilateral brain damage to result in a switch of hemispheric dominance in 21% of all cases of damage to the naturally dominant hemisphere, which results in the observed 17% probability of left-handedness. Since there are more NRH than natural NLH, the incidence of pathological left-handedness (PLH) is elevated compared to the incidence of pathological right-handedness (PRH). Overall, this early theory assumes left-handedness to be influenced by both genetic (natural) and environmental (pathological) factors.

In support of the concept of pathological left-handedness, studies have shown that a variety of left-hemispheric pathologies like unilateral seizures, head injuries or cerebral vascular insult are related to a higher frequency of left-handedness (Orsini and Satz, 1986). When investigating specific clinical symptoms, left-hemispheric congenital hemiplegia led to 89% of left-handedness in children and also affected other functional hemispheric asymmetries like language lateralization (Carlsson et al., 1992). In epileptic patients, the chance of being left-handed was increased in those with left-hemispheric seizures (Dellatolas et al., 1993). The assessment of handedness in children having overcome bacterial meningitis revealed that the strength of meningitis was associated to left-handedness (Ramadhani et al., 2006). Children with left unilateral coronal synostosis showed an increased incidence of left-handedness (44.4%) compared to right-sided coronal fusion (20.4%) and healthy controls (11.4%). This finding suggests that early constraint on the brain might affect its growth and therefore alter hemispheric asymmetries (Oh et al., 2009).

Despite these supporting findings, the concept of pathological left-handedness remains controversial. McManus (1983) criticized that supporting studies implied knowledge about natural handedness, which is not ascertained. Furthermore, pathological left-handers still represent a small fraction of the left-handed population. While pathologies can give insight into mechanisms, it does not necessarily imply that the explanation for pathological left-handedness is identical to the generic cause of handedness direction. As Bishop (1990) noted, the association between left-handedness and pathology could be a pathology-specific manifestation of the disruption of the mechanisms by which handedness normally develops, rather than indicative of the mechanism itself.

Weller (1990) reported a case study of monozygotic twins, one of which was right-handed and free from psychiatric diseases while the other one was left-handed and suffered from schizophrenia. Moreover, this affected twin displayed left-hemispheric EEG irregularities and left-sided temporo-parietal dysfunction. Although it certainly does not represent proof for pathological left-handedness, this case study nicely fits into this concept.

2. Environmental factors influencing handedness

As illustrated by Weller's case report (1990), monozygotic twins are not 100% concordant for handedness. This is in line with the assumption that environmental factors play a significant role in handedness development. Several lines of evidence suggest a role of environmental influences on lateralization in animal models. For example, Collins (1969) found the distribution of paw preference

to be unaffected by selective breeding of mice showing a left or right paw preference, respectively. By designing environments that are more easily handled with one paw compared to the other he successfully induced paw preference towards the corresponding direction (Collins, 1975). He therefore concluded that the environment fully determines the distribution of paw preference. Reviewing the literature, Schaafsma et al. (2009) concluded that rearing conditions, steroid hormone exposure, social modulation and asymmetric light input are likely to be involved in the development of lateralized behavior. For humans, an early twin study has shown low heritability for handedness direction and a better fit for a common environment in contrast to a dominance genetic model (Neale, 1988). Risch and Pringle (1985) found a generational effect on handedness that is consistent with environmental influence on handedness. Several lines of research trying to identify such factors have been pursued over the last decades. The literature on environmental factors possibly influencing handedness is organized in Table 1. For quality of evidence, the criteria proposed by Bryden et al. (1994) are applied. It cannot be ruled out that some of the observed associations are false positives, since positive results tend to be published more often. Typical hints against false positives are replication from independent researchers or positive results obtained from meta-analysis (Kennedy, 2004). Therefore, the existence of meta-analyses arguing for or against a relationship between handedness and the environmental factor is also listed in Table 1.

2.1. Seasonal anisotropy in handedness

Among the environmental factors that have been associated with handedness, season of conception is the first in individual ontogenesis. The first investigation of season of birth with regards to handedness was performed by Leviton and Kilty (1979). The authors found that among 586 school children, left-handed girls were most often born in November. Subsequent studies obtained conflicting results. While some studies showed no association between birth month and handedness (Hicks and Dusek, 1980; Karev, 2008; McManus, 1980; Milenković et al., 2008; Tonetti et al., 2012), others showed significantly higher frequencies of left-handers being born in winter or early spring (Abel and Kruger, 2004; Marzullo and Fraser, 2009; Preti et al., 2008). This finding was partly replicated for only male (Badian, 1983; Stoyanov et al., 2011; Tran et al., 2014) or only female participants (Hicks et al., 1980a; Nicholls, 1998). Other studies found the opposite effect, an elevated frequency of left-handers being born in the summer months. While this was only a trend in two large-scale studies (Cosenza and Mingoti, 1995; Dellatolas et al., 1993), Rogerson (1994) found a significant effect on handedness by being born in summer in a reanalysis of the Dellatolas et al. (1993) and two additional datasets. This finding was supported by Martin and Jones (1999) and Brenner et al. (2004) as well as a meta-analysis conducted by Jones and Martin (2008). However, the meta-analysis has been criticized for including studies with strongly varying methodology (Beaton, 2008). Marzullo and Fraser (2009) found a peak of left-handed subjects born in February and March among 6932 baseball players. Interestingly, extreme right-handers were most often born in August and September. The authors came up with an elegant explanation for this finding: Individuals born in late winter in the Northern hemisphere are conceived in the beginning of June, just a few weeks before the summer solstice. This time of maximal sunlight falls together with the fourth embryonic week, where body asymmetries develop. In contrast, individuals born in late summer are conceived in the beginning of December, just a few weeks before the winter solstice, which decreases the chances of exposure to sunlight in the fourth embryonic week (Marzullo and Boklage, 2011). Since asymmetry development is liable to oxidant stress, which is partly represented by solar radiation (Pourzand and Tyrrell, 1999), the authors

Table 1
A summary of the evidence concerning environmental effects on handedness using the criteria by Bryden et al. (1994). Rating: **+2:** Several empirical studies by independent groups of researchers provide unequivocal support for a relationship between the environmental factor and handedness; **+1:** Empirical evidence which is generally consistent with a relationship between the environmental factor and handedness; **0:** Existing studies seriously methodologically flawed or evidence totally ambiguous; **−1:** Empirical evidence inconsistent, but some good studies inconsistent with a relationship between the environmental factor and handedness; **−2:** Several empirical studies are consistent and contradictory to a relationship between the environmental factor and handedness. Studies (+) refers to the number of studies showing a relationship between the environmental factor and handedness. Studies (−) refers to the number of studies showing no relationship between the environmental factor and handedness. Meta-analysis indicates if there are meta-analyses on the environment-handedness relationship and if so, in which direction.

Environmental factor	Rating	Studies (+)	Studies (−)	Meta-analysis
2.1. Seasonal anisotropy	+1	12	7	1(+)
2.2. Intrauterine environment				
2.2.1. Maternal stress	+2	5	0	0
2.2.2. Hormonal influence				
Testosterone from amniotic fluid	0	1	1	0
CAH exposure	−1	2	3	1(−)
DES exposure	+2	3	0	0
Female or male co-twin	−1	1	3	0
2D:4D ratio	0	5	6	0
AR gene	+2	3	0	0
2.2.3. Ultrasound exposure	−1	2	3	2 (+, −)
2.3. Birth order	−1	6	16	1 (−)
2.3. Birth complications	+1	18	14	1 (+)
2.4. Early childhood experiences				
2.4.1. Early visual experience	+2	7	0	0
2.4.2. Early social environment				
Breastfeeding	+2	2	0	0
Social status	−2	0	1	0
2.5. Education and Culture				
2.5.1. Schooling	0	2	3	0
2.5.2. Family	+2	5	0	0
2.5.3. Cultural influence	+2	17	0	1(+)

hypothesize that the oxidative effects of sunlight cause an elevated chance of left-handedness in individuals born in February and March. In contrast, the anti-oxidative effect of darkness would lead to a reduced chance of left-handedness in individuals born in August and September. For example, melatonin has anti-oxidative effects and is responsive to length of day in humans, i.e. secretion is higher in the winter months (Macchi and Bruce, 2004). Marzullo and Boklage (2011) assume that the chance of being left-handed in dependence on birth month may be mediated genetically or epigenetically. This in turn corresponds to the findings that functional asymmetries in birds like right eye (i.e. left hemisphere) dominance for visual object analysis (Rogers, 1982) and inter-hemispheric crosstalk (Manns and Romling, 2012) depend on asymmetric light input during embryonic development. On the other hand, dark incubated birds lacking this asymmetrical light input display the opposite hemispheric lateralization pattern (Letzner et al., 2014). This animal model suggests a critical role of light-induced environmental mechanisms in the ontogenesis of lateralization. Moreover, one study revealed that being born in late winter or early spring might increase the risk of developing schizophrenia (Davies et al., 2003), which might tighten the link between schizophrenia and left-handedness. Overall, most of the studies found an association between season of birth and handedness (see Table 1). However, it must be kept in mind that the suggested birth months were not always the same or even similar across studies. As Badian (1983) argued, different study locations could also result in differences regarding climatic region or day length during embryonic development. However, hardly any study reported asking their subjects for place of birth. Future studies should control for effects of climate or day length.

Although not in the context of lateralization, molecular genetic studies have shown that season of birth as well as light exposure itself have the potential to alter DNA methylation patterns. In an epigenome-wide association study in 367 subjects, season of birth-related DNA methylation was found at 92 CpG sites. Differentially methylated genes were strongly related to embryonic development, cell cycle and cell death (Lockett et al., 2016). Sunlight exposure, measured as sunlight duration on the day the blood sample was taken, showed an epigenome-wide significant positive association to DNA methylation status at a CpG site in the protein kinase C zeta gene *PRKCZ*. This result suggests that increased exposure to sunlight decreases *PRKCZ* expression. However, this result, found in an American sample, could not be replicated in a Mediterranean sample (Aslibekyan et al., 2014). A direct influence of light exposure on DNA methylation in brain tissue has been shown in the mouse model, where exposure to altered light conditioning led to global changes in DNA methylation in the suprachiasmatic nucleus of the hypothalamus (Azzi et al., 2014).

2.2. Intrauterine environment

Handedness ontogenesis starts early in embryonic development. This has been revealed in a study observing thumb sucking of more than 250 fetuses via ultrasound. 90% of fetuses showed a right thumb preference whereas a minority of 10% preferred sucking their left thumb. Moreover, thumb preference was significantly correlated to head position preference in the newborn (Hepper et al., 1991, 1990). Interestingly, 75 of these infants were followed up at school age. It turned out that early thumb preference is a strong predictor of handedness: All of the children having shown a right thumb preference prenatally were right-handed. Among the children having shown a left thumb preference prenatally, 75% were left-handed (Hepper et al., 2005), which makes prenatal circumstances very important to consider.

Complementary to behavioral asymmetries, structural asymmetries have first been reported in a post mortem investigation of 207 fetal brains between 10 and 44 gestational weeks. Left-right asymmetries were found for the transverse temporal gyri, sylvian fissures, and planum temporale (Chi et al., 1977a), which is larger in the left hemisphere in most samples (Chi et al., 1977b). In utero magnetic resonance imaging (MRI) of 197 fetuses from 18 gestational weeks to term revealed that 73.8% showed a longer left-hemispheric temporal lobe and a deeper right-hemispheric superior temporal sulcus (Kasprian et al., 2011). Among white matter pathways, higher left-hemispheric fractional anisotropy was found in the inferior longitudinal fasciculus pathway at 15 gestational weeks (Song et al., 2015). Geschwind and Galaburda (1985a) argued that in search of factors influencing handedness, emphasis must be placed on genetic or intrauterine influences on handedness. A number of studies on environmental factors have focused those influencing fetal development, of which prenatal stress, hormones and ultrasound exposure are the most investigated.

2.2.1. Maternal stress

The influence of maternal stress during pregnancy on epigenetic changes in the offspring brain and different health outcomes is well documented in animal models as well as in human research (Babenko et al., 2015; Vaiserman, 2015). Interestingly, prenatal stress in rats increases DNA methylation in the brain derived neurotrophic factor *Bdnf* promoter, which reduces offspring *Bdnf* expression in the amygdala and hippocampus (Boersma et al., 2014). BDNF is interesting in the context of hemispheric asymmetries since it has been found to induce lateralization in visuomotor processing in pigeons (Manns et al., 2008). In humans, maternal depressive symptoms during pregnancy decreases infant *BDNF IV* DNA methylation (Braithwaite et al., 2015).

Environmental stress has been shown to exert strong effects on brain development and function via miRNA expression (Hollins and Cairns, 2016). In the rat model, maternal exposure to stress altered miRNA expression and gene expression in the offspring's brain: 131 miRNAs were downregulated and 205 miRNAs were upregulated in response to gestational stress with corresponding changes in the expression of target genes. Among the differentially expressed miRNAs, many were associated to neuropsychiatric diseases like bipolar disorder or schizophrenia (Zucchi et al., 2013). Interestingly, there is also evidence of transgenerational programing: Altered miRNA and gene expression profiles were found in the frontal lobes of the F2 offspring of female rats exposed to stress compared to non-stressed controls. Again, differentially expressed miRNAs and target genes were associated with neuropsychiatric disorders. Moreover, multigenerational stress induced altered expression of miRNAs and genes associated to preterm birth in humans. This was in line with shortened gestational length and reduced gestational weight gain across subsequent generations (Yao et al., 2014).

An effect of maternal stress on offspring lateralization has also first been found in animal research. In rats, prenatal stress goes along with altered tail posture and rotational behavior (Fride and Weinstock, 1989), T-maze side preference (Alonso et al., 1991), and is accompanied by reduced cerebral asymmetry and behavioral deviations comparable to human depressive and schizotypal symptoms (Weinstock, 2001). On the neural level, maternal chronic unpredictable stress is associated with asymmetrical dopaminergic activity in rats (Huang et al., 2013). Moreover, the development of the corpus callosum is altered in infant monkeys whose mothers have been stressed during pregnancy (Coe et al., 2002).

A recently published study compared the F4 generation of multi-generationally prenatally stressed rats (i.e. parental female rats were stressed during pregnancy in the F0, F1, F2, and F3

generation) with the F4 generation of transgenerationally prenatally stressed rats (i.e. parental female rats in the F0 generation were stressed) regarding laterality and hemispheric dominance. While prenatal stress had no impact on laterality in the F1 generation, recurrent prenatal stress accumulated over several generations and was associated with a shift in male rats' paw preference towards the left. This altered pattern of lateralization goes along with a right hemisphere dominance in terms of increased dendritic complexity and spine density. The cumulative programming of left-handedness by stress across five successive generations represents a strong predictor of epigenetic mechanisms that are linked to altered neuroplasticity (Ambeskovic et al., 2017).

In humans, prenatal stress was associated with an increase in the children's risk of schizophrenia (Negron-Oyarzo et al., 2016), ADHD (Park et al., 2014; Zhu et al., 2015), and autism (Walder et al., 2014), which resembles the psychiatric diseases associated to left-handedness. Obel et al. (2003) found that psychological distress and traumatic life events in the third trimester are associated with a higher probability of children being mixed-handed at 3 years of age. In a sample of more than 7000 pregnant women, maternal anxiety at 18, but not at 32 gestational weeks was predictive of an enhanced chance of offspring mixed-handedness (Glover et al., 2004). These results were supported by studies finding greater trait anxiety (Gutteling et al., 2007), depressive symptoms and critical life events (Rodriguez and Waldenström, 2008) to be associated with a higher probability of having mixed-handed children. Moreover, Reissland et al. (2015) found that maternal stress is associated with more fetal self-touch with the left hand. Overall, there are only few studies on human subjects, but evidence so far is completely consistent with an involvement of maternal stress in handedness ontogenesis (see Table 1).

2.2.2. Hormonal influence

Testosterone exposure in early embryonic development has been proposed to alter offspring global DNA methylation patterns in the zebrafish model. The unaffected F1 generation also showed global hypomethylation patterns, which suggests transgenerational changes in the epigenome caused by early, but not late, prenatal androgen exposure (Xu et al., 2014).

Several hypotheses regarding the influence of testosterone on hemispheric asymmetries have been proposed with slightly different implications on direction and strength of lateralization (Pfannkuche et al., 2009). For example, Geschwind and Galaburda (1985a) proposed that prenatal testosterone weakens growth in the normally dominant left hemisphere, which induces right hemisphere dominance. Consequently, the standard dominance pattern (strong left-hemisphere dominance for language and handedness; strong right-hemisphere dominance for other functions) is modified, which is referred to as anomalous dominance. This in turn results in a predisposition to left-handedness. The amount of intrauterine testosterone might be affected by the season of conception, since testosterone levels are related to the length of photoperiod (Geschwind and Galaburda, 1985a, 1985b, 1985c). It is important to point out that the hypothesized effects are attributed to organizational, i.e. pre- and neonatal effects of testosterone, which are permanent and induce irreversible alterations in the brain in critical developmental periods. Activational effects on the other hand are defined as inducing short-term alterations in the adult brain (Phoenix et al., 1959). Therefore, studies investigating testosterone from saliva or blood of adult subjects are not suitable to investigate environmental or epigenetic long-term influences on handedness, especially since prenatal and salivary testosterone are not significantly correlated (Neave et al., 2003).

The methods to measure prenatal testosterone in humans are limited. Its direct assessment from amniotic fluid requires longitudinal studies, of which only few have been conducted. In a study by Grimshaw et al. (1995), girls with exposure to higher prenatal testosterone in gestational week 16 displayed stronger right-handedness at the age of 10 years than girls with exposure to low levels of prenatal testosterone. Exposure to testosterone accounted for 17% in handedness variance in girls, while no handedness-effect was found for boys. In contrast, Lust et al. (2011) found that higher exposure to prenatal testosterone is associated with less pronounced strength of handedness in a sample of children with a mean age of 6 years. The authors explain this negative relationship with a hypothetical influence of prenatal testosterone on structural properties of the corpus callosum or the left or right hemisphere, dependent on initial handedness. In accordance with this observation, Lombardo et al. (2012) found that differences in prenatal testosterone exposure are predictive for gray matter volume of sexually dimorphic brain regions, which could represent an underlying factor for differences in subsequent handedness.

