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Atypical lateralization in neurodevelopmental and psychiatric disorders: What is the role of stress?

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ABSTRACT

Hemispheric asymmetries are a major organizational principle of the human brain. In different neurodevelopmental and psychiatric disorders, like schizophrenia, autism spectrum disorders, depression, dyslexia and posttraumatic stress disorder, functional and/or structural hemispheric asymmetries are altered compared to healthy controls. The question, why these disorders all share the common characteristic of altered hemispheric asymmetries despite vastly different etiologies and symptoms remains one of the unsolved mysteries of laterality research. This review is aimed at reviewing potential reasons for why atypical lateralization is so common in many neurodevelopmental and psychiatric disorders. To this end, we review the evidence for overlaps in the genetic and non-genetic factors involved in the ontogenesis of different disorders and hemispheric asymmetries. While there is evidence for genetic overlap between different disorders, only few asymmetry-related loci have also been linked to disorders and importantly, those effects are mostly specific to single disorders. However, there is evidence for shared non-genetic influences between disorders and hemispheric asymmetries. Most neurodevelopmental and psychiatric disorders show alterations in the hypothalamic-pituitary adrenocortical (HPA) axis and maternal as well as early life stress have been implicated in their etiology. Stress has also been suggested to affect hemispheric asymmetries. We propose a model in which early life stress as well as chronic stress not only increases the risk for psychiatric and neurodevelopmental disorders but also changes structural and functional hemispheric asymmetries leading to the aberrant lateralization patterns seen in these disorders. Thus, pathology-related changes in hemispheric asymmetries are not a factor causing disorders, but rather a different phenotype that is affected by partly overlapping ontogenetic factors, primarily stress.

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1. Introduction

Hemispheric asymmetries, e.g. functional, physiological or structural differences between the left and the right hemisphere, are a major organizational principle of the human brain (Ocklenburg & Güntürkün, 2018). For most asymmetrically organized cognitive systems, both left- and right-hemispheric networks contribute to neuronal processing or behavioral output, but are relevant for different aspects and show differences in overall activity. For example, in the language system left-hemispheric networks are relevant for syntactic and grammatical processing, while right-hemispheric networks are relevant for processing of prosody (Friederici, 2011). Overall, the left hemisphere shows greater activation during speech processing in the large majority of the population. This is a classic example of typical lateralization, namely types and directions of behavioral or structural asymmetry seen in the majority of the population. For example, 90% of the population is right-handed (Papadatou-Pastou et al., 2019). It is, however, important to stress that this dominance is relative and there are also some individuals who show right-hemispheric language dominance. For example, it has been shown that 4% of strong right-handers, 15% of ambidextrous individuals and 27% of strong left-handers show atypical rightward language dominance (Knecht et al., 2000). This, on the other hand, is a form of atypical lateralization, namely a pattern of asymmetry that is not common or at least not predominant in the population (Van der Haegen & Brysbaert, 2018).

Besides this variation of typical and atypical hemispheric asymmetries in the healthy population, a striking finding has emerged in clinical neuroscience. In several psychiatric and neurodevelopmental disorders such as schizophrenia (Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001), autism spectrum disorders (Lindell & Hudry, 2013), dyslexia (Eglinton & Annett, 1994), depression (Thibodeau, Jorgensen, & Kim, 2006) and post-traumatic stress disorder (PTSD) (Metzger et al., 2004), atypical hemispheric asymmetries are more common than in healthy controls (for details see the following sections). For example, handedness as a prime example of lateralized behavior shows atypical patterns of lateralization in several psychiatric and neurodevelopmental disorders. Patients with schizophrenia frequently display a higher prevalence of mixed- and left-handedness with patients having a 61% higher prevalence of non-right handedness (Sommer et al., 2001). Moreover, it has been proposed that patients with schizophrenia also show more ambiguous handedness (Green, Satz, Smith, & Nelson, 1989; Satz & Green, 1999), namely inconsistent hand use within the same task. This phenomenon does not seem to occur in the healthy population (Satz, Nelson, & Green, 1989). This coincides with the evidence for reduced right-handedness as the majority of healthy subjects consistently use their right hand for most tasks (Annett, 1972). An increase in non-right-handedness has also been reported for Autism Spectrum Disorders, with 18–57% incidence of left handedness and 17–47% incidence of mixed handedness (Lindell & Hudry, 2013) and dyslexia (Eglinton & Annett, 1994). Left-handedness has been associated with higher depression scores, where left-handedness is associated with a 5.2% higher probability of being depressed (Denny, 2009). In combat veterans, mixed-handedness has been associated with PTSD with 10.2% prevalence of PTSD in the whole sample and up to 22.6% prevalence in the mixed-handed subsample (Boscarino & Hoffman, 2007). As handedness is established early during ontogenesis (Hepper, Mccartney, & Shannon, 1998) and is often used as behavioral predictor for cerebral lateralization (Knecht et al., 2000), this poses the question if atypical patterns of hemispheric lateralization are typical for these disorders. It needs to be kept in mind however that non-right-handedness does not necessarily imply psychiatric or neurodevelopmental disorders nor does handedness alone constitute a sufficient proxy for all cerebral lateralization (Kushner, 2017). Thus, we will not only focus on changes of handedness but also other functional and structural asymmetries in the following sections.