Pfannkuche et al. (2009) conducted a meta-analysis over studies on prenatal testosterone levels and handedness, most of which compared congenital adrenal hyperplasia (CAH) patients, who are exposed to massive testosterone levels *in utero*, to healthy controls. However, the authors could not confirm a relationship between prenatal testosterone influence and handedness (Pfannkuche et al., 2009). Similar studies have been performed to investigate the influence of diethylstilbestrol (DES) on handedness, since it exerts organizational effects on the brain which are comparable to testosterone (Schachter, 1994). DES had been prescribed to pregnant women in prevention of birth complications until it was disadvised in 1971 due to massive side effects (Reed and Fenton, 2013). The distribution of handedness was significantly shifted to the left in women exposed to DES *in utero* when compared to controls in several studies (Schachter, 1994; Scheirs and Vingerhoets, 1995; Smith and Hines, 2000).

Since prenatal testosterone passes between twins, fetuses having male co-twins should be exposed to higher levels of testosterone in their intrauterine environment than fetuses with female co-twins. Therefore, individuals with male co-twins should more likely be left-handed if testosterone enhances the probability of left-handedness. However, a number of studies found no differences in the incidence of left-handedness in females and males having a male co-twin compared to those having a female co-twin (Elkadi et al., 1999; Medland et al., 2009; Ooki, 2006). The most recent study with 4736 twin subjects found the opposite pattern from the one predicted, i.e. lower prevalence of left-handedness in females having a male twin brother (Vuoksimaa et al., 2010). Organizational effects of testosterone on motor asymmetries have been verified experimentally in animal studies. For example, prenatal injection of testosterone propionate reverses the leftward bias in female rats' tail posture (Rosen et al., 1983). In rhesus monkeys, neonatal elevation of testosterone is associated with stronger hand preferences (Drea et al., 1995). The injection of testosterone at day 4 also alters paw preferences of gerbils (Clark et al., 1991, 1996, 1993) and reverses the pattern of brain asymmetries in male chicks when injected two days after hatch (Zappia and Rogers, 1987). Schwarz and Rogers (1992) found that testosterone treatment to the chick embryo reverses or erases structural asymmetries in the visual pathway.

Since due to obvious ethical reasons testosterone levels cannot be manipulated in human research and as an alternative to protracted longitudinal studies, the ratio between the length of the second and fourth digit (2D:4D ratio) has been applied as a marker for prenatal testosterone. A low 2D:4D ratio is considered as a marker for elevated prenatal testosterone levels (Putz et al., 2004;

Ventura et al., 2013). Accordingly, the 2D:4D ratio is higher in women than in men (and also higher in female than in male fetuses; Malas et al., 2006) and stable across development (Manning et al., 1998). Moreover, lower 2D:4D ratios have been found in CAH patients compared to controls (Brown et al., 2002; Ökten et al., 2002). The complete androgen insensitivity syndrome (CAIS) manifests in a 46,XY karyotype, which results in a female phenotype due to lacking prenatal androgen exposure. Higher 2D:4D ratios than control men and similar ratios to control women have been found for CAIS women (Berenbaum et al., 2009). Although it does not provide a perfect estimate of testosterone exposure, the 2D:4D ratio has been proposed as the best available marker of prenatal androgen stimulation (Breedlove, 2010).

Low 2D:4D ratios have been associated with less right-sided dominance performance in motor tasks in Jamaican (Manning et al., 2000) and Austrian children (Fink et al., 2004) as well as adults (Nicholls et al., 2008; Voracek et al., 2006). Interestingly, in the study by Manning et al. (2000), handedness was best predicted by the difference between the 2D:4D ratios of both hands (D_{L-R}; left 2D:4D ratio − right 2D:4D ratio) with high values for D_{L-R} being correlated towards a more left-sided dominance pattern. These results were confirmed in a large internet-based sample (Manning and Peters, 2009) and a small Bulgarian sample (Stoyanov et al., 2011). Beaton et al. (2011) did not find any direct relationship of the 2D:4D ratio to handedness, but D_{R-L} predicted sensitivity to prenatal testosterone levels. In all these studies, a higher 2D:4D ratio in the left compared to the right hand was associated with a tendency towards left-handedness. However, there have been failures of replication (Baker et al., 2013; Gillam et al., 2008; Jackson, 2008; Robertson et al., 2008; Ypsilanti et al., 2008) and the literature is heavily influenced by findings from one lab (Voracek and Loibl, 2009).

An aspect that has often been neglected is that hormone levels should always be considered in the context of receptor binding capacity. Within the androgen receptor gene *AR*, the length of the polymorphic polyglutamine CAG repeat serves as a marker for the capacity of the androgen receptor to respond to testosterone. Medland et al. (2005) found the number of CAG repeats to increase the probability of left-handedness in women while they found a decrease of likelihood in men. However, another study with a sample including 180 left-, mixed- and right-handed men revealed shorter CAG repeats in mixed-handed compared to right-handed men (Hampson and Sankar, 2012). The relation between *AR* and handedness was further examined in a study that accounted for X chromosome inactivation in female subjects heterozygous for CAG repeat lengths. Longer CAG repeats, which are related to less *AR* function, were associated with stronger left-handedness in both sexes (Arning et al., 2015). Interestingly, the right hand 2D:4D ratio as well as the D_{R-L} value has been shown to positively correlate with the number of CAG repeats, which is in line with a predictive value for a low sensitivity to testosterone (Manning et al., 2002, 2003).

Overall, evidence for an involvement of testosterone in the ontogenesis of handedness seems to depend on the method of investigation. While evidence is inconsistent for studies using the 2D:4D ratio or CAH exposure as markers for prenatal hormonal influence or testosterone measured from amniotic fluid, studies on female and male co-twins do not seem suitable to detect hormonal influences on handedness. However, studies on DES exposure as well as an involvement of *AR* on handedness support this relationship (see Table 1).

2.2.3. Ultrasound exposure

Ultrasound exposure has been debated as a potential influence on neuronal migration and neurological development, which led Salvesen et al. (1993) to propose a possible relationship between fetal ultrasound exposure and left-handedness in childhood. 1663 women who had participated in ultrasound screenings during pregnancy reported hand preferences of their 8–9 year old children. Although non-significant, the authors found an increased probability of left-handedness among those exposed to ultrasound. Using a similar study design, Kieler et al. (1998) found no difference in handedness between exposed and non-exposed children, but when gender-specific subgroup analysis was applied, there was a significant association between ultrasound exposure and left-handedness for boys. A subsequent meta-analysis of the two studies supported this result (Salvesen and Eik-Nes, 1999). Kieler et al. (2001) found similar probabilities of left-handedness for exposed and unexposed males born between 1973 and 1975. In contrast, in males born between 1976 and 1978 – when ultrasound screening was more common – the prevalence of left-handedness was larger in exposed subjects (Odds ratio = 1.32). However, Salvesen (2002) argued that ultrasound screenings have been a routine procedure in Europe for the past 20–30 years. An increase in left-handedness of this sort should already have been observable by 2002. Including all studies mentioned above, the Cochrane Review revealed no significant difference in handedness in dependence on ultrasound screening, although results were only presented for all subjects instead of a subdivision per gender (Whitworth et al., 2015). Directly testing the relationship between ultrasound, handedness, and gender, Heikkilä et al. (2011) could not confirm an association for neither boys nor girls, irrespective of handedness definition as writing hand or lateralization quotient. Another study found no relationship between the number of ultrasound scans and handedness (Rodriguez and Waldenström, 2008). Overall, the involvement of ultrasound exposure as a possible environmental and epigenetic factor for handedness ontogeny remains unclear, but empirical evidence seems rather weak (see Table 1).

2.3. Birth complications

Birth complications have been shown to influence offspring DNA methylation, especially in terms of preterm births (Parets et al., 2013). Behnia et al. (2015) found fetal membrane oxytocin receptor gene *OXTR* hypermethylation in preterm births. Similarly, global DNA methylation is higher in umbilical cord blood of children delivered by Caesarian birth (Schlinzig et al., 2009). An influence of birth weight on DNA methylation has been found in adult MZ twins discordant for birth weight (Chen et al., 2016; Tsai et al., 2015). In 150 twin pairs, Chen et al. (2016) discovered significant differential DNA methylation in a genomic region on chromosome 1. In a similar study design, Tsai et al. (2015) found the Insulin-like growth factor 1 receptor gene *IGF1R* to be significantly associated to birth weight at whole-genome level.

The observation that left-handedness is more frequent in first born students as well as students who were born fourth or later ("high-risk birth positions") let Bakan (1971) introduce the idea that handedness depends on birth order, especially in males, but by trend also in women. Although confirmed by some authors (Annett and Ockwell, 1980; Badian, 1983; Bakan, 1977; Bakan et al., 1973; Leviton and Kilty, 1976), this finding was not replicated in many studies, some of which included large sample sizes (Leiber and Axelrod, 1981b; McManus, 1981; Teng et al., 1976), as well as a subsequent meta-analysis (Searleman et al., 1989). This led to the assumption that birth order is not the determining factor influencing handedness, but rather a by-product of birth complications and birth stress in general (Bakan, 1977; Searleman et al., 1989). Therefore, birth order is separated from birth complications in Table 1.

Indeed, some studies found that a higher proportion of left-handed compared to right-handed subjects had suffered from birth

stress in terms of a composite score from questionnaires including multiple births, premature birth, prolonged labor, Caesarian birth, breech birth, blue baby and breathing difficulty at birth (Bakan et al., 1973; Hicks et al., 1980b; Leiber and Axelrod, 1981b). Bakan et al. (1973) hypothesized that oxygen deprivation caused by stress and complications affects primarily the left motor cortex. Other studies found specific birth complications affecting handedness, specifically Rh incompatibility (i.e. the mother has Rh-negative blood and the offspring has Rh-positive blood) (Kocel, 1977; Tan and Nettleton, 1980) or being firstborn to a mother over 30 (Bakan et al., 1973) or 38 years (Smart et al., 1980). Other factors that have been found to affect handedness are breathing difficulty at birth (Barnes, 1975), low birth weight (O'Callaghan et al., 1987; van Strien et al., 1987), high blood pressure during pregnancy, short labor, induction of labor, jaundice of the newborn (van Strien et al., 1987), and Caesarian birth (McManus, 1981 in a reanalysis by Searleman et al., 1989). On the other hand, no evidence for a relationship between any birth complication and handedness was found in large-scale prospective studies (Ehrlichman et al., 1982; McManus, 1981). According to a meta-analysis by Searleman et al. (1989) including 23 studies there is a small, but statistically significant effect of Rh incompatibility, low birth weight, Caesarian birth and a composite score of birth complications on left-handedness for the whole sample. Sex specific analyses revealed an effect of similar birth complications on left-handedness in males, but not in females.

Subsequent studies found maternal age (Bailey and McKeever, 2004; Coren, 1990; McKeever et al., 1995), smoking during pregnancy (Bakan, 1991), resuscitation after birth (Williams et al., 1992), multiple birth (Coren, 1995; Williams et al., 1992), Rh incompatibility, Caesarian section (Coren, 1995), infertility treatment and being born despite intake of oral contraceptives (Zhu et al., 2009) to increase the probability of left-handedness. Jones et al. (2011) measured cerebral blood flow in 140 8–9 year old children via tympanic membrane temperature. Interestingly, children with low birth weight expressed stronger blood flow in the right than in the left hemisphere. The effect was even stronger immediately after stress induction via the child version of the Trier Social Stress Test (TSST). However, a large-scale study with a sample size of approximately 10,000 subjects did not confirm any association of birth complications with either hand preference or its degree (Nicholls et al., 2012). Van der Elst et al. (2011) found the variance in handedness explained by birth stress to be only 0.36%, which is similar to the conclusion of Bailey and McKeever (2004) and Searleman et al. (1989). Overall, despite small effect sizes there seems to be only a minor effect of birth complications on handedness (see Table 1).

2.4. Early childhood experiences

Long-lasting epigenetic changes are often attributed to pre- or perinatal circumstances, but early childhood experiences also have an impact on DNA methylation. For example, growing up under adverse conditions including social deprivation and childhood abuse is related to elevated DNA methylation in the in the promoter-regulatory region of the cytochrome P450 2E1 gene *CYP2E1* (Kumsta et al., 2016). Correspondingly, preliminary forms of handedness are already visible *in utero* (Hepper et al., 2005), but early childhood experiences have also been shown to play a role for handedness development.

2.4.1. Early visual experience

Head turning preferences in early childhood might increase visual experience with one hand compared to the other and therefore facilitate a hand preference in that direction. Studies typically involve maintaining the newborn's head in a midline position to investigate head turning preference after release. Early studies suggested that most newborns prefer turning their head to the right side (Liederman and Kinsbourne, 1980; Turkewitz and Creighton, 1975), which makes them more responsive to right-sided compared to left-sided sensory stimulation (Turkewitz, 1977). It has been shown that most mothers prefer holding their infants in their left arm when cradling, which provides right-sided auditory and tactile sensory input and might support head turning to the right side (Donnot and Vauclair, 2007). Interestingly, head turning preference to the right is less pronounced in preterm infants (Geerdink et al., 1994) and newborns having suffered from respiratory distress syndrome (Fox and Lewis, 1982), so the influence of head turning might be mediated by birth stress. Head turning in newborns results in the Asymmetric Tonic Neck Reflex: The arm contralateral to head turning is flexed, while the ipsilateral arm is extended and more visible to the infant (Clopton et al., 2000), which might be important in the first weeks of life, when newborns start discovering their hands (Coryell and Henderson, 1979; Liederman and Coryell, 1981). The Moro Reflex is a response to head- or body-drop of the newborn and involves an abduction of the upper arm in combination with an extension of the forearm and fingers. This reflex is elicited faster in the right than in the left arm in infants with a right-sided head turning preference as they have explored their right hand in more detail (Ronnqvist et al., 1998).

More importantly, head orientation preference is a strong indicator of preferred hand use in reaching tasks in infants aged 16 to 22 weeks (Coryell and Michel, 1978; Michel, 1981) and up to 18 months of age (Konishi et al., 1986; Michel and Harkins, 1986). In a field study, observations of kissing couples revealed that the right-turning preference persists into adulthood (Güntürkün, 2003). This right-turning bias is not only associated with a higher consistency in head turning while kissing (van der Kamp and Canal-Bruland, 2011), but is also correlated with handedness, with right-kissers showing a stronger lateralization towards the right hand than left-kissers (Ocklenburg and Güntürkün, 2009). Barrett et al. (2006) did not confirm this relationship; however, handedness was assessed by hand writing only. In a study on children suffering from inborn muscular torticollis in which the head is slightly tilted towards either the left or the right side, Ocklenburg et al. (2010) could show that the visual experience associated with head turning is related to handedness. More precisely, children who had visual experience with their right hand more often were stronger lateralized towards the right hand at the age of 8 years. In summary, evidence for early visual experience influencing handedness is strong (see Table 1). Importantly, molecular genetic studies have indeed shown that visual experience generates neuroplasticity via epigenetic influence on the visual cortex (Tiraboschi et al., 2013; Tognini et al., 2015).

2.4.2. Early social environment

Besides visual experience, studies have suggested associations of other childhood factors with handedness. The influence of the early social environment in terms of breastfeeding (Obermann-Borst et al., 2013), socioeconomic status (SES) or parenting (Beach et al., 2016; King et al., 2015; Stringhini et al., 2015) can be transmitted via DNA methylation. Interestingly, the influence of low SES on transcription can be counteracted by maternal warmth (Chen et al., 2011), which highlights the importance of taking into account interactions between environmental factors.

Denny (2012) found that children who experienced breastfeeding for at least one month were significantly less likely to be left-handed at age 7 than children who were not or rarely breastfed. This result is discussed with regard to prolactin and oxytocin release elicited by breastfeeding, which might improve mother-child-interaction. Similarly, Johnston et al. (2010) found the

probability of being left-handed to be reduced by 1.5% in children who have been breastfed. A significant effect of rearing condition on hand preference has also been found in rhesus monkeys, who displayed stronger bias towards the left hand in the tube task when reared in a neonatal nursery than when reared by their biological mother (Bennett et al., 2008). Weaver et al. (2004) found that licking and grooming in rats alters methylation patterns of a glucocorticoid receptor (*GR*) gene promoter in the offspring's hippocampus, implying beneficial epigenetic effects of maternal care on neuronal development. Mother-child-interaction during play seems to differ between right-handed and left-handed mothers: Whereas right-handed mothers exert almost all activities with the right hand and tend to give toys in their infant's right hand, left-handed mothers are less biased regarding their hand use (Michel et al., 2013).

SES has been found to correlate with quality of neighborhood or parental presence. Children classified in lower SES groups were less lateralized in terms of visual, auditory and tactile stimulus processing. Unfortunately, the variable handedness was not investigated in this study (Boles, 2011). However, a large scale study on children's handedness showed that the chance of being left-handed is not significantly associated with family composition, parental employment, or household income, although left-handedness was related to reduced cognitive abilities (Johnston et al., 2009). Interestingly, an effect of ecological challenges on lateralization has been shown in the animal model. Comparing wild poeciliid fish from areas with a high or low number of predators revealed that females from high-predation areas as well as their offspring display stronger consistency of hemispheric bias, i.e. stronger lateralization than females and offspring from low-predation areas (Brown et al., 2007).

In conclusion, evidence from human research concerning early social environment is almost completely restricted to the two studies that unequivocally support a relationship between breastfeeding and handedness (Denny, 2012; Johnston et al., 2010). Despite evidence for a relationship of childhood social status and lateralization, there is no evidence for an association with handedness (see Table 1).

2.5. Education and culture

2.5.1. Schooling

Since many items on hand preference questionnaires require previous exposure, education was hypothesized as influencing handedness direction as measured by these questionnaires. However, early studies did not provide support for any relationship (Ardila et al., 1989; Teng et al., 1979). Connolly and Bishop (1992) found no statistically significant result, but – if any – a trend for uneducated subjects to be more right-handed. Educational background was investigated with regard to handedness in a Papuan non-industrial population. Instead of common handedness preference questionnaires, Geuze et al. (2012) used activities more familiar to the subjects. The authors found that individuals who had attended school had a higher probability of reporting strong right-hand preference, although there was no relationship with hand skill. Similarly, Dronamraju (1975) compared handedness of 431 members of the Koya Doras, Sugalis and Konda Reddis tribes and 86 Hindus. Among the tribe members, who were mostly uneducated, about 15% of males and 8% of females were left-handed, while among the educated Hindus, roundabout 7% of males and 5% of females were left-handed. This is in line with the assumption that school education and writing might promote right-handedness, although evidence is ambiguous (see Table 1).

However, education clearly depends on societal norms, which vary strongly between countries. For example, increased rates of left-handedness over time have been reported for the Netherlands. Here, 100% of left-handers born between 1910 and 1939 reported writing with their right hand, while 100% of left-handers born between 1965 and 1979 reported writing with their left hand, which is most likely due to altered educational attitudes towards left-handedness after 1945 (Beukelaar and Kroonenberg, 1986). For Australia and New Zealand, however, this shift in attitude began already at the end of the 19th century, but took 90 years to complete (Brackenridge, 1981). Medland et al. (2009) confirmed this pattern for both Australian and Dutch samples. In US samples, an increase of left-handedness over the years has also been attributed to a greater degree of lenience towards personal hand preference in schools (Levy, 1974). Taken together, evidence suggests that cultural biases tend to support right-handedness (Barsley, 1970). The overall effects of growing up in different countries are presented in Section 2.5.3. (Cultural influence).

2.5.2. Family

Familial influences on handedness range from model learning via implicit reinforcement for using the right hand to explicit parental instructions and punishment for using the left hand (Laland, 2008). Bryden et al. (1993) assumed that positive reinforcement at specific age stages is capable of inducing right-handedness. Ashton (1982) found that left-handed mothers are more likely than left-handed fathers to have left-handed children, which is attributed to the offspring rather copying the mother in childhood. Similarly, the highest rate of left-handedness were found in school children whose mother was left- and whose father was right-handed (Falek, 1959). Since most mothers were not employed at that time, the author's explanation based on their inexperience of social downsides from being left-handed, so no pressure was exerted on their offspring on changing hands. In contrast, left-handed fathers did not want their children to face the same social stressors, which made them motivate their offspring switching hand preference towards the right hand.

Other studies have collected data on pressure on hand switching: Among university students and faculty members, 3.5% of individuals reported having switched handedness in the past, which was most likely due to school or parental pressure. The highest probability of switching handedness occurred in older subjects, which indicates a decrease in parental pressure on handedness (Leiber and Axelrod, 1981a). In contrast, Porac et al. (1986) found 11.2% of young adults to have experienced hand switching attempts from their parents, mostly before the age of 8 years. Within this group, young women were more liable to external pressure and more often reported successful hand switching. Strong parental encouragement for right-hand use (Konishi et al., 1986) and maternal negative stereotypes about left-handedness (Uwaezuoke et al., 2015) have been reported for Japan and Nigeria in combination with low rates of left-handedness. Almost 90% of Malawian subjects reported that left-handers should be forced to switch hands, especially for greeting, drawing and writing. Most of the converted right-handers reported that parents and close relatives exert pressure regarding right-hand-use (Zverev, 2006). Overall, there is strong evidence for familial influences on handedness (see Table 1). Moreover, these results suggest that there is also a strong cultural influence on pressures regarding left-handedness.

2.5.3. Cultural influence

The overall effect of country on handedness has been affirmed in a review and meta-analysis of 81 samples from 14 countries and over 1 million subjects (Raymond and Pontier, 2004). Similarly, a large international study found the prevalence of left-handedness in terms of writing hand to range from 2.5% in Mexico to 12.8% in Canada (Perelle and Ehrman, 1994). In an attempt to categorize geographical regions, Dawson (1977) proposed that left-

handedness is more common in more permissive countries with a history of hunting than in more restrictive agricultural countries that seek for conformity. However, evidence for history of hunting influencing handedness is restricted to this work. In contrast, a number of earlier as well as more recent studies reports evidence for societal permissiveness influencing handedness. Examples for more permissive countries with relatively high numbers of left-handers are the Netherlands (Beukelaar and Kroonenberg, 1986), the USA and Caribbean countries (Saunders and Campbell, 1985), and Canada (Porac et al., 1986). On the other hand, left-handedness is actively repressed by society in several countries, for example China (Kushner, 2013; Teng et al., 1976, 1979). The same has applied for Muslim African countries like Ivory Coast and Sudan, where the left hand is considered as dirty, although left-hand preference also seems to increase in younger generations (de Agostini et al., 1997). However, a low incidence of left-handedness might not be restricted to Muslim countries, since there are only 3% left-handed school children in Malawi, which is mostly Christian-influenced. Interestingly, 6% of right-handed children reported having switched the dominant hand, which implies natural left-handedness (Zverev, 2004). In Christian Nigerian children, 7.5% were found to be left-handed (Uwaezuoke et al., 2015). Payne (1987) provided weak support for a higher prevalence of left-handedness in Muslim compared to Christian Nigerian subjects, although Muslim subjects insisted more strongly on using the right hand. Similar results have been found in a comparison of Muslims and Hindus in an Indian sample, in which the prevalence of left-handedness was low in both religious groups, but Muslim subjects especially insisted on using the right hand in eating-related activities (Singh and Kindu, 1994; Singh et al., 2001). In Japan, only 3% of individuals were found to be left-handed in the 1970s and 1980s (Hatta and Nakatsuka, 1976; Shimizu and Endo, 1983). Interestingly, left-handedness did increase in the following decade, resulting in a probability of 11% for men and 6% for women to be left-handed (Hatta and Kawakami, 1994). However, only 4% of subjects reported being left-handed in a Korean sample (Kang and Harris, 2000).

Overall, the prevalence of left-handedness is rather low in African and Asian countries compared to the USA, Canada, or Western Europe (Porac et al., 1990). Porac and Martin (2007) found no difference in the prevalence of converted right-handers between Brazilian and Canadian subjects. Two studies found exclusively right-handers in a rural and highly permissive group of Tucano (Colombia). The subjects were less rigid in their answers and rarely indicated to “always” use the right hand for certain activities. It might be that a more permissive culture does not necessarily promote a higher frequency of left-handedness, but at times results in more flexibility in hand use (Ardila et al., 1989; Bryden et al., 1993). Overall, the prevalence of left-handedness in South American countries remains unclear, while there is a clear pattern of a higher frequency in North America and Western Europa and a low frequency in Asia and Africa. Kushner (2013) concluded that being left-handed results in stigma for about two thirds of the world’s population. Evidence for cultural influence on handedness is very strong (see Table 1).

3. Possible molecular mechanisms

A major limitation of previous studies investigating the influence of non-genetic factors on hemispheric asymmetries is that they exclusively focused environment and behavior, while molecular mechanisms representing the link between those two have been neglected in human research so far.

Geschwind and Miller (2001) introduced the idea that hemispheric asymmetries have their roots in asymmetrical gene expression in the developing central nervous system. Indeed, it has been shown that specific genes involved in gene expression regulation, signal transduction, and cortical development show differential expression in the left and right human fetal cortex (Sun et al., 2005). However, comparing gene expression between analogous regions of two adult human brains revealed symmetric gene expression between cerebral hemispheres (Hawrylycz et al., 2012). Accordingly, Pletikos et al. (2014) reported no gene expression asymmetries from the investigation of 57 brains in different life stages spanning a period from embryonic development to late adulthood. Nevertheless, Karlebach and Francks (2015) hypothesized lateralization of gene expression and performed re-analysis of the two datasets of Hawrylycz et al. (2012) and Pletikos et al. (2014). Instead of investigating anatomical regions across the whole brain, the authors focused on cortical areas directly involved in language production and perception, the superior temporal sulcus and Heschl’s Gyrus. Asymmetrical gene expression was not only found for individual genes, but also especially on the level of functional gene groups. These lateralized functional groups were associated with neuronal electrophysiology, synaptic transmission (especially the G-protein coupled receptor protein signaling pathway), nervous system development, and glutamate receptor activity (Karlebach and Francks, 2015).

In addition to cortical gene expression asymmetries, spinal cord gene expression asymmetries have recently been highlighted as a potential determinant of handedness (de Kovel et al., 2017; Ocklenburg et al., 2017). This suggestion is based on the observation that asymmetric movements of the arms are visible in ultrasound before the motor cortex is functionally connected to the spinal cord via the corticospinal tract (Hepper, 2013; Hepper et al., 1990, 2005; ten Donkelaar et al., 2004), making an exclusively cortical origin of handedness unlikely. Two recent studies (de Kovel et al., 2017; Ocklenburg et al., 2017) compared gene expression in the spinal cord at different time points during embryogenesis. Interestingly, the studies revealed pronounced time-dependent differences in the occurrence of gene expression differences between the left and right spinal cord. The study by Ocklenburg et al. (2017) found that the spinal cord segments innervating hands and arms showed most pronounced gene expression asymmetries at 8 weeks post conception (about 3.29% of investigated genes), with the large majority of genes showing rightward expression asymmetries. Before and after this time point, the amount of expression asymmetries was considerably lower (de Kovel et al., 2017; Ocklenburg et al., 2017), suggesting a critical time window in which spinal cord gene expression asymmetries affect neural development. Interestingly, 8 weeks post conception is also the starting point of asymmetrical prenatal hand movements, with about 85% of embryos showing a preference to move the right hand more often than the left at this time point (de Vries et al., 1985). These findings suggest an influence of prenatal environmental factors on gene expression asymmetries that might start in the spinal cord and are transferred to the cortex. The role of environmental factors for the establishment of hemispheric asymmetries has also been revealed in bird models. Here, it has been shown that lateralized light stimulation through the eggshell induces structural asymmetries in the brain during a critical phase during late incubation, e.g. between embryonic days 17 to 21 in chicken and embryonic days 15 to 17 in pigeons (Manns and Güntürkün, 2009; Ströckens et al., 2013a).

It is important to notice at this point that a central role for prenatal asymmetries in gene expression does not preclude prenatal, early experience, or cultural factors being causally important to the development of handedness; rather, such asymmetries could be a critical part of the mechanism by which these environmental factors exert their influence. This is in line

with animal models implying that adult motor behavior is also affected by changes in gene expression. Cheung et al. (2013) compared motor cortical gene expression before and after training rats a motor skill task and found genes associated with synaptic plasticity and synaptogenesis to change expression patterns in dependence on motor skills. Moreover, synaptic rewiring has been shown to occur and persist in the contralateral motor cortex after motor skill learning in mice (Xu et al., 2009). Epigenetic programing might be the underlying factor that alters behavior not only at the individual level, but also transgenerationally (Ambeskovic et al., 2017). Future research on non-genetic influences on handedness should therefore explore by which epigenetic mechanisms environmental factors modulate the development and function of brain areas relevant for individual lateralization.

3.1. DNA methylation

Particularly intrauterine stressors have been shown to have a strong impact on DNA methylation (Turecki and Meaney, 2016). Klengel et al. (2013) revealed that the amount of DNA methylation of the FK506 binding protein 5 gene *FKBP5* (a gene important for the regulation of stress reaction) is associated to right, but not left hippocampus volume, which indicates an involvement of DNA methylation in the development of structural asymmetries.

So far, two groups have investigated the association of DNA methylation obtained from buccal cells and handedness in healthy human adults. The first paper found higher DNA methylation levels in a block of CpG sites in the *LRRTM1* promoter region to be associated with less consistent handedness (Leach et al., 2014). The most recent paper found that DNA methylation in the promoter regions of three asymmetrically expressed genes (*LMO4* as asymmetrically expressed in the study by Sun et al. (2005), and *MT2A* and *STK35* as asymmetrically expressed in the study by Ocklenburg et al. (2017)) significantly predicted left- or right-handedness. DNA methylation in the promoter regions of *LRRTM1* and *NEUROD6* tentatively predicted handedness direction (Schmitz et al., 2017).

Moreover, a role of CpG site methylation for handedness development was also suggested in the aforementioned spinal cord gene expression asymmetry study by Ocklenburg et al. (2017). Here, it was shown that at 8 weeks post conception when the most pronounced gene expression asymmetries were observed, there were also pronounced left-right differences in DNA methylation in the same spinal cord tissue. While 31,278 CpG sites showed significantly higher DNA methylation in the left spinal cord, only 8615 CpG sites showed rightward DNA methylation asymmetries (see Fig. 2B–C). Integrative analysis of gene expression and DNA methylation data revealed that 27% of asymmetrically expressed genes were asymmetrically methylated (within the gene and 1500 nucleotides upstream) towards the opposite direction (see Fig. 2D), indicating an important role of DNA methylation for the occurrence of spinal cord gene expression asymmetries.

Moreover, there are a number of studies pointing to an important role of DNA methylation of different genes involved in schizophrenia (Shorter and Miller, 2015), a disorder strongly linked to atypical handedness. Interestingly, reduced DNA methylation of the *LRRTM1* promoter displayed a significant association with psychosis independently of DNA sequence variation (Brucato et al., 2014). The investigation of gene expression and DNA methylation in post-mortem fronto-cortical tissue samples revealed hypomethylation in the *COMT* promoter in schizophrenic and bipolar disorder patients compared to matched healthy controls. Interestingly, *COMT* promoter DNA methylation was strongly asymmetric in controls with higher DNA methylation levels in the left frontal lobe, while this asymmetry was absent in patients. Correspondingly, gene expression was negatively correlated with DNA methylation, which suggests an overexpression of *COMT* in schizophrenia and bipolar disorder patients compared to healthy controls, especially in the left frontal lobe (Abdolmaleky et al., 2006). Since schizophrenia is associated with reduced functional lateralization and might share developmental factors with hemispheric asymmetries (Ocklenburg et al., 2013), these data on candidate genes for handedness might be a hint towards the relevance of DNA methylation in their development.

3.2. Histone modifications

In a candidate gene study on handedness, Ocklenburg et al. (2015b) found that healthy adults homozygous for a haplotype in the SET domain bifurcated 2 gene *SETDB2* were significantly less right-handed than heterozygous subjects. *SETDB2* is especially interesting for epigenetics, because its encoded SET domain containing protein modifies gene expression via histone H3 and probably acts as a histone H3 methyltransferase (Xu et al., 2010), which highlights the importance of investigating the role of not only DNA methylation, but also histone modifications in relation to handedness.

3.3. Post-transcriptional regulation by miRNAs

An important influence of miRNAs on neuronal asymmetry has been proposed in *Caenorhabditis elegans* (*C. elegans*) (Alqadah et al., 2013). The *lsy-6* miRNA controls neuronal asymmetry of chemosensory taste receptor neurons (Cochella and Hobert, 2012; Johnston and Hobert, 2003). Similarly, *mir-71* miRNA influences calcium signaling and induces olfactory neuron asymmetry in *C. elegans* (Hsieh et al., 2012). Findings like these might serve as a basis for understanding the function of miRNAs in higher organisms (Alqadah et al., 2013). For example, Levchenko et al. (2014) sequenced five candidate genes for inducing cerebral asymmetry (*LMO4*, *LRRTM1*, *FOXP2*, *PCDH11X/Y*, and *SRY*) in a sample of patients suffering from schizophrenia and schizotypal disorder and found 17 new variants which are absent in the general population. Investigating the miRNA-bindings sites of the single base pair substitutions within the 3′-UTRs revealed that variations in the untranslated regions of *FOXP2* and *PCDH11X* might create new binding sites for 10 miRNAs (miR-409, miR-1294, miR-373, miR-3616, let-7b, miR-3156-1, miR-944, miR-766, miR-5588, and miR-3074), which might alter mRNA regulation, protein production and finally induce cerebral lateralization (Levchenko et al., 2014). Moreover, spinal gene expression asymmetries in the study by Ocklenburg et al. (2017) were in part triggered by asymmetries in miRNA expression. At 8 weeks post conception, 1.66% of expressed miRNAs were more strongly expressed in the right compared to the left spinal cord (see Fig. 2A). These miRNAs were involved in the TGF-ß signaling pathway, which comprises two key proteins for the establishment of body asymmetries during embryonic development [nodal growth differentiation factor (Nodal) and left-right determination factor (Lefty)] (Mittwoch, 2008; Shiratori and Hamada, 2014). In addition to the variance in gene expression asymmetries explained by DNA methylation patterns, 1% of variance was explained by a combination of miRNA expression and differential DNA methylation and 3% of variance were due to differential miRNA expression alone (see Fig. 2D).