In contrast, there is almost no empirical evidence for elevated hemispheric asymmetries in any psychiatric or neurodevelopmental disorder. Why so many different disorders consistently show a higher prevalence of atypical hemispheric asymmetries, despite vastly different symptoms, developmental trajectories and neuronal correlates is currently unknown. The matter is also complicated by the fact that it is presently unclear whether atypical hemispheric asymmetries are a cause, correlative epiphenomenon or consequence of psychiatric and neurodevelopmental disorders. Recent research suggests that in the case of dyslexia, altered hemispheric asymmetries are more likely to be a consequence of impaired language learning than the cause of dyslexia (Bishop, 2013). However, for other disorders this relation is still unclear.

The aim of the present review article is to discuss possible reasons why atypical hemispheric asymmetries are so common across different psychiatric and neurodevelopmental disorders. To this end, we first give a short overview about atypical hemispheric asymmetries in different disorders. As these often have already been in the focus of excellent review articles, we concentrated on key findings, relying on meta-analytic results whenever possible. We then discuss genetic and non-genetic factors involved in the ontogenesis of hemispheric asymmetries and psychiatric and neurodevelopmental disorders with the aim of identifying potential overlaps.

2. Neurobiological changes in psychiatric and neurodevelopmental disorders

In the following section, we will shortly summarize neurobiological changes in several neurodevelopmental and psychiatric disorders that have been associated with changes in asymmetries. Here, structural changes in gray and white matter as well as changes in function will be discussed. Also, alterations in functional connectivity, patterns of synchronized activity between different parts of the brain (Allen & DeYoung, 2017), and their network organizations will be mentioned.

2.1. Autism spectrum disorders

Autism spectrum disorders (ASD) comprise different disorders like autism, developmental disorder not otherwise specified and Asperger Syndrome. While the degree of overall impairment can vary significantly, ASD is characterized by deficits in social interactions, development and use of language as well as repetitive and stereotyped behaviors (Halter, Rolin-Kenny, & Dzurec, 2013).

Because there is major variation within ASD, it is difficult to pin down neurobiological changes underlying the disorder (Jumah, Ghannam, Jaber, Adeeb, & Tubbs, 2016). Structural changes in frontotemporal and frontoparietal cortex and cingulate regions have been associated with ASD (Ecker, Bookheimer, & Murphy, 2015), while the cerebellum, brainstem and basal ganglia seen to be spared (Brambilla, 2003). This change in cortical surface area might be driven by atypical brain maturation in early childhood: children with ASD show an aberrant neurodevelopmental trajectory with early cortical overgrowth followed by arrested growth in adolescence and accelerated decrease in cortical volume later in life (Ecker et al., 2015). This early overgrowth has been speculated to lead to excessive pruning and thus reduced long range functional connectivity between cortical areas and compensatory increased local connectivity later in life (Rane et al., 2015). Indeed, subjects with ASD not only show alterations in gray matter structure but in white matter structure as well. Here, reduction in white matter integrity in the superior longitudinal fasciculus, occipitofrontal fasciculus, cingulum, internal capsule and corpus callosum have been reported (Rane et al., 2015).

Similar to structural and functional changes in schizophrenia, neurobiological alterations in autism have been linked to specific functional networks like language and motor functions. Here, deviations from typical asymmetry patterns have been documented consistently. Compared to typically developing children, subjects with ASD show leftward volume reduction and underconnectivity, and rightward volume increase and overconnectivity in the motor system leading to a greater atypical involvement of the right hemisphere in motor-related function. This might be underlying the behavioral motor abnormalities seen in ASD (Floris & Howells, 2018). Moreover, subjects with ASD display atypical asymmetries in the language system: subjects show rightward asymmetry of the planum temporale (Gage et al., 2009) and altered white matter asymmetries (Lo et al., 2011), which are linked to impaired language function (Fossé et al., 2004). Also functional language lateralization is impaired leading to the notion that these changes underlie the language deficit commonly observed in ASD (Lindell und Hudry, 2013).