3.4. Other potential mechanisms

Besides DNA methylation, histone modifications and miRNAs, there are other epigenetic mechanisms worth being mentioned. In humans, 15% of X-linked genes escape X-chromosome inactivation, leading to sex differences in transcription and gene expression

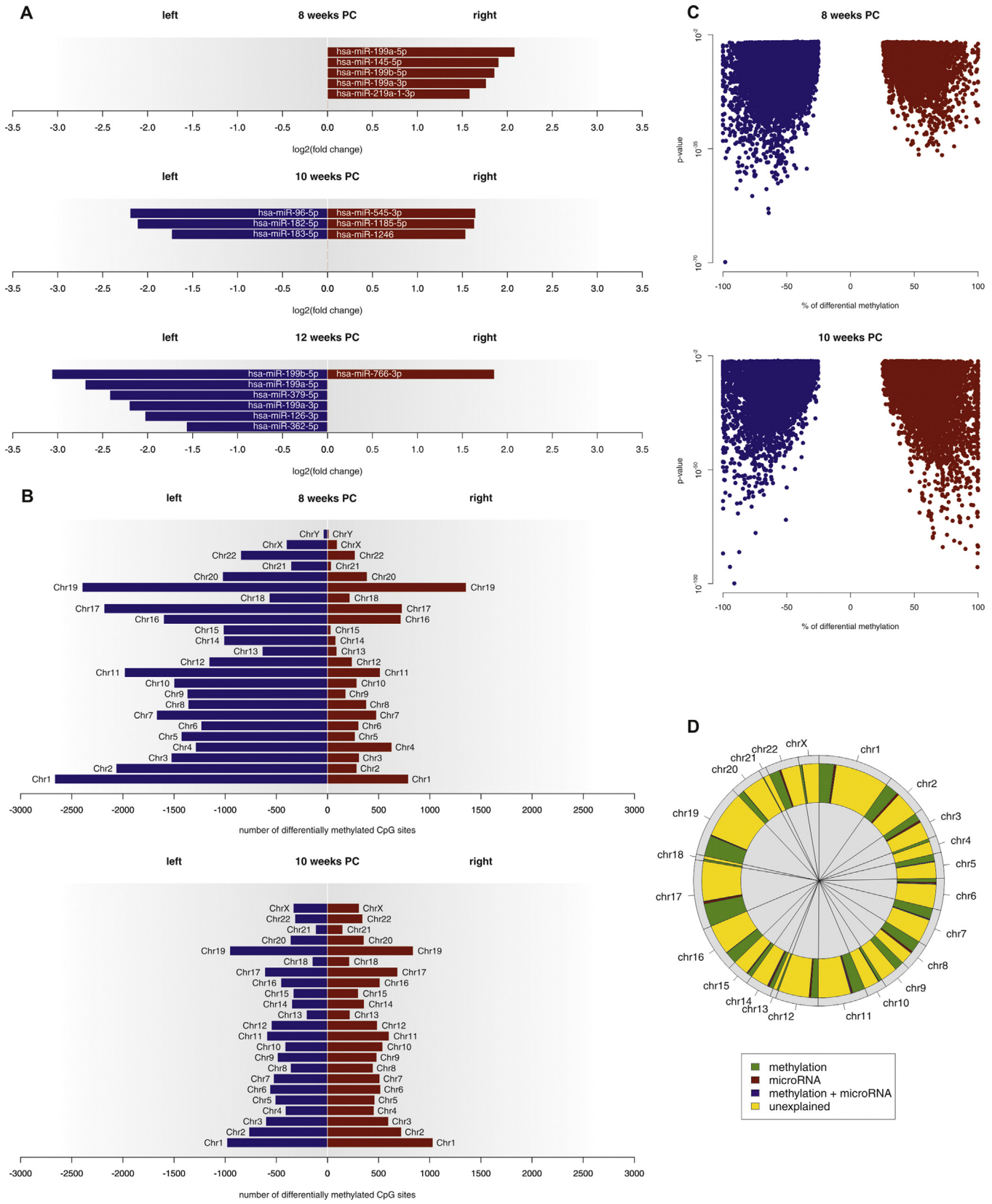

Fig. 2. Regulation of gene expression asymmetries between left and right fetal spinal cord via miRNA expression and DNA methylation at 8, 10, and 12 weeks post conception. (A) miRNA expression asymmetries at different stages of development. (B) Asymmetrical DNA methylation per chromosome at different developmental stages. (C) p-value and amount of asymmetrical DNA methylation. (D) Explanation of variance in asymmetrical gene expression by miRNA expression and/or DNA methylation (within and 1500 nucleotides upstream of the genes). Figure from Ocklenburg et al. (2017), published under a CC-BY license und used in accordance to that license.

(Carrel et al., 1999; Carrel and Willard, 2005). Since X-linked genes have an impact on brain structure (Cutter et al., 2006), this mechanism might be associated to the well-documented sex difference in handedness with a higher probability of left-handedness in men (Papadatou-Pastou et al., 2008). This is also in line with the finding that the androgen receptor *AR* gene is a candidate gene for handedness (Arning et al., 2015).

4. Integrating genes and environment

In conclusion, the integration of genes and environment is essential to fully comprehend the ontogenesis of handedness. Initially, research has focused on either DNA sequence variation or environmental influences. One model integrating genetic and environmental factors has been proposed by Laland et al. (1995). Gene-culture coevolutionary models suggest that selection pressures in the last 100,000 years have favored genetic variants that in term have triggered self-imposed selection pressures like agriculture. Applied on handedness, the authors suggest that right-handedness might have had some evolutionary advantage, which raised the number of right-handed people. This in turn increased the number of people being raised by right-handed parents, who then exert a cultural influence that further increments the incidence of right-handedness. However, since genetic variation in handedness is suggested to have reached an equilibrium, all humans are supposed to have a genetic predisposition of 78% of being right-handed. Growing up with right-handed parents is expected to raise the probability due to parental influence like imitation or direct instruction, whereas growing up with left-handed parents has the opposite effect (Laland et al., 1995). Laland (2017) assumes that shaping of children's hand use could also be mediated by epigenetic mechanisms. This is in line with the theory on the origin of cerebral asymmetry proposed by Crow (2010), postulating a fixed right-shift factor that is present in all individuals and a random epigenetic component that is transmitted over a limited amount of generations. The strand-specific imprinting and segregation model (Klar, 2004) postulates somatic strand-specific imprinting and patterned segregation mechanism to cause asymmetric cell division in embryogenesis. Specifically, the model proposes production of diverging sister chromatids, one of which expresses a hypothetical gene specifying the dominant hemisphere, while this gene is epigenetically silenced in the other chromatid. A hypothetical segregation site induces patterned distribution of these chromatids to direction-specific daughter cells. This is assumed to lead to the development of hemispheric asymmetries (Klar, 2004).

Another model including genes and environment has been proposed by Fagard (2013), who conducted a hypothetical scenario for the combination of both factors. The model is based on a genetic factor establishing a preliminary hand preference that is modified by environmental influences. Specifically, a rudimental, genetically predisposed form of handedness is visible in the human fetus that is strengthened by different reinforcing factors in different developmental stages. Based on the findings by Sun et al. (2005), the author proposes asymmetrical gene expression between the hemispheres as a conceivable neural correlate for this intrinsic factor. Fagard (2013) further proposes that factors like head-turning asymmetries or lying on the left body side are reinforcing right-handedness already in utero, since the fetus is encouraged to move the right hand due to more space or shorter distance to its head. The model proposes that specialization and imitation of close relatives finally lead to stabilization of handedness. This model is compatible with the assumption that these environmental factors exert their influence via epigenetic mechanisms.

Recent research has shown that the understanding of handedness ontogenesis has to be shifted towards an epigenetic approach on the level of DNA methylation, histone modifications and

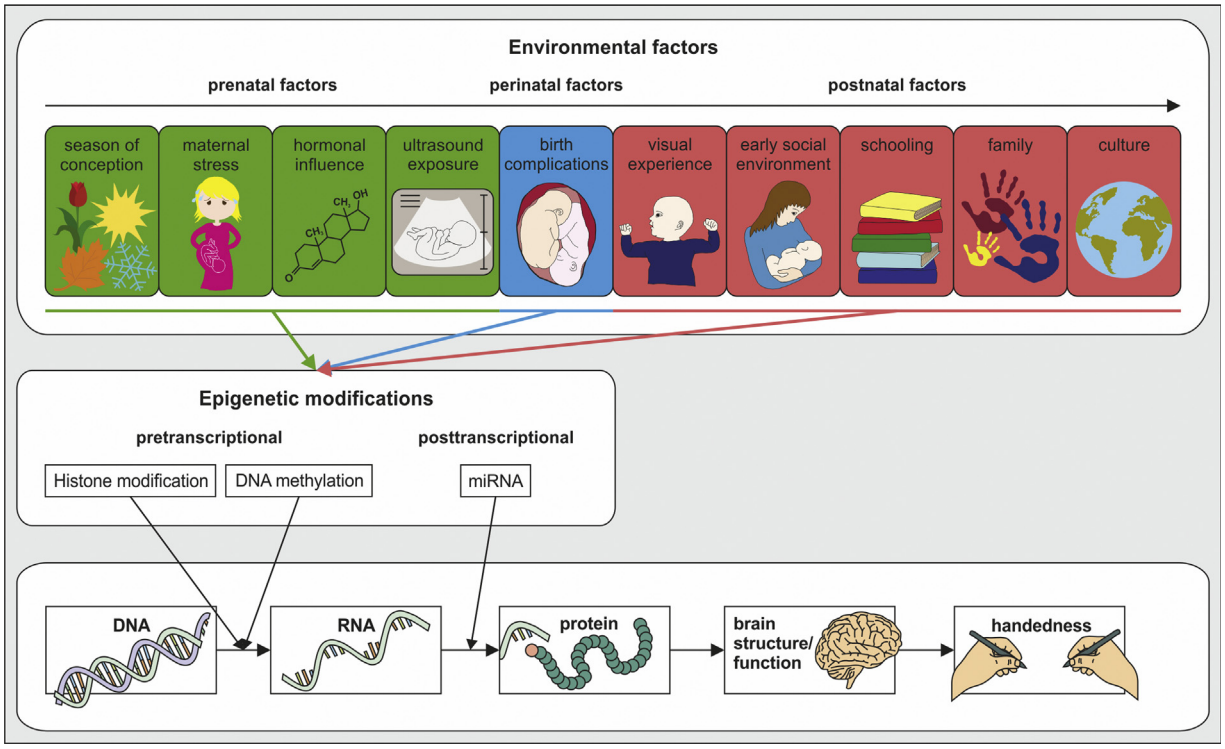

Fig. 3. Proposed model of handedness ontogenesis including all environmental factors previously associated with handedness ontogenesis. These environmental factors might induce epigenetic modifications, thereby influencing protein synthesis via pre- or posttranscriptional mechanisms, which affects brain structure and/or function and ultimately handedness.

miRNAs. Instead of DNA variations alone, gene expression and protein synthesis might be mediating factors when it comes to the development of complex traits such as handedness (see Fig. 3). The key in exploring its ontogenesis is not to determine whether genes or environment matter more for handedness development. 'Nature or nurture?' might be the wrong question to ask; instead, their complex interaction must be taken into account. Future studies on handedness ontogenesis should therefore incorporate the evaluation of environmental factors and DNA methylation analysis in order to evaluate epigenetic effects on handedness. Another interesting approach is the inclusion of other forms of lateralization into future research. For example, the relationship between handedness and language lateralization or gestures is still not well understood (Knecht et al., 2000; Kroliczak et al., 2011; Somers et al., 2015a). A model of partial pleiotropy with shared as well as independent ontogenetic influencing factors has been proposed by Ocklenburg et al. (2014).

Another approach potentially leading to an advanced understanding of hemispheric asymmetries will be the establishment of combining genetic and imaging techniques, e.g. magnetic resonance imaging (MRI) for structural studies of hemispheric asymmetries. In two imaging genetics studies, the *APOE-4* allele of the apolipoprotein E gene *APOE* was associated to a thinner left-hemispheric entorhinal cortex (Donix et al., 2013; Shaw et al., 2007). A recent GWAS found a SNP in the vitrin gene *VIT* (rs11691187) to account for a large proportion of interindividual cortical surface area asymmetry, which was confirmed in an independent sample (Tadayon et al., 2016). Another study has yielded genes involved in 'steroid hormone receptor activity' and 'steroid metabolic process' as promising candidate genes for planum temporale asymmetry (Guadalupe et al., 2015). However, all of these studies included only right-handed participants or did not report participants' handedness. Thus, left-handed participants should be incorporated in future studies (Willems et al., 2014). Interestingly, *VIT* gene expression in samples from left anterior cingulate cortex showed a positive correlation with overall brain asymmetry in donors of the Allen Human Brain Atlas (Tadayon et al., 2016). This connection illustrates that imaging epigenetics is a promising strategy to shed light on the ontogenesis of hemispheric asymmetries. The first study integrating epigenetics and imaging methods investigated DNA methylation of a SNP in *COMT*. Reduced DNA methylation interacted with lifetime stress to modulate brain activity during a working memory task (Ursini et al., 2011). This study showed the first evidence that DNA methylation (in a gene previously associated with handedness) and non-genetic factors induce alterations in brain function (Wiers, 2012). In the recent years, imaging epigenetics have become a powerful tool in the investigation of human brain development (Lista et al., 2013). In a recent study, Sparrow et al. (2016) performed epigenome-wide analysis of DNA methylation and diffusion magnetic resonance imaging (dMRI) in preterm born vs. control infants and found differential DNA methylation in 25 gene bodies and 58 promoters of protein-coding genes. Most importantly, the authors found a relationship between DNA methylation and right corticospinal tract shape, inferring that an effect of preterm birth on brain structure is carried out via altered DNA methylation. The fact that only one side of the corticospinal tract is affected by epigenetic variation is highly interesting in the context of the ontogenesis of hemispheric asymmetries.

Recently, another interesting approach has successfully investigated epigenetic activity in the living human brain for the first time (Wey et al., 2016). Histone deacetylases (HDACs) regulate gene expression by removing acetyl groups from histones, thereby reducing transcription. Using positron emission tomography (PET) with [^{11}C]Martinostat, a radiochemical acting as a HDAC inhibitor, the authors could show differing distribution patterns between gray and white matter and between brain areas. The investigation of epigenetic processes in living human participants will provide a powerful technique for future studies to reveal mechanisms of the epigenetic background of brain structure and function in general and specifically for shedding light on the ontogenesis of hemispheric asymmetries and handedness.

Conflict of interest

The authors declare no conflicts of interest.

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References

Abdolmaleky, H.M., Cheng, K.-H., Faraone, S.V., Wilcox, M., Glatt, S.J., Gao, F., Smith, C.L., Shafa, R., Aeali, B., Carnevale, J., Pan, H., Papageorgis, P., Ponte, J.F., Sivaraman, V., Tsuang, M.T., Thiagalingam, S., 2006. Hypomethylation of MB-COMT promoter is a major risk factor for schizophrenia and bipolar disorder. Hum. Mol. Genet. 15, 3132–3145.
Abdolmaleky, H.M., Zhou, J.-R., Thiagalingam, S., 2015. An update on the epigenetics of psychotic diseases and autism. Epigenomics 7, 427–449.
Abel, E.L., Kruger, M.L., 2004. Relation of handedness with season of birth of professional baseball players revisited. Percept. Mot. Skills 98, 44–46.
Allen, A.J., Griss, M.E., Folley, B.S., Hawkins, K.A., Pearlson, G.D., 2009. Endophenotypes in schizophrenia: a selective review. Schizophr. Res. 109, 24–37.
Alonso, J., Castellano, M.A., Rodriguez, M., 1991. Behavioral lateralization in rats: prenatal stress effects on sex differences. Brain Res. 539, 45–50.
Alqadah, A., Hsieh, Y.-W., Chuang, C.-F., 2013. microRNA function in left-right neuronal asymmetry: perspectives from C. elegans. Front. Cell. Neurosci. 7, 158.
Ambeskovic, M., Soltanpour, N., Falkenberg, E.A., Zucchi, F.C.R., Kolb, B., Metz, G.A.S., 2017. Ancestral exposure to stress generates new behavioral traits and a functional hemispheric dominance shift. Cereb. Cortex 27, 2126–2138.
Annett, M., Ockwell, A., 1980. Birth order, birth stress and handedness. Cortex 16, 181–187.
Annett, M., 1998. Handedness and cerebral dominance: the right shift theory. J. Neuropsychiatry Clin. Neurosci. 10, 459–469.
Ardila, A., Ardila, O., Bryden, M.P., Ostrosky, F., Rosselli, M., Steenhuis, R., 1989. Effects of cultural background and education on handedness. Neuropsychologia 27, 893–897.
Armour, J.A., Davison, A., McManus, I.C., 2014. Genome-wide association study of handedness excludes simple genetic models. Heredity 112, 221–225.
Arning, L., Ocklenburg, S., Schulz, S., Ness, V., Gerding, W.M., Hengstler, J.G., Falkenstein, M., Epplen, J.T., Güntürkün, O., Beste, C., 2013. VNTR polymorphism is associated with degree of handedness but not direction of handedness. PLoS One 8, e67251.
Arning, L., Ocklenburg, S., Schulz, S., Ness, V., Gerding, W.M., Hengstler, J.G., Falkenstein, M., Epplen, J.T., Güntürkün, O., Beste, C., 2015. Handedness and the X chromosome: the role of androgen receptor CAG-repeat length. Sci. Rep. 5, 8325.
Ashton, G.C., 1982. Handedness: an alternative hypothesis. Behav. Genet. 12, 125–147.
Aslibekyan, S., Dashti, H.S., Tanaka, T., Sha, J., Ferrucci, L., Zhi, D., Bandinelli, S., Borecki, I.B., Absher, D.M., Arnett, D.K., Ordovas, J.M., 2014. PRKCZ methylation is associated with sunlight exposure in a North American but not a Mediterranean population. Chronobiol. Int. 31, 1034–1040.
Azzi, A., Dallmann, R., Casserly, A., Rehrauer, H., Patrignani, A., Maier, B., Kramer, A., Brown, S.A., 2014. Circadian behavior is light-reprogrammed by plastic DNA methylation. Nat. Neurosci. 17, 377–382.
Babenko, O., Kovalchuk, I., Metz, G.A.S., 2015. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci. Biobehav. Rev. 48, 70–91.
Badian, N.A., 1983. Birth order, maternal age, season of birth, and handedness. Cortex 19, 451–463.
Bailey, L.M., McKeever, W.F., 2004. A large-scale study of handedness and pregnancy/birth risk events: implications for genetic theories of handedness. Laterality 9, 175–188.
Bakan, P., Dibb, G., Reed, P., 1973. Handedness and birth stress. Neuropsychologia 11, 363–366.
Bakan, P., 1971. Handedness and birth order. Nature 229, 195.
Bakan, P., 1977. Left handedness and birth order revisited. Neuropsychologia 15, 837–839.
Bakan, P., 1991. Handedness and maternal smoking during pregnancy. Int. J. Neurosci. 56, 161–168.

Baker, J., Kungl, A.-M., Pabst, J., Strauß, B., Büsch, D., Schorer, J., 2013. Your fate is in your hands? Handedness, digit ratio (2D:4D), and selection to a national talent development system. Laterality 18, 710–718.
Barnes, F., 1975. Temperament, adaptability, and left-handers. New Sci. 67, 202–203.
Barrett, D., Greenwood, J.G., McCullagh, J.F., 2006. Kissing laterality and handedness. Laterality 11, 573–579.
Barsley, Michael, 1970. Left-handed Man in a Right-handed World. Pitman, London.
Beach, S.R.H., Lei, M.-K., Brody, G.H., Kim, S., Barton, A.W., Dogan, M.V., Philibert, R. A., 2016. Parenting, socioeconomic status risk, and later young adult health: exploration of opposing indirect effects via DNA methylation. Child Dev. 87, 111–121.
Beaton, A.A., Rudling, N., Kissling, C., Taurines, R., Thome, J., 2011. Digit ratio (2D. 4D), salivary testosterone, and handedness. laterality: asymmetries of body. Brain Cogn. 16, 136–155.
Beaton, A.A., 2008. Handedness assessment in studies of seasonal anisotropy. Cortex 44, 97–98.
Behnia, F., Parets, S.E., Kechichian, T., Yin, H., Dutta, E.H., Saade, G.R., Smith, A.K., Menon, R., 2015. Fetal DNA methylation of autism spectrum disorders candidate genes: association with spontaneous preterm birth. Am. J. Obstet. Gynecol. 212 (533), e1–9.
Bennett, A.J., Suomi, S.J., Hopkins, W.D., 2008. Effects of early adverse experiences on behavioural lateralisation in rhesus monkeys (Macaca mulatta). Laterality 13, 282–292.
Berenbaum, S.A., Bryk, K.K., Nowak, N., Quigley, C.A., Moffat, S., 2009. Fingers as a marker of prenatal androgen exposure. Endocrinology 150, 5119–5124.
Beukelaar, L.J., Kroonenberg, P.M., 1986. Changes over time in the relationship between hand preference and writing hand among left-handers. Neuropsychologia 24, 301–303.
Biederman, 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, 171–184.
Bishop, D.V.M., 1990. Handedness and Developmental Disorder. Mac Keith Press; Blackwell Scientific Publications; Lippincott, Oxford, Philadelphia (Clinics in developmental medicine, no. 110).
Bloss, C.S., Delis, D.C., Salmon, D.P., Bondi, M.W., 2010. APOE genotype is associated with left-handedness and visuospatial skills in children. Neurobiol. Aging 31, 787–795.
Boersma, G.J., Lee, R.S., Cordner, Z.A., Ewald, E.R., Purcell, R.H., Moghadam, A.A., Tamashiro, K.L., 2014. Prenatal stress decreases Bdnf expression and increases methylation of Bdnf exon IV in rats. Epigenetics 9, 437–447.
Boles, D.B., 2011. Socioeconomic status, a forgotten variable in lateralization development. Brain Cogn. 76, 52–57.
Bourrat, P., Lu, Q., Jablonka, E., 2017. Why the missing heritability might not be in the DNA. Bioessays 39.
Brackenridge, C.J., 1981. Secular variation in handedness over ninety years. Neuropsychologia 19, 459–462.
Braithwaite, E.C., Kundakovic, M., Ramchandani, P.G., Murphy, S.E., Champagne, F.A., 2015. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. Epigenetics 10, 408–417.
Brandler, W.M., Paracchini, S., 2014. The genetic relationship between handedness and neurodevelopmental disorders. Trends Mol. Med. 20, 83–90.
Brandler, W.M., Morris, A.P., Evans, D.M., Scerri, T.S., Kemp, J.P., Timpson, N.J., St Pourcain, B., Smith, G.D., Ring, S.M., Stein, J., Monaco, A.P., Talcott, J.B., Fisher, S. E., Webber, C., Paracchini, S., 2013. Common variants in left/right asymmetry genes and pathways are associated with relative hand skill. PLoS Genet. 9, e1003751.
Breedlove, S.M., 2010. Minireview: organizational hypothesis: instances of the fingerpost. Endocrinology 151, 4116–4122.
Brenner, A.V., Linet, M.S., Shapiro, W.R., Selker, R.G., Fine, H.A., Black, P.M., Inskip, P. D., 2004. Season of birth and risk of brain tumors in adults. Neurology 63, 276–281.
Brown, W.M., Hines, M., Fane, B.A., Breedlove, S.M., 2002. Masculinized finger length patterns in human males and females with congenital adrenal hyperplasia. Horm. Behav. 42, 380–386.
Brown, C., Western, J., Braithwaite, V.A., 2007. The influence of early experience on, and inheritance of, cerebral lateralization. Anim. Behav. 74, 231–238.
Brucato, N., DeLisi, L.E., Fisher, S.E., Francks, C., 2014. Hypomethylation of the paternally inherited LRRTM1 promoter linked to schizophrenia. Am. J. Med. Genet. B Neuropsychiatr. Genet. 165B, 555–563.
Bryden, M.P., Ardila, A., Ardila, O., 1993. Handedness in native amazonians. Neuropsychologia 31, 301–308.
Bryden, M.P., McManus, I.C., Bulmanfleming, M.B., 1994. Evaluating the empirical support for the Geschwind-Behan-Galaburda model of cerebral lateralization. Brain Cogn. 26, 103–167.
Cariaga-Martinez, A., Saiz-Ruiz, J., Alelu-Paz, R., 2016. From linkage studies to epigenetics: what we know and what we need to know in the neurobiology of schizophrenia. Front. Neurosci. 10, 202.
Carlsson, G., Hugdahl, K., Uvebrant, P., Wiklund, L.M., von Wendt, L., 1992. Pathological left-handedness revisited: dichotic listening in children with left vs right congenital hemiplegia. Neuropsychologia 30, 471–481.
Carrel, L., Willard, H.F., 2005. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434, 400–404.
Carrel, L., Cottle, A.A., Goglin, K.C., Willard, H.F., 1999. A first-generation X-inactivation profile of the human X chromosome. Proc. Natl. Acad. Sci. U. S. A. 96, 14440–14444.
Carter-Saltzman, L., 1980. Biological and sociocultural effects on handedness: comparison between biological and adoptive families. Science 209, 1263–1265.
Chapman, H.L., Grimshaw, G.M., Nicholls, M.E.R., 2011. Going beyond students: an association between mixed-hand preference and schizotypy subscales in a general population. Psychiatry Res. 187, 89–93.
Chen, E., Miller, G.E., Kobor, M.S., Cole, S.W., 2011. Maternal warmth buffers the effects of low early-life socioeconomic status on pro-inflammatory signaling in adulthood. Mol. Psychiatry 16, 729–737.
Chen, M., Baumbach, J., Vandin, F., Rottger, R., Barbosa, E., Dong, M., Frost, M., Christiansen, L., Tan, Q., 2016. Differentially methylated genomic regions in birth-weight discordant twin pairs. Ann. Hum. Genet. 80, 81–87.
Cheung, V.K., Deboer, C., Hanson, E., Tunesi, M., D'Onofrio, M., Arisi, I., Brandi, R., Cattaneo, A., Goosens, K.A., 2013. Gene expression changes in the motor cortex mediating motor skill learning. PLoS One 8, e61496.
Chi, J.G., Dooling, E.C., Gilles, F.H., 1977a. Gyral development of the human brain. Ann. Neurol. 1, 86–93.
Chi, J.G., Dooling, E.C., Gilles, F.H., 1977b. Left-right asymmetries of the temporal speech areas of the human fetus. Arch. Neurol. 34, 346–348.
Clark, M.M., Crews, D., Galef Jr, B.G., 1991. Concentrations of sex steroid hormones in pregnant and fetal Mongolian gerbils. Physiol. Behav. 49, 239–243.
Clark, M.M., Robertson, R.K., Galef Jr, B.G., 1993. Intrauterine position effects on sexually dimorphic asymmetries of Mongolian gerbils: testosterone, eye opening, and paw preference. Dev. Psychobiol. 26, 185–194.
Clark, M.M., Robertson, R.K., Galef Jr, B.G., 1996. Effects of perinatal testosterone on handedness of gerbils: support for part of the Geschwind-Galaburda hypothesis. Behav. Neurosci. 110, 413–417.
Clopton, N.A., Duvall, T., Ellis, B., Musser, M., Varghese, S., 2000. Investigation of trunk and extremity movement associated with passive head turning in newborns. Phys. Ther. 80, 152–159.
Cochella, L., Hobert, O., 2012. Embryonic priming of a miRNA locus predetermines postmitotic neuronal left/right asymmetry in C. elegans. Cell 151, 1229–1242.
Coe, C.L., Lulbach, G.R., Schneider, M.L., 2002. Prenatal disturbance alters the size of the corpus callosum in young monkeys. Dev. Psychobiol. 41, 178–185.
Colby, K.M., Parkison, C., 1977. Handedness in autistic children. J. Autism Child. Schizophr. 7, 3–9.
Collins, R.L., 1969. On the inheritance of handedness. II. Selection for sinistrality in mice. J. Hered. 60, 117–119.
Collins, R.L., 1975. When left-handed mice live in right-handed worlds. Science 187, 181–184.
Connolly, K.J., Bishop, D.V., 1992. The measurement of handedness: a cross-cultural comparison of samples from England and Papua New Guinea. Neuropsychologia 30, 13–26.
Contestabile, A., Sintoni, S., 2013. Histone acetylation in neurodevelopment. Curr. Pharm. Des. 19, 5043–5050.
Coren, S., 1990. Left-handedness in offspring as a function of maternal age at parturition. N. Engl. J. Med. 322, 1673.
Coren, S., 1995. Family patterns in handedness: evidence for indirect inheritance mediated by birth stress. Behav. Genet. 25, 517–524.
Coryell, J., Henderson, A., 1979. Role of the asymmetrical tonic neck reflex in hand visualization in normal infants. Am. J. Occup. Ther. 33, 255–260.
Coryell, J.F., Michel, G.F., 1978. How supine postural preferences of infants can contribute toward the development of handedness. Infant Behav. Dev. 1, 245–257.
Cosenza, R.M., Mingoti, S.A., 1995. Season of birth and handedness revisited. Percept. Mot. Skills 81, 475–480.
Crow, T.J., 1997. Schizophrenia as failure of hemispheric dominance for language. Trends Neurosci. 20, 339–343.
Crow, T.J., 2010. A theory of the origin of cerebral asymmetry: epigenetic variation superimposed on a fixed right-shift. Laterality 15, 289–303.
Cutter, W.J., Daly, E.M., Robertson, D.M.W., Chitnis, X.A., van Amelsvoort, T.A.M.J., Simmons, A., Ng, V.W.K., Williams, B.S., Shaw, P., Conway, G.S., Skuse, D.H., Collier, D.A., Craig, M., Murphy, D.G.M., 2006. Influence of X chromosome and hormones on human brain development: a magnetic resonance imaging and proton magnetic resonance spectroscopy study of Turner syndrome. Biol. Psychiatry 59, 273–283.
Dalton, V.S., Kolshus, E., McLoughlin, D.M., 2014. Epigenetics and depression: return of the repressed. J. Affect. Disord. 155, 1–12.
Davies, G., Welham, J., Chant, D., Torrey, E.F., McGrath, J., 2003. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. Schizophr. Bull. 29, 587–593.
Dawson, J.L., 1977. Alaskan Eskimo hand, eye, auditory dominance and cognitive style. Psychologia 20, 121–135.
Day, J.J., Kennedy, A.J., Sweatt, J.D., 2015. DNA methylation and its implications and accessibility for neuropsychiatric therapeutics. Annu. Rev. Pharmacol. Toxicol. 55, 591–611.
de Agostini, M., Khamis, A.H., Ahui, A.M., Dellatolas, G., 1997. Environmental influences in hand preference: an African point of view. Brain Cogn. 35, 151–167.
Dellatolas, G., Luciani, S., Castresana, A., Rémy, C., Jallon, P., Laplane, D., Bancaud, J., 1993. Pathological left-handedness: left-handedness correlatives in adult epileptics. Brain 116 (Pt 6), 1565–1574.
de Kovel, C.G.F., Lisgo, S., Karlebach, G., Ju, J., Cheng, G., Fisher, S.E., Francks, C., 2017. Left-right asymmetry of maturation rates in human embryonic neural development. Biol. Psychiatry 82, 204–212.
Denny, K., 2009. Handedness and depression: evidence from a large population survey. Laterality 14, 246–255.

Denny, K., 2011. Handedness and drinking behaviour. Br. J. Health Psychol. 16, 386–395.
Denny, K., 2012. Breastfeeding predicts handedness. Laterality 17, 361–368.
de Vries, J.I., Visser, G.H., Prechtl, H.F., 1985. The emergence of fetal behaviour. II. Quantitative aspects. Early Hum. Dev. 12, 99–120.
Donix, M., Burggren, A.C., Scharf, M., Marschner, K., Suthana, N.A., Siddarth, P., Krupa, A.K., Jones, M., Martin-Harris, L., Ercoli, L.M., Miller, K.J., Werner, A., von Kummer, R., Sauer, C., Small, G.W., Holthoff, V.A., Bookheimer, S.Y., 2013. APOE associated hemispheric asymmetry of entorhinal cortical thickness in aging and Alzheimer's disease. Psychiatry Res. 214, 212–220.
Donnot, J., Vauclair, J., 2007. Infant holding preferences in maternity hospitals: testing the hypothesis of the lateralized perception of emotions. Dev. Neuropsychol. 32, 881–890.
Downes, J.C., Birsoy, B., Chipman, K.C., Rothman, J.H., 2012. Handedness of a motor program in C: elegans is independent of left-right body asymmetry. PLoS One 7, e52138.
Dragovic, M., Hammond, G., 2005. Handedness in schizophrenia: a quantitative review of evidence. Acta Psychiatr. Scand. 111, 410–419.
Drea, C.M., Wallen, K., Akinbami, M.A., Mann, D.R., 1995. Neonatal testosterone and handedness in yearling rhesus monkeys (Macaca mulatta). Physiol. Behav. 58, 1257–1262.
Dronamraju, K.R., 1975. Frequency of left-handedness among the Andhra Pradesh people. Acta Genet. Med. Gemellol. 24, 161–162.
Ehrlichman, H., Zoccolotti, P., Owen, D., 1982. Perinatal factors in hand and eye preference: data from the Collaborative Perinatal Project. Int. J. Neurosci. 17, 17–22.
Eichler, E.E., Flint, J., Gibson, G., Kong, A., Leal, S.M., Moore, J.H., Nadeau, J.H., 2010. Missing heritability and strategies for finding the underlying causes of complex disease. Nat. Rev. Genet. 11, 446–450.
Elias, L.J., Saucier, D.M., Guylee, M.J., 2001. Handedness and depression in university students: a sex by handedness interaction. Brain Cogn. 46, 125–129.
Elkadi, S., Nicholls, M.E., Clode, D., 1999. Handedness in opposite and same-sex dizygotic twins: testing the testosterone hypothesis. Neuroreport 10, 333–336.
Eriksson, N., Macpherson, J.M., Tung, J.Y., Hon, L.S., Naughton, B., Saxonov, S., Avey, L., Wojcicki, A., Pe'er, I., Mountain, J., 2010. Web-based, participant-driven studies yield novel genetic associations for common traits. PLoS Genet. 6, e1000993.
Fagard, J., 2013. The nature and nurture of human infant hand preference. Ann. N. Y. Acad. Sci. 1288, 114–123.
Falek, A., 1959. Handedness: a family study. Am. J. Hum. Genet. 11, 52–62.
Feldman, M.W., Otto, S.P., 1997. Twin studies, heritability, and intelligence. Science 278, 1383–1384 author reply 1386–7.
Fink, B., Manning, J.T., Neave, N., Tan, U., 2004. Second to fourth digit ratio and hand skill in Austrian children. Biol. Psychol. 67, 375–384.
Forrester, G.S., Pegler, R., Thomas, M.S.C., Mareschal, D., 2014. Handedness as a marker of cerebral lateralization in children with and without autism. Behav. Brain Res. 268, 14–21.
Foundas, A.L., Corey, D.M., Angeles, V., Bollich, A.M., Crabtree-Hartman, E., Heilman, K.M., 2003. Atypical cerebral laterality in adults with persistent developmental stuttering. Neurology 61, 1378–1385.
Foundas, A.L., Bollich, A.M., Feldman, J., Corey, D.M., Hurley, M., Lemen, L.C., Heilman, K.M., 2004. Aberrant auditory processing and atypical planum temporale in developmental stuttering. Neurology 63, 1640–1646.
Fox, N., Lewis, M., 1982. Motor asymmetries in preterm infants: effects of prematurity and illness. Dev. Psychobiol. 15, 19–23.
Francks, C., Maegawa, S., Lauren, J., Abrahams, B.S., Velayos-Baeza, A., Medland, S.E., Colella, S., Groszer, M., McAuley, E.Z., Caffrey, T.M., Timmusk, T., Pruunsild, P., Koppel, I., Lind, P.A., Matsumoto-Itaba, N., Nicod, J., Xiong, L., Joober, R., Enard, W., Krinsky, B., Nanba, E., Richardson, A.J., Riley, B.P., Martin, N.G., Strittmatter, S. M., Moller, H.-J., Rujescu, D., St Clair, D., Muglia, P., Roos, J.L., Fisher, S.E., Wade-Martins, R., Rouleau, G.A., Stein, J.F., Karayiorgou, M., Geschwind, D.H., Ragoussis, J., Kendler, K.S., Airaksinen, M.S., Oshimura, M., DeLisi, L.E., Monaco, A.P., 2007. LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. Mol. Psychiatry 12, 1129–1139 (1057).
Frasnelli, E., Vallortigara, G., Rogers, L.J., 2012. Left-right asymmetries of behaviour and nervous system in invertebrates. Neurosci. Biobehav. Rev. 36, 1273–1291.
Fride, E., Weinstock, M., 1989. Alterations in behavioral and striatal dopamine asymmetries induced by prenatal stress. Pharmacol. Biochem. Behav. 32, 425–430.
Güntürkün, O., 2003. Human behaviour: adult persistence of head-turning asymmetry. Nature 421, 711.
Gaillard, F., Satz, P., 1989. Handedness and reading disability: a developmental study. Arch. Clin. Neuropsychol. 4, 63–69.
Geerdink, J.J., Hopkins, B., Hoeksma, J.B., 1994. The development of head position preference in preterm infants beyond term age. Dev. Psychobiol. 27, 153–168.
Geschwind, N., Behan, P., 1982. Left-handedness: association with immune disease, migraine, and developmental learning disorder. Proc. Natl. Acad. Sci. U. S. A. 79, 5097–5100.
Geschwind, N., Galaburda, A.M., 1985a. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch. Neurol. 42, 428–459.
Geschwind, N., Galaburda, A.M., 1985b. Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. Arch. Neurol. 42, 521–552.
Geschwind, N., Galaburda, A.M., 1985c. Cerebral lateralization. Biological mechanisms, associations, and pathology: III. A hypothesis and a program for research. Arch. Neurol. 42, 634–654.
Geschwind, D.H., Miller, B.L., 2001. Molecular approaches to cerebral laterality. Development and neurodegeneration. Am. J. Med. Genet. 101, 370–381.
Geuze, R.H., Schaafsma, S.M., Lust, J.M., Bouma, A., Schiefenhövel, W., Groothuis, T.G. G., 2012. Plasticity of lateralization: schooling predicts hand preference but not hand skill asymmetry in a non-industrial society. Neuropsychologia 50, 612–620.
Ghanizadeh, A., 2013. Lack of association of handedness with inattention and hyperactivity symptoms in ADHD. J. Atten. Disord. 17, 302–307.
Gilger, J.W., Pennington, B.F., Green, P., Smith, S.M., Smith, S.D., 1992. Reading disability, immune disorders and non-right-handedness: twin and family studies of their relations. Neuropsychologia 30, 209–227.
Gillam, L., McDonald, R., Ebling, F.J.P., Mayhew, T.M., 2008. Human 2D (index) and 4D (ring) finger lengths and ratios: cross-sectional data on linear growth patterns, sexual dimorphism and lateral asymmetry from 4 to 60 years of age. J. Anat. 213, 325–335.
Glover, V., O'Connor, T.G., Heron, J., Golding, J., 2004. Antenatal maternal anxiety is linked with atypical handedness in the child. Early Hum. Dev. 79, 107–118.
Grimshaw, G.M., Bryden, M.P., Finegan, J.-A.K., 1995. Relations between prenatal testosterone and cerebral lateralization in children. Neuropsychology 9, 68–79.
Guadalupe, T., Zwiers, M.P., Wittfeld, K., Teumer, A., Vasquez, A.A., Hoogman, M., Hagoort, P., Fernandez, G., Buitelaar, J., van Bokhoven, H., Hegenscheid, K., Volzke, H., Franke, B., Fisher, S.E., Grabe, H.J., Francks, C., 2015. Asymmetry within and around the human planum temporale is sexually dimorphic and influenced by genes involved in steroid hormone receptor activity. Cortex 62, 41–55.
Guo, H., Ingolia, N.T., Weissman, J.S., Bartel, D.P., 2010. Mammalian microRNAs predominantly act to decrease target mRNA levels. Nature 466, 835–840.
Gutteling, B.M., de Weerth, C., Buitelaar, J.K., 2007. Prenatal stress and mixed-handedness. Pediatr. Res. 62, 586–590.
Hampson, E., Sankar, J.S., 2012. Hand preference in humans is associated with testosterone levels and androgen receptor gene polymorphism. Neuropsychologia 50, 2018–2025.
Hardie, S.M., Wright, L., Clark, L., 2016. Handedness and social anxiety: using Bryden's research as a catalyst to explore the influence of familial sinistrality and degree of handedness. Laterality 1–19.
Hatta, T., Kawakami, A., 1994. Cohort effects in the lateral preference of Japanese people. J. Gen. Psychol. 121, 377–380.
Hatta, T., Nakatsuka, Z., 1976. Note on hand preference of Japanese people. Percept. Mot. Skills 42, 530.
Hawrylycz, M.J., Lein, E.S., Guillozet-Bongaarts, A.L., Shen, E.H., Ng, L., Miller, J.A., van de Lagemaat, L.N., Smith, K.A., Ebbert, A., Riley, Z.L., Abajian, C., Beckmann, C.F., Bernard, A., Bertagnolli, D., Boe, A.F., Cartagena, P.M., Chakravarty, M.M., Chapin, M., Chong, J., Dalley, R.A., Daly, B.D., Dang, C., Datta, S., Dee, N., Dolbeare, T.A., Faber, V., Feng, D., Fowler, D.R., Goldy, J., Gregor, B.W., Haradon, Z., Haynor, D.R., Hohmann, J.G., Horvath, S., Howard, R.E., Jeromin, A., Jochim, J.M., Kinnunen, M., Lau, C., Lazarz, E.T., Lee, C., Lemon, T.A., Li, L., Li, Y., Morris, J.A., Overly, C.C., Parker, P.D., Parry, S.E., Reding, M., Royall, J.J., Schulkin, J., Sequeira, P.A., Slaughterbeck, C.R., Smith, S.C., Sodt, A.J., Sunkin, S.M., Swanson, B.E., Vawter, M. P., Williams, D., Wohnoutka, P., Zielke, H.R., Geschwind, D.H., Hof, P.R., Smith, S. M., Koch, C., Grant, S.G.N., Jones, A.R., 2012. An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 489, 391–399.
Heard, E., Martienssen, R.A., 2014. Transgenerational epigenetic inheritance: myths and mechanisms. Cell 157, 95–109.
Heikkilä, K., Vuoksimaa, E., Oksava, K., Saari-Kemppainen, A., Iivanainen, M., 2011. Handedness in the helsinki ultrasound trial. Ultrasound Obstet. Gynecol. 37, 638–642.
Hepper, P.G., Shahidullah, S., White, R., 1990. Origins of fetal handedness. Nature 347, 431.
Hepper, P.G., Shahidullah, S., White, R., 1991. Handedness in the human fetus. Neuropsychologia 29, 1107–1111.
Hepper, P.G., Wells, D.L., Lynch, C., 2005. Prenatal thumb sucking is related to postnatal handedness. Neuropsychologia 43, 313–315.
Hepper, P.G., 2013. The developmental origins of laterality: fetal handedness. Dev. Psychobiol. 55, 588–595.
Hicks, R.A., Dusek, C., 1980. Is there seasonal variation in the birth of left-handed schoolgirls? Arch. Neurol. 37, 254–255.
Hicks, R.E., Kinsbourne, M., 1976. Human handedness: a partial cross-fostering study. Science 192, 908–910.
Hicks, R.A., Pellegrini, R.J., 1978. Handedness and anxiety. Cortex 14, 119–121.
Hicks, R.A., Dusek, C., Larsen, F., Pellegrini, R.J., 1980a. Reliability of seasonal variation in births of left-handed women. Percept. Mot. Skills 50, 81–82.
Hicks, R.A., Dusek, C., Larsen, F., Williams, S., Pellegrini, R.J., 1980b. Birth complications and the distribution of handedness. Cortex 16, 483–486.
Hirnstein, M., Hugdahl, K., 2014. Excess of non-right-handedness in schizophrenia: meta-analysis of gender effects and potential biases in handedness assessment. Br. J. Psychiatry 205, 260–267.
Hobert, O., 2014. Development of left/right asymmetry in the Caenorhabditis elegans nervous system: from zygote to postmitotic neuron. Genesis 52, 528–543.
Hollins, S.L., Cairns, M.J., 2016. MicroRNA: Small RNA mediators of the brains genomic response to environmental stress. Prog. Neurobiol. 143, 61–81.

Hopkins, W.D., Misiura, M., Pope, S.M., Latash, E.M., 2015. Behavioral and brain asymmetries in primates: a preliminary evaluation of two evolutionary hypotheses. Ann. N. Y. Acad. Sci. 1359, 65–83.
Hopkins, W.D., Meguerditchian, A., Coulon, O., Misiura, M., Pope, S., Mareno, M.C., Schapiro, S.J., 2017. Motor skill for tool-use is associated with asymmetries in Broca's area and the motor hand area of the precentral gyrus in chimpanzees (Pan troglodytes). Behav. Brain Res. 318, 71–81.
Hsieh, Y.-W., Chang, C., Chuang, C.-F., 2012. The microRNA mir-71 inhibits calcium signaling by targeting the TIR-1/Sarm1 adaptor protein to control stochastic L/R neuronal asymmetry in C elegans. PLoS Genet. 8, e1002864.
Huang, Y., Chen, S., Xu, H., Yu, X., Lai, H., Ho, G., Huang, Q., Shi, X., 2013. Pre-gestational stress alters stress-response of pubertal offspring rat in sexually dimorphic and hemispherically asymmetric manner. BMC Neurosci. 14, 67.
Hubacek, J.A., Piper, B.J., Pikhart, H., Peasey, A., Kubinova, R., Bobak, M., 2013. Lack of an association between left-handedness and APOE polymorphism in a large sample of adults: results of the Czech HAPIEE study. Laterality 18, 513–519.
Irwin, P., 1985. Greater brain response of left-handers to drugs. Neuropsychologia 23, 61–67.
Jablonka, E., Raz, G., 2009. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. Q. Rev. Biol. 84, 131–176.
Jackson, C., 2008. Prediction of hemispheric asymmetry as measured by handedness from digit length and 2D:4D digit ratio. Laterality 13, 34–50.
Jaenisch, R., Bird, A., 2003. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat. Genet. 33, 245–254 (Suppl).
Jancke, L., Hanggi, J., Steinmetz, H., 2004. Morphological brain differences between adult stutterers and non-stutterers. BMC Neurol. 4, 23.
Johnston, R.J., Hobert, O., 2003. A microRNA controlling left/right neuronal asymmetry in Caenorhabditis elegans. Nature 426, 845–849.
Johnston, D.W., Nicholls, M.E.R., Shah, M., Shields, M.A., 2009. Nature's experiment?: Handedness and early childhood development. Demography 46, 281–301.
Johnston, D.W., Nicholls, M., Shah, M., Shields, M.A., 2010. Handedness, Health and Cognitive Development: Evidence from Children in the NLSY. IZA Discussion Paper 4774. .
Jones, G.V., Martin, M., 2008. Seasonal anisotropy in handedness. Cortex 44, 8–12.
Jones, A., Osmond, C., Godfrey, K.M., Phillips David, I.W., 2011. Evidence for developmental programming of cerebral laterality in humans. PLoS One 6, e17071.
Kang, Y., Harris, L.J., 2000. Handedness and footedness in Korean college students. Brain Cogn. 43, 268–274.
Karev, G.B., 2008. Season of birth and parental age in right, mixed and left handers. Cortex 44, 79–81.
Karlebach, G., Francks, C., 2015. Lateralization of gene expression in human language cortex. Cortex 67, 30–36.
Kasprian, G., Langs, G., Brugger, P.C., Bittner, M., Weber, M., Arantes, M., Prayer, D., 2011. The prenatal origin of hemispheric asymmetry: an in utero neuroimaging study. Cereb. Cortex 21, 1076–1083.
Kavaklioglu, T., Ajmal, M., Hameed, A., Francks, C., 2016. Whole exome sequencing for handedness in a large and highly consanguineous family. Neuropsychologia 93, 342–349.
Kennedy, D., 2004. The old file-drawer problem. Science 305, 451.
Kieler, H., Axelsson, O., Haglund, B., Nilsson, S., Salvesen, K.A., 1998. Routine ultrasound screening in pregnancy and the children's subsequent handedness. Early Hum. Dev. 50, 233–245.
Kieler, H., Cnattingius, S., Haglund, B., Palmgren, J., Axelsson, O., 2001. Sinistrality–a side-effect of prenatal sonography: a comparative study of young men. Epidemiology 12, 618–623.
Kilpinen, H., Dermitzakis, E.T., 2012. Genetic and epigenetic contribution to complex traits. Hum. Mol. Genet. 21, R24–8.
King, K., Murphy, S., Hoyo, C., 2015. Epigenetic regulation of Newborns' imprinted genes related to gestational growth: patterning by parental race/ethnicity and maternal socioeconomic status. J. Epidemiol. Community Health 69, 639–647.
Klar, A.J.S., 2004. An epigenetic hypothesis for human brain laterality, handedness, and psychosis development. Cold Spring Harb. Symp. Quant. Biol. 69, 499–506.
Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., Pace Thaddeus, W.W., Mercer, K.B., Mayberg, H.S., Bradley, B., Nemeroff, C.B., Holsboer, F., Heim, C.M., Ressler, K.J., Rein, T., Binder, E.B., 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 16, 33–41.
Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., Ringelstein, E.B., Henningsen, H., 2000. Handedness and hemispheric language dominance in healthy humans. Brain 123 (Pt 12), 2512–2518.
Kocel, K.M., 1977. Cognitive abilities: handedness, familial sinistrality, and sex. Ann. N. Y. Acad. Sci. 299, 233–243.
Konishi, Y., Mikawa, H., Suzuki, J., 1986. Asymmetrical head-turning of preterm infants: some effects on later postural and functional lateralities. Dev. Med. Child Neurol. 28, 450–457.
Kroliczak, G., Piper, B.J., Frey, S.H., 2011. Atypical lateralization of language predicts cerebral asymmetries in parietal gesture representations. Neuropsychologia 49, 1698–1702.
Kubota, T., Miyake, K., Hariya, N., Mochizuki, K., 2014. Epigenetics as a basis for diagnosis of neurodevelopmental disorders: challenges and opportunities. Expert Rev. Mol. Diagn. 14, 685–697.
Kumsta, R., Marzi, S.J., Viana, J., Dempster, E.L., Crawford, B., Rutter, M., Mill, J., Sonuga-Barke, E.J.S., 2016. Severe psychosocial deprivation in early childhood is associated with increased DNA methylation across a region spanning the transcription start site of CYP2E1. Transl. Psychiatry 6, e830.
Kushner, H.I., 2012. Retraining left-handers and the aetiology of stuttering: the rise and fall of an intriguing theory. Laterality 17, 673–693.
Kushner, H.I., 2013. Why are there (almost) no left-handers in China? Endeavour 37, 71–81.
Laland, K.N., Kumm, J., Van Horn, J.D., Feldman, M.W., 1995. A gene-culture model of human handedness. Behav. Genet. 25, 433–445.
Laland, K.N., 2008. Exploring gene-culture interactions: insights from handedness, sexual selection and niche-construction case studies. Philos. Trans. R Soc. Lond. B Biol. Sci. 363, 3577–3589.
Laland, Kevin N., 2017. Darwin's Unfinished Symphony. How Culture Made the Human Mind Princeton. Princeton University Press, Oxford.
Leach, E.L., Prefontaine, G., Hurd, P.L., Crespi, B.J., 2014. The imprinted gene LRRTM1 mediates schizotypy and handedness in a nonclinical population. J. Hum. Genet. 59, 332–336.
Leiber, L., Axelrod, S., 1981a. Intra-familial learning is only a minor factor in manifest handedness. Neuropsychologia 19, 273–288.
Leiber, L., Axelrod, S., 1981b. Not all sinistrality is pathological. Cortex 17, 259–271.
Letzner, S., Patzke, N., Verhaal, J., Manns, M., 2014. Shaping a lateralized brain: asymmetrical light experience modulates access to visual interhemispheric information in pigeons. Sci. Rep. 4, 4253.
Levchenko, A., Davtian, S., Petrova, N., Malashichev, Y., 2014. Sequencing of five left-right cerebral asymmetry genes in a cohort of schizophrenia and schizotypal disorder patients from Russia. Psychiatr. Genet. 24, 75–80.
Leviton, A., Kilty, T., 1976. Letter: birth order and left-handedness. Arch. Neurol. 33, 664.
Leviton, A., Kilty, T., 1979. Seasonal variation in the birth of left-handed schoolgirls. Arch. Neurol. 36, 115–116.
Levy, J., 1974. Psychobiological implications of bilateral asymmetry. In: Dimond, S., Beaumont, J. (Eds.), Hemisphere Function in the Human Brain. Elek Science, London.
Lewis, B.P., Shih, I.-h., Jones-Rhoades, M.W., Bartel, D.P., Burge, C.B., 2003. Prediction of mammalian microRNA targets. Cell 115, 787–798.
Liederman, J., Coryell, J., 1981. Right-hand preference facilitated by rightward turning biases during infancy. Dev. Psychobiol. 14, 439–450.
Liederman, J., Kinsbourne, M., 1980. The mechanism of neonatal rightward turning bias. A sensory or motor asymmetry? Infant Behav. Dev. 3, 223–238.
Lista, S., Garaci, F.G., Toschi, N., Hampel, H., 2013. Imaging epigenetics in Alzheimer's disease. Curr. Pharm. Des. 19, 6393–6415.
Lockett, G.A., Soto-Ramírez, N., Ray, M.A., Everson, T.M., Xu, C.J., Patil, V.K., Terry, W., Kaushal, A., Rezwan, F.I., Ewart, S.L., Gehring, U., Postma, D.S., Koppelman, G.H., Arshad, S.H., Zhang, H., Karmaus, W., Holloway, J.W., 2016. Association of season of birth with DNA methylation and allergic disease. Allergy 71, 1314–1324.
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, 249–256.
Lombardo, M.V., Ashwin, E., Auyeung, B., Chakrabarti, B., Taylor, K., Hackett, G., Bullmore, E.T., Baron-Cohen, S., 2012. Fetal testosterone influences sexually dimorphic gray matter in the human brain. J. Neurosci. 32, 674–680.
Ludwig, K.U., Mattheisen, M., Muhleisen, T.W., Roeske, D., Schmal, C., Breuer, R., Schulte-Korne, G., Muller-Myhsok, B., Nothen, M.M., Hoffmann, P., Rietschel, M., Cichon, S., 2009. Supporting evidence for LRRTM1 imprinting effects in schizophrenia. Mol. Psychiatry 14, 743–745.
Lust, J.M., Geuze, R.H., van de Beek, C., Cohen-Kettenis, P.T., Bouma, A., Groothuis, T. G.G., 2011. Differential effects of prenatal testosterone on lateralization of handedness and language. Neuropsychology 25, 581–589.
Lyle, K.B., Chapman, L.K., Hatton, J.M., 2013. Is handedness related to anxiety? New answers to an old question. Laterality 18, 520–535.
Macchi, M.M., Bruce, J.N., 2004. Human pineal physiology and functional significance of melatonin. Front. Neuroendocrinol. 25, 177–195.
Maher, B., 2008. Personal genomes: the case of the missing heritability. Nature 456, 18–21.
Malas, M.A., Dogan, S., Evcil, E.H., Desdicioglu, K., 2006. Fetal development of the hand, digits and digit ratio (2D:4D). Early Hum. Dev. 82, 469–475.
Mandal, M.K., Bhushan, B., Kumar, A., Gupta, P., 2000. Side-bias in alcohol and heroin addicts. Alcohol Alcoholism 35, 381–383.
Manning, J.T., Peters, M., 2009. Digit ratio (2D:4D) and hand preference for writing in the BBC Internet Study. Laterality 14, 528–540.
Manning, J.T., Scutt, D., Wilson, J., Lewis-Jones, D.I., 1998. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum. Reprod. 13, 3000–3004.
Manning, J.T., Trivers, R.L., Thornhill, R., Singh, D., 2000. The 2nd:4th digit ratio and asymmetry of hand performance in Jamaican children. Laterality 5, 121–132.
Manning, J.T., Bundred, P.E., Flanagan, B.F., 2002. The ratio of 2nd to 4th digit length: a proxy for transactivation activity of the androgen receptor gene? Med. Hypotheses 59, 334–336.
Manning, J.T., Bundred, P.E., Newton, D.J., Flanagan, B.F., 2003. The second to fourth digit ratio and variation in the androgen receptor gene. Evol. Hum. Behav. 24, 399–405.
Manns, M., Güntürkün, O., 2009. Dual coding of visual asymmetries in the pigeon brain: the interaction of bottom-up and top-down systems. Exp. Brain Res. 199, 323–332.

Manns, M., Romling, J., 2012. The impact of asymmetrical light input on cerebral hemispheric specialization and interhemispheric cooperation. Nat. Commun. 3, 696.
Manns, M., Freund, N., Leske, O., Güntürkün, O., 2008. Breaking the balance: ocular BDNF-injections induce visual asymmetry in pigeons. Dev. Neurobiol. 68, 1123–1134.
Martin, M., Jones, G.V., 1999. Handedness and season of birth: a gender-invariant relation. Cortex 35, 123–128.
Marzullo, G., Boklage, C.E., 2011. Bimodal rhythms of general conceptions and the birth-month phenomenon in schizophrenia, neural tube defects, and laterality: a solstitial hypothesis. Birth Defects Res. Part A Clin. Mol. Teratol. 91, 249–257.
Marzullo, G., Fraser, F.C., 2009. Conception season and cerebral asymmetries among American baseball players: implications for the seasonal birth effect in schizophrenia. Psychiatry Res. 167, 287–293.
McKeever, W.F., Suter, P.J., Rich, D.A., 1995. Maternal age and parity correlates of handedness: gender, but no parental handedness modulation of effects. Cortex 31, 543–553.
McManus, I.C., Bryden, M.P., 1992. The genetics of handedness, cerebral dominance and lateralization. In: Rapin, I., Segalowitz, S.J. (Eds.), Handbook of Neuropsychology, vol. 6. Elsevier, Amsterdam, pp. 115–144 (Section 10, Bd. 6).
McManus, I.C., 1980. Season of birth of left-Handers. Arch. Neurol. 37, 63.
McManus, I.C., 1981. Handedness and birth stress. Psychol. Med. 11, 485–496.
McManus, I.C., 1983. Pathologic left-handedness: does it exist. J. Commun. Disord. 16, 315–344.
McManus, I.C., 1985. Handedness, language dominance and aphasia: a genetic model. Psychol. Med. Monogr. Suppl. 8, 1–40.
Medland, S.E., Duffy, D.L., Spurdle, A.B., Wright, M.J., Geffen, G.M., Montgomery, G. W., Martin, N.G., 2005. Opposite effects of androgen receptor CAG repeat length on increased risk of left-handedness in males and females. Behav. Genet. 35, 735–744.
Medland, S.E., Duffy, D.L., Wright, M.J., Geffen, G.M., Martin, N.G., 2006. Handedness in twins: joint analysis of data from 35 samples. Twin Res Hum Genet 9, 46–53.
Medland, S.E., Duffy, D.L., Wright, M.J., Geffen, G.M., Hay, D.A., Levy, F., van-Beijsterveldt Catherina, E.M., Willemsen, G., Townsend, G.C., White, V., Hewitt, A.W., Mackey, D.A., Bailey, J.M., Slutske, W.S., Nyholt, D.R., Treloar, S.A., Martin, N.G., Boomsma, D.I., 2009. Genetic influences on handedness: data from 25,732 Australian and Dutch twin families. Neuropsychologia 47, 330–337.
Michel, G.F., Harkins, D.A., 1986. Postural and lateral asymmetries in the ontogeny of handedness during infancy. Dev. Psychobiol. 19, 247–258.
Michel, G.F., Nelson, E.L., Babik, I., Campbell, J.M., Marcinowski, E.C., 2013. Multiple trajectories in the developmental psychobiology of human handedness. Adv. Child Dev. Behav. 45, 227–260.
Michel, G.F., 1981. Right-handedness: a consequence of infant supine head-orientation preference? Science 212, 685–687.
Milenković, S., Rock, D., Dragović, M., Janca, A., 2008. Season of birth and handedness in Serbian high school students. Ann. Gen. Psychiatry 7, 2.
Mittwoch, U., 2008. Different gene expressions on the left and the right: a genotype/phenotype mismatch in need of attention. Ann. Hum. Genet. 72, 2–9.
Molfese, D.L., 2011. Advancing neuroscience through epigenetics: molecular mechanisms of learning and memory. Dev. Neuropsychol. 36, 810–827.
Neale, M.C., 1988. Handedness in a sample of volunteer twins. Behav. Genet. 18, 69–79.
Neave, N., Laing, S., Fink, B., Manning, J.T., 2003. Second to fourth digit ratio, testosterone and perceived male dominance. Proc. Biol. Sci. 270, 2167–2172.
Negron-Oyarzo, I., Lara-Vasquez, A., Palacios-Garcia, I., Fuentealba, P., Aboitiz, F., 2016. Schizophrenia and reelin: a model based on prenatal stress to study epigenetics, brain development and behavior. Biol. Res. 49, 16.
Nicholls, M.E.R., Orr, C.A., Yates, M.J., Loftus, A.M., 2008. A new means of measuring index/ring finger (2D:4D) ratio and its association with gender and hand preference. Laterality 13, 71–91.
Nicholls, M.E., Johnston, D.W., Shields, M.A., 2012. Adverse birth factors predict cognitive ability, but not hand preference. Neuropsychology 26, 578–587.
Nicholls, M.E., 1998. Seasonal trends in the birth of sinistrals. Laterality 3, 241–253.
Nikolova, Y.S., Hariri, A.R., 2015. Can we observe epigenetic effects on human brain function? Trends Cogn. Sci. 19, 366–373.
Nowakowska, C., Sachs, G.S., Zarate, C.A., Marangell, L.B., Calabrese, J.R., Goldberg, J. F., Ketter, T.A., 2008. Increased rate of Non-Right Handedness in patients with bipolar disorder. J. Clin. Psychiatry 69, 866–867.
O'Callaghan, M.J., Tudehope, D.I., Dugdale, A.E., Mohay, H., Burns, Y., Cook, F., 1987. Handedness in children with birthweights below 1000 g. Lancet 1, 1155.
Obel, C., Hedegaard, M., Brink, T., Secher, N.J., Olsen, J., 2003. Psychological factors in pregnancy and mixed-handedness in the offspring. Dev. Med. Child Neurol. 45, 557–561.
Obermann-Borst, S.A., Eilers, P.H.C., Tobi, E.W., de Jong, F.H., Slagboom, P.E., Heijmans, B.T., Steegers-Theunissen, R.P.M., 2013. Duration of breastfeeding and gender are associated with methylation of the LEPTIN gene in very young children. Pediatr. Res. 74, 344–349.
Ocklenburg, S., Güntürkün, O., 2009. Head-turning asymmetries during kissing and their association with lateral preference. Laterality 14, 79–85.
Ocklenburg, S., Bürger, C., Westermann, C., Schneider, D., Biedermann, H., Güntürkün, O., 2010. Visual experience affects handedness. Behav. Brain Res. 207, 447–451.
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, 410–418.
Ocklenburg, S., Beste, C., Arning, L., Peterburs, J., Güntürkün, O., 2014. The ontogenesis of language lateralization and its relation to handedness. Neurosci. Biobehav. Rev. 43, 191–198.
Ocklenburg, S., Arning, L., Gerding, W., Hengstler, J., Epplen, J., Güntürkün, O., Beste, C., Akkad, D., 2015a. Left-right axis differentiation and functional lateralization: a haplotype in the methyltransferase encoding gene SETDB2 might mediate handedness in healthy adults. Mol. Neurobiol. 1–7.
Ocklenburg, S., Güntürkün, O., Hugdahl, K., Hirnstein, M., 2015b. Laterality and mental disorders in the postgenomic age–a closer look at schizophrenia and language lateralization. Neurosci. Biobehav. Rev. 59, 100–110.
Ocklenburg, S., Schmitz, J., Moinfar, Z., Moser, D., Klose, R., Lor, S., Kunz, G., Tegenthoff, M., Faustmann, P., Francks, C., Epplen, J.T., Kumsta, R., Güntürkün, O., 2017. Epigenetic regulation of lateralized fetal spinal gene expression underlies hemispheric asymmetries. eLife 6, 276.
Oertel-Knochel, V., Linden, D.E.J., 2011. Cerebral asymmetry in schizophrenia. Neuroscientist 17, 456–467.
Oh, A.K., Mulliken, J.B., LaBrie, R.A., Rogers, G.F., 2009. Increased frequency of left-handedness in patients with unilateral coronal synostosis. Cleft Palate. Craniofac. J. 46, 237–244.
Ökten, A., Kalyoncu, M., Yariş, N., 2002. The ratio of second- and fourth-digit lengths and congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Early Hum. Dev. 70, 47–54.
Ooki, S., 2006. Nongenetic factors associated with human handedness and footedness in Japanese twin children. Environ. Health Prev. Med. 11, 304–312.
Ooki, S., 2014. An overview of human handedness in twins. Front. Psychol. 5, 10.
Orme, J.E., 1970. Left-handedness, ability and emotional instability. Br. J. Soc. Clin. Psychol. 9, 87–88.
Orsini, D.L., Satz, P., 1986. A syndrome of pathological left-handedness: correlates of early left hemisphere injury. Arch. Neurol. 43, 333–337.
Overby, L.A., 1994. The relationship of handedness to depression in male and female college students. Pers Indiv Differ 16, 537–541.
Papadatou-Pastou, M., Martin, M., Munafo, M.R., Jones, G.V., 2008. Sex differences in left-handedness: a meta-analysis of 144 studies. Psychol. Bull. 134, 677–699.
Paracchini, S., Diaz, R., Stein, J., 2016. Advances in dyslexia genetics-new insights into the role of brain asymmetries. Adv. Genet. 96, 53–97.
Parets, S.E., Conneely, K.N., Kilaru, V., Fortunato, S.J., Syed, T.A., Saade, G., Smith, A.K., Menon, R., 2013. Fetal DNA methylation associates with early spontaneous preterm birth and gestational age. PLoS One 8, e67489.
Park, S., Cho, S.-C., Kim, J.-W., Shin, M.-S., Yoo, H.-J., Oh, S.M., Han, D.H., Cheong, J.H., Kim, B.-N., 2014. Differential perinatal risk factors in children with attention-deficit/hyperactivity disorder by subtype. Psychiatry Res. 219, 609–616.
Pascual, A., Huang, K.-L., Neveu, J., Preat, T., 2004. Neuroanatomy: brain asymmetry and long-term memory. Nature 427, 605–606.
Payne, M.A., 1987. Impact of cultural pressures on self-reports of actual and approved hand use. Neuropsychologia 25, 247–258.
Perelle, I.B., Ehrman, L., 1994. An international study of human handedness: the data. Behav. Genet. 24, 217–227.
Perkins, T.J., Stokes, M.A., McGillivray, J.A., Mussap, A.J., Cox, I.A., Maller, J.J., Bittar, R. G., 2014. Increased left hemisphere impairment in high-functioning autism: a tract based spatial statistics study. Psychiatry Res. 224, 119–123.
Pfannkuche, K.A., Bouma, A., Groothuis, T.G., 2009. Does testosterone affect lateralization of brain and behaviour? A meta-analysis in humans and other animal species. Philos. Trans. R. Soc. Lond. B: Biol. Sci. 364, 929–942.
Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369–382.
Piper, B.J., Yasen, A.L., Taylor, A.E., Ruiz, J.R., Gaynor, J.W., Dayger, C.A., Gonzalez-Gross, M., Kwon, O.D., Nilsson, L.-G., Day Ian, N.M., Raber, J., Miller, J.K., 2013. Non-replication of an association of Apolipoprotein E2 with sinistrality. Laterality 18, 251–261.
Pletikos, M., Sousa, A.M.M., Sedmak, G., Meyer, K.A., Zhu, Y., Cheng, F., Li, M., Kawasawa, Y.I., Sestan, N., 2014. Temporal specification and bilaterality of human neocortical topographic gene expression. Neuron 81, 321–332.
Porac, C., Martin, W.L., 2007. A cross-cultural comparison of pressures to switch left-hand writing: Brazil versus Canada. Laterality 12, 273–291.
Porac, C., Coren, S., Searleman, A., 1986. Environmental factors in hand preference formation: evidence from attempts to switch the preferred hand. Behav. Genet. 16, 251–261.
Porac, C., Rees, L., Buller, T., 1990. Switching hands: a place for left hand use in a right hand worldIn: Coren, S. (Ed.), Advances in Psychology: Advances in Psychology vol. 67. , pp. 259–290. . (Chapter 9. North-Holland, Online verfügbar unter) http://www.sciencedirect.com/science/article/pii/S0166411508612509.
Pourzand, C., Tyrrell, R.M., 1999. Apoptosis, the role of oxidative stress and the example of solar UV radiation. Photochem. Photobiol. 70, 380–390.
Preslar, J., Kushner, H.I., Marino, L., Pearce, B., 2014. Autism, lateralisation, and handedness: a review of the literature and meta-analysis. Laterality 19, 64–95.
Preti, A., Lai, A., Serra, M., Zurrida, G.G., 2008. Mixed handedness prevails among children and adolescents with infantile asthma and diabetes. Pediatr. Allergy Immunol. 19, 769–772.
Putz, D.A., Gaulin, S.J., Sporter, R.J., McBurney, D.H., 2004. Sex hormones and finger length. Evol Hum Behav 25, 182–199.
Ramadhani, M.K., Koomen, I., Grobbee, D.E., van Donselaar, C.A., van Marceline Furth, A., Uiterwaal Cuno, S.P.M., 2006. Increased occurrence of left-handedness after severe childhood bacterial meningitis: support for the pathological left-handedness hypothesis. Neuropsychologia 44, 2526–2532.

Raymond, M., Pontier, D., 2004. Is there geographical variation in human handedness? Laterality 9, 35–51.
Reed, C.E., Fenton, S.E., 2013. Exposure to diethylstilbestrol during sensitive life stages: a legacy of heritable health effects. Birth Defect Res. C 99, 134–146.
Reid, H.M., Norvilitis, J.M., 2000. Evidence for anomalous lateralization across domain in ADHD children as well as adults identified with the Wender Utah rating scale. J. Psychiatr. Res. 34, 311–316.
Reissland, N., Aydin, E., Francis, B., Exley, K., 2015. Laterality of foetal self-touch in relation to maternal stress. Laterality 20, 82–94.
Renteria, M.E., 2012. Cerebral asymmetry: a quantitative, multifactorial, and plastic brain phenotype. Twin Res. Hum. Genet. 15, 401–413.
Risch, N., Pringle, G., 1985. Segregation analysis of human hand preference. Behav. Genet. 15, 385–400.
Robertson, J., Zhang, W., Liu, J.J., Muir, K.R., Maciewicz, R.A., Doherty, M., 2008. Radiographic assessment of the index to ring finger ratio (2D:4D) in adults. J. Anat. 212, 42–48.
Robinson, K.J., Hurd, P.L., Read, S., Crespi, B.J., 2016. The PCSK6 gene is associated with handedness, the autism spectrum, and magical ideation in a non-clinical population. Neuropsychologia 84, 205–212.
Rodriguez, A., Waldenström, U., 2008. Fetal origins of child non-right-handedness and mental health. J. Child Psychol. Psychiatry 49, 967–976.
Rogers, L.J., 1982. Light experience and asymmetry of brain function in chickens. Nature 297, 223–225.
Rogerson, P.A., 1994. On the relationship between handedness and season of birth for men. Percept. Mot. Skills 79, 499–506.
Ronnqvist, L., Hopkins, B., van Emmerik, R., de Groot, L., 1998. Lateral biases in head turning and the Moro response in the human newborn: are they both vestibular in origin? Dev. Psychobiol. 33, 339–349.
Rosen, G.D., Berrebi, A.S., Yutzey, D.A., Denenberg, V.H., 1983. Prenatal testosterone causes shift of asymmetry in neonatal tail posture of the rat. Brain Res. 285, 99–101.
Roth, T.L., 2012. Epigenetics of neurobiology and behavior during development and adulthood. Dev. Psychobiol. 54, 590–597.
Rothbart, S.B., Strahl, B.D., 2014. Interpreting the language of histone and DNA modifications. Biochim. Biophys. Acta 1839, 627–643.
Roussigne, M., Blader, P., Wilson, S.W., 2012. Breaking symmetry: the zebrafish as a model for understanding left-right asymmetry in the developing brain. Dev. Neurobiol. 72, 269–281.
Rysstad, A.L., Pedersen, A.V., 2016. Brief report: non-right-handedness within the autism spectrum disorder. J. Autism Dev. Disord. 46, 1110–1117.
Salihović, N., Sinanović, O., 2000. Stuttering and left-handedness. Med. Arh. 54, 173–175.
Salvesen, K.A., Eik-Nes, S.H., 1999. Ultrasound during pregnancy and subsequent childhood non-right handedness: a meta-analysis. Ultrasound Obstet. Gynecol. 13, 241–246.
Salvesen, K.A., Vatten, L.J., Eik-Nes, S.H., Hugdahl, K., Bakketeig, L.S., 1993. Routine ultrasonography in utero and subsequent handedness and neurological development. BMJ 307, 159–164.
Salvesen, K.A., 2002. Ultrasound and left-handedness: a sinister association? Ultrasound Obstet. Gynecol. 19, 217–221.
Satz, P., Soper, H.V., 1986. Left-handedness, dyslexia, and autoimmune disorder: a critique. J. Clin. Exp. Neuropsychol. 8, 453–458.
Satz, P., 1972. Pathological left-handedness: an explanatory model. Cortex 8, 121–135.
Saunders, D.A., Campbell, A.L., 1985. Handedness incidence in a population of black university students. Percept. Mot. Skills 60, 355–360.
Savitz, J., van der Merwe, L., Solms, M., Ramesar, R., 2007. Lateralization of hand skill in bipolar affective disorder. Genes Brain Behav. 6, 698–705.
Scerri, T.S., Brandler, W.M., Paracchini, S., Morris, A.P., Ring, S.M., Richardson, A.J., Talcott, J.B., Stein, J., Monaco, A.P., 2011. PCSK6 is associated with handedness in individuals with dyslexia. Hum. Mol. Genet. 20, 608–614.
Schaafsma, S.M., Riedstra, B.J., Pfannkuche, K.A., Bouma, A., Groothuis, T.G.G., 2009. Epigenesis of behavioural lateralization in humans and other animals. Philos. Trans. R Soc. Lond. B Biol. Sci. 364, 915–927.
Schachter, S.C., 1994. Handedness in women with intrauterine exposure to diethylstilbestrol. Neuropsychologia 32, 619–623.
Scheirs, J.G., Vingerhoets, A.J., 1995. Handedness and other laterality indices in women prenatally exposed to DES. J. Clin. Exp. Neuropsychol. 17, 725–730.
Schlinzig, T., Johansson, S., Gunnar, A., Ekstrom, T.J., Norman, M., 2009. Epigenetic modulation at birth – altered DNA-methylation in white blood cells after Caesarean section. Acta Paediatr. 98, 1096–1099.
Schmitz, J., Kumsta, R., Moser, D., Güntürkün, O., Ocklenburg, S., 2017. DNA methylation in candidate genes for handedness predicts handedness direction. Laterality 1–21.
Schwarz, I.M., Rogers, L.J., 1992. Testosterone: a role in the development of brain asymmetry in the chick. Neurosci. Lett. 146, 167–170.
Searleman, A., Porac, C., Coren, S., 1989. Relationship between birth order, birth stress, and lateral preferences: a critical review. Psychol. Bull. 105, 397–408.
Shaw, G.A., Brown, G., 1991. Laterality, implicit memory and attention disorder. Educ Stud 17, 15–23.
Shaw, P., Lerch, J.P., Pruessner, J.C., Taylor, K.N., Rose, A.B., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N., 2007. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms. An observational study. Lancet Neurol. 6, 494–500.
Shimizu, A., Endo, M., 1983. Comparison of patterns of handedness between twins and singletons in Japan. Cortex 19, 345–352.
Shiratori, H., Hamada, H., 2014. TGFbeta signaling in establishing left-right asymmetry. Semin. Cell Dev. Biol. 32, 80–84.
Shorter, K.R., Miller, B.H., 2015. Epigenetic mechanisms in schizophrenia. Prog. Biophys. Mol. Biol. 118, 1–7.
Sicotte, N.L., Woods, R.P., Mazziotta, J.C., 1999. Handedness in twins: a meta-analysis. Laterality 4, 265–286.
Singh, M., Kindu, A., 1994. Hand preference and approval among Hindus and Muslims in India. Int. J. Neurosci. 75, 19–29.
Singh, M., Manjary, M., Dellatolas, G., 2001. Lateral preferences among indian school children. Cortex 37, 231–241.
Smart, J.L., Jeffery, C., Richards, B., 1980. A retrospective study of the relationship between birth history and handedness at six years. Early Hum. Dev. 4, 79–88.
Smith, L.L., Hines, M., 2000. Language lateralization and handedness in women prenatally exposed to diethylstilbestrol (DES). Psychoneuroendocrinology 25, 497–512.
Somers, M., Sommer, I.E., Boks, M.P., Kahn, R.S., 2009. Hand-preference and population schizotypy: a meta-analysis. Schizophr. Res. 108, 25–32.
Somers, M., Aukes, M.F., Ophoff, R.A., Boks, M.P., Fleer, W., de Visser, K.C.L., Kahn, R.S., Sommer, I.E., 2015a. On the relationship between degree of hand-preference and degree of language lateralization. Brain Lang. 144, 10–15.
Somers, M., Ophoff, R.A., Aukes, M.F., Cantor, R.M., Boks, M.P., Dauwan, M., de Visser, K.L., Kahn, R.S., Sommer, I.E., 2015b. Linkage analysis in a Dutch population isolate shows no major gene for left-handedness or atypical language lateralization. J. Neurosci. 35, 8730–8736.
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.
Song, J.W., Mitchell, P.D., Kolasinski, J., Ellen Grant, P., Galaburda, A.M., Takahashi, E., 2015. Asymmetry of white matter pathways in developing human brains. Cereb. Cortex 25, 2883–2893.
Sparrow, S., Manning, J.R., Cartier, J., Anblagan, D., Bastin, M.E., Piyasena, C., Pataky, R., Moore, E.J., Semple, S.I., Wilkinson, A.G., Evans, M., Drake, A.J., Boardman, J.P., 2016. Epigenomic profiling of preterm infants reveals DNA methylation differences at sites associated with neural function. Transl. Psychiatry 6, e716.
Sperling, W., Frank, H., Martus, P., Mader, R., Barocka, A., Walter, H., Lesch, M., 2000. The concept of abnormal hemispheric organization in addiction research. Alcohol Alcoholism 35, 394–399.
Stoyanov, Z., Nikolova, P., Pashalieva, I., 2011. Season of birth, Geschwind and Galaburda hypothesis, and handedness. Laterality 16, 607–619.
Ströckens, F., Freund, N., Manns, M., Ocklenburg, S., Güntürkün, O., 2013a. Visual asymmetries and the ascending thalamofugal pathway in pigeons. Brain Struct. Funct. 218, 1197–1209.
Ströckens, F., Güntürkün, O., Ocklenburg, S., 2013b. Limb preferences in non-human vertebrates. Laterality 18, 536–575.
Stringhini, S., Polidoro, S., Sacerdote, C., Kelly, R.S., van Veldhoven, K., Agnoli, C., Grioni, S., Tumino, R., Giurdanella, M.C., Panico, S., Mattiello, A., Palli, D., Masala, G., Gallo, V., Castagne, R., Paccaud, F., Campanella, G., Chadeau-Hyam, M., Vineis, P., 2015. Life-course socioeconomic status and DNA methylation of genes regulating inflammation. Int. J. Epidemiol. 44, 1320–1330.
Stuffrein-Roberts, S., Joyce, P.R., Kennedy, M.A., 2008. Role of epigenetics in mental disorders. Aust. N. Z. J. Psychiatry 42, 97–107.
Sullivan, R.M., 2004. Hemispheric asymmetry in stress processing in rat prefrontal cortex and the role of mesocortical dopamine. Stress 7, 131–143.
Sun, T., Patoine, C., Abu-Khalil, A., Visvader, J., Sum, E., Cherry, T.J., Orkin, S.H., Geschwind, D.H., Walsh, C.A., 2005. Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. Science 308, 1794–1798.
Tadayon, S.H., Vaziri-Pashkam, M., Kahali, P., Ansari Dezfouli, M., Abbassian, A., 2016. Common genetic variant in VIT is associated with human brain asymmetry. Front. Hum. Neurosci. 10, 236.
Takasaki, S., 2015. Roles of microRNAs in cancers and development. Methods Mol. Biol. 1218, 375–413.
Tammen, S.A., Friso, S., Choi, S.-W., 2013. Epigenetics: the link between nature and nurture. Mol. Aspects Med. 34, 753–764.
Tan, L.E., Nettleton, N.C., 1980. Left handedness, birth order and birth stress. Cortex 16, 363–373.
ten Donkelaar, H.J., Lammens, M., Wesseling, P., Hori, A., Keyser, A., Rotteveel, J., 2004. Development and malformations of the human pyramidal tract. J. Neurol. 251, 1429–1442.
Teng, E.L., Lee, P.H., Yang, K.S., Chang, P.C., 1976. Handedness in a Chinese population: biological, social, and pathological factors. Science 193, 1148–1150.
Teng, E.L., Lee, P.-H., Yang, K.-S., Chang, P.C., 1979. Lateral preferences for hand, foot and eye, and their lack of association with scholastic achievement, in 4143 Chinese. Neuropsychologia 17, 41–48.
Tiraboschi, E., Guirado, R., Greco, D., Auvinen, P., Maya-Vetencourt, J.F., Maffei, L., Castren, E., 2013. Gene expression patterns underlying the reinstatement of plasticity in the adult visual system. Neural Plast. 2013, 605079.
Tognini, P., Napoli, D., Tola, J., Silingardi, D., Della Ragione, F., D'Esposito, M., Pizzorusso, T., 2015. Experience-dependent DNA methylation regulates plasticity in the developing visual cortex. Nat. Neurosci. 18, 956–958.
Tonetti, L., Adan, A., Caci, H., Fabbri, M., Natale, V., 2012. Season of birth and handedness in young adults. Laterality 17, 597–601.
Tran, U.S., Stieger, S., Voracek, M., 2014. Latent variable analysis indicates that seasonal anisotropy accounts for the higher prevalence of left-handedness in men. Cortex 57, 188–197.
Tsai, P.-C., van Dongen, J., Tan, Q., Willemsen, G., Christiansen, L., Boomsma, D.I., Spector, T.D., Valdes, A.M., Bell, J.T., 2015. DNA methylation changes in the IGF1R

gene in birth weight discordant adult monozygotic twins. Twin Res Hum Genet 18, 635–646.
Tsuang, H.-C., Chen, W.J., Kuo, S.-Y., Hsiao, P.-C., 2013. The cross-cultural nature of the relationship between schizotypy and mixed-handedness. Laterality 18, 476–490.
Turecki, G., Meaney, M.J., 2016. Effects of the social environment and stress on glucocorticoid receptor gene methylation. A systematic review. Biol. Psychiatry 79, 87–96.
Turkewitz, G., Creighton, S., 1975. Changes in lateral differentiation of head posture in the human neonate. Dev. Psychobiol. 8, 85–89.
Turkewitz, G., 1977. The development of lateral differentiation in the human infant. Ann. N. Y. Acad. Sci. 299, 309–318.
Ursini, G., Bollati, V., Fazio, L., Porcelli, A., Iacovelli, L., Catalani, A., Sinibaldi, L., Gelao, B., Romano, R., Rampino, A., Taurisano, P., Mancini, M., Di Giorgio, A., Popolizio, T., Baccarelli, A., de Blasi, A., Blasi, G., Bertolino, A., 2011. Stress-related methylation of the catechol-O-methyltransferase Val 158 allele predicts human prefrontal cognition and activity. J. Neurosci. 31, 6692–6698.
Uwaezuoke, S.N., Eke, C.B., Nwobi, E.A., 2015. Left-hand dominance in children: prevalence and maternal stereotypes in a South-East Nigerian city. Laterality 20, 530–542.
Vaiserman, A.M., 2015. Epigenetic programming by early-life stress: evidence from human populations. Dev. Dyn. 244, 254–265.
Van der Elst, W., Hurks Petra, P.M., Wassenberg, R., Meijs Celeste, J.C., Van Boxtel Martin, P.J., Jolles, J., 2011. On the association between lateral preferences and pregnancy/birth stress events in a nonclinical sample of school-aged children. J. Clin. Exp. Neuropsychol. 33, 1–8.
van der Kamp, J., Canal-Bruland, R., 2011. Kissing right? On the consistency of the head-turning bias in kissing. Laterality 16, 257–267.
van Dyck, L.I., Pittman, B.P., Blumberg, H.P., 2012. Non-right-handedness in adolescents and adults with bipolar disorder. Bipolar Disord. 14, 571–572.
van Strien, J.W., Bouma, A., Bakker, D.J., 1987. Birth stress, autoimmune diseases, and handedness. J. Clin. Exp. Neuropsychol. 9, 775–780.
Ventura, T., Gomes, M.C., Pita, A., Neto, M.T., Taylor, A., 2013. Digit ratio (2D:4D) in newborns: influences of prenatal testosterone and maternal environment. Early Hum. Dev. 89, 107–112.
Voracek, M., Loibl, L.M., 2009. Scientometric analysis and bibliography of digit ratio (2D:4D) research, 1998–2008. Psychol. Rep. 104, 922–956.
Voracek, M., Reimer, B., Ertl, C., Dressler, S.G., 2006. Digit ratio (2D:4D), lateral preferences, and performance in fencing. Percept. Mot. Skills 103, 427–446.
Vuoksimaa, E., Koskenvuo, M., Rose, R.J., Kaprio, J., 2009. Origins of handedness: a nationwide study of 30,161 adults. Neuropsychologia 47, 1294–1301.
Vuoksimaa, E., Eriksson, C.P., Pulkkinen, L., Rose, R.J., Kaprio, J., 2010. Decreased prevalence of left-handedness among females with male co-twins. Evidence suggesting prenatal testosterone transfer in humans? Psychoneuroendocrinology 35, 1462–1472.
Walder, D.J., Laplante, D.P., Sousa-Pires, A., Veru, F., Brunet, A., King, S., 2014. Prenatal maternal stress predicts autism traits in 6(1/2) year-old children: project Ice Storm. Psychiatry Res. 219, 353–360.
Weaver, I.C.G., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854.
Webb, J.R., Schroeder, M.I., Chee, C., Dial, D., Hana, R., Jefee, H., Mays, J., Molitor, P., 2013. Left-Handedness among a community sample of psychiatric outpatients suffering from mood and psychotic disorders. SAGE Open 3.
Webster, W.G., Poulos, M., 1987. Handedness distributions among adults who stutter. Cortex 23, 705–708.
Weinstock, M., 2001. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. Prog. Neurobiol. 65, 427–451.
Weller, M.P., 1990. Left handedness in an identical twin discordant to his co-twin for handedness and schizophrenia, with neurological and psychometric evidence of left hemisphere damage. Postgrad. Med. J. 66, 224–226.
Wey, H.-Y., Gilbert, T.M., Zurcher, N.R., She, A., Bhanot, A., Taillon, B.D., Schroeder, F. A., Wang, C., Haggarty, S.J., Hooker, J.M., 2016. Insights into neuroepigenetics through human histone deacetylase PET imaging. Sci. Transl. Med. 8, 351ra106.
Whitworth, M., Bricker, L., Mullan, C., 2015. Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst. Rev. 7, CD007058.
Wienrich, A.M., Wells, P.A., McManus, C., 1982. Handedness, anxiety and sex differences. Br. J. Psychol. 73, 69–72.
Wiers, C.E., 2012. Methylation and the human brain: towards a new discipline of imaging epigenetics. Eur. Arch. Psychiatry Clin. Neurosci. 262, 271–273.
Willems, R.M., van der Haegen, L., Fisher, S.E., Francks, C., 2014. On the other hand: including left-handers in cognitive neuroscience and neurogenetics. Nat. Rev. Neurosci. 15, 193–201.
Williams, C.S., Buss, K.A., Eskenazi, B., 1992. Infant resuscitation is associated with an increased risk of left-handedness. Am. J. Epidemiol. 136, 277–286.
Wright, L., Hardie, S.M., 2012. Are left-handers really more anxious? Laterality 17, 629–642.
Xu, T., Yu, X., Perlik, A.J., Tobin, W.F., Zweig, J.A., Tennant, K., Jones, T., Zuo, Y., 2009. Rapid formation and selective stabilization of synapses for enduring motor memories. Nature 462, 915–919.
Xu, P.-F., Zhu, K.-Y., Jin, Y., Chen, Y., Sun, X.-J., Deng, M., Chen, S.-J., Chen, Z., Liu, T.X., 2010. Setdb2 restricts dorsal organizer territory and regulates left-right asymmetry through suppressing fgf8 activity. Proc. Natl. Acad. Sci. 107, 2521–2526.
Xu, N., Chua, A.K., Jiang, H., Liu, N.-A., Goodarzi, M.O., 2014. Early embryonic androgen exposure induces transgenerational epigenetic and metabolic changes. Mol. Endocrinol. 28, 1329–1336.
Yüksel, R., Sengezer, T., Dilbaz, N., Dane, S., 2012. Handedness, eyedness, and hand–eye crossed dominance in patients with different addictions. Neurol Psychiat Br 18, 181–185.
Yamamoto, M., Hatta, T., 1982. Handedness and imbalance lateralization on the Tapping Test in MBD children. Int. J. Neurosci. 17, 215–218.
Yao, Y., Robinson, A.M., Zucchi, F.C.R., Robbins, J.C., Babenko, O., Kovalchuk, O., Kovalchuk, I., Olson, D.M., Metz, G.A.S., 2014. Ancestral exposure to stress epigenetically programs preterm birth risk and adverse maternal and newborn outcomes. BMC Med. 12, 121.
Ypsilanti, A., Ganou, M., Koidou, I., Grouios, G., 2008. Digit ratio (2D:4D) in individuals with intellectual disability: investigating the role of testosterone in the establishment of cerebral lateralisation. Laterality 13, 527–544.
Zappia, J.V., Rogers, L.J., 1987. Sex differences and reversal of brain asymmetry by testosterone in chickens. Behav. Brain Res. 23, 261–267.
Zhu, J.L., Obel, C., Basso, O., Bech, B.H., Henriksen, T.B., Olsen, J., 2009. Infertility, infertility treatment, and mixed-handedness in children. Early Hum. Dev. 85, 745–749.
Zhu, P., Hao, J.-H., Tao, R.-X., Huang, K., Jiang, X.-M., Zhu, Y.-D., Tao, F.-B., 2015. Sex-specific and time-dependent effects of prenatal stress on the early behavioral symptoms of ADHD: a longitudinal study in China. Eur. Child Adolesc. Psychiatry 24, 1139–1147.
Zucchi, F.C.R., Yao, Y., Ward, I.D., Ilnytskyy, Y., Olson, D.M., Benzies, K., Kovalchuk, I., Kovalchuk, O., Metz, G.A.S., 2013. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One 8, e56967.
Zverev, Y., 2004. Prevalence of the three categories of handedness among Malawian school children. Coll. Antropol. 28, 755–760.
Zverev, Y.P., 2006. Cultural and environmental pressure against left-hand preference in urban and semi-urban Malawi. Brain Cogn. 60, 295–303.