2.2. Dyslexia

In contrast to ASD, developmental dyslexia is a rather circumscribed disorder that is characterized by difficulties with accurate and fluent word recognition and spelling. Patients display unimpaired intelligence and adequate sensory abilities (Peterson & Pennington, 2012). Diagnosis of developmental dyslexia often overlaps with other reading disorders and is frequently comorbid with language impairment, speech sound disorder and ADHD. Patients with developmental dyslexia frequently display changes in gray matter structure. Patients show lower total brain volume and lower total cortical surface area as well as focal reductions in gray matter volume in left orbitofrontal cortex, left posterior superior temporal sulcus and right cerebellum (Eckert, Berninger, Vaden, Gebregziabher, & Tsu, 2016). However, the reliability of these results has recently been questioned, as studies on developmental dyslexia have been chronically underpowered and the exact location of gray matter changes often do not overlap (Ramus, Altarelli, Jednoróg, Zhao, & Di Scotto Covella, 2018). Out of all structural asymmetries in dyslexia, the reduced leftward asymmetry of planum temporale surface area stands out as the most reliable finding (Altarelli et al., 2014). As reading depends on the language system (Price, 2012), one would expect patients with dyslexia to display abnormalities in these regions. Indeed, patients with dyslexia show hypoactivation in the left-hemispheric language network, especially in temporoparietal and occipitotemporal regions (Norton, Beach, & Gabrieli, 2015). Because of these functional abnormalities in the language network, developmental dyslexia has also been labeled a disconnection syndrome (Peterson & Pennington, 2012), in which white matter changes in left temporoparietal regions account for the typical phonological problems in dyslexia. Indeed, patients show lower fractional anisotropy in frontotemporal white matter, especially in the left arcuate fasciculus and corona radiata (Vandermosten, Boets, Wouters, & Ghesquière, 2012).

2.3. Schizophrenia

Schizophrenia is a severe psychiatric disorder characterized by three different types of symptoms: positive symptoms like hallucinations and psychosis, negative symptoms like impaired speech and social withdrawal and symptoms of cognitive impairment (Joyce & Roiser, 2007). The disorder is accompanied by changes in gray and white matter structure as well as altered cerebral functioning patterns. Moreover, subjects with schizophrenia frequently display changes in frontal and temporal structural connectivity, although precise location of these changes does not always overlap (Fitzsimmons, Kubicki, & Shenton, 2013).

Compared to healthy controls, subjects with schizophrenia show a reduction in typical cerebral torque (Crow, Chance, Priddle, Radua, & James, 2013) as well as changes in cortical folding (Palaniyappan, Park, Balain, Dangi, & Liddle, 2015) and local gray matter reductions (Haijma et al., 2013). Moreover, schizophrenia has been repeatedly associated with changes in structural hemispheric asymmetries. Prominently, patients often show a reduction in planum temporale macrostructural asymmetry (Sommer et al., 2001). Reduction in white matter asymmetry in the uncinate fasciculus (Miyata et al., 2012), the occipito-frontal fasciculi (Kunimatsu et al., 2008) and the anterior cingulum bundle (Fujiwara et al., 2007) have been reported. Moreover, patients display reduced hemispheric asymmetry of global integration and nodal efficiency (Sun, Chen, Collinson, Bezerianos, & Sim, 2017). These reductions were associated with decreased functional language lateralization (Ocklenburg, Beste, Arning, Peterburs, & Güntürkün, 2014) and increased positive symptomatology (Geoffroy

et al., 2014). This reduction in structural and functional asymmetry has been speculated to play a key role in the origin of auditory verbal hallucinations as they have been proposed to be misinterpretations of internally generated speech lateralized to the left temporal lobe (Hugdahl et al., 2008). These findings could however not be consistently replicated (Shapleske, Rossell, Simmons, David, & Woodruff, 2001). A meta-analysis of dichotic listening studies implied that reduced language lateralization is a strong marker for the experience of auditory verbal hallucinations in patients with schizophrenia rather than schizophrenia diagnosis itself (Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013).

Patients also display altered functional connectivity. In a recent study, Agcaoglu et al. (2018) not only found reduced overall connectivity in patients but also decreased hemispheric network asymmetries. These functional changes could result from the afore mentioned structural changes and from reduced interhemispheric connectivity resulting in a failure for the left hemisphere to establish dominance (Ribolsi, Daskalakis, Siracusano, & Koch, 2014). These changes in functional connectivity could constitute a biomarker for schizophrenia, as they seem to be typical for the disorder (Royer et al., 2015). Therefore, not only gray matter but also white matter changes as well as alterations in functional connectivity seem to influence the symptomatology.

However, the origin of these changes is still not well understood. Studies suggest that about a third of the trait variance is caused by genetic influences (Purcell et al., 2009). Beyond that, it is important to note that schizophrenia might not be a single disorder, but a group of heritable disorders caused by different genetic and neurodevelopmental mechanisms (Arnedo et al., 2015) as the heterogeneous symptoms are unlikely originating from the same neuronal systems. Thus, only certain symptom groups might be linked to genes that are associated with laterality ontogenesis (Ocklenburg, Güntürkün, Hugdahl, & Hirnstein, 2015). In addition to that, schizophrenia has been linked to environmental influences (Owen, Sawa, & Mortensen, 2016) like urbanity and maternal stress so influences other than genetics are likely.

2.4. *Depression*

Major depressive disorder (MDD) has been identified as the leading cause for disability worldwide and is proposed to be the second biggest contributor to mortality in 2020 (Whiteford et al., 2013). This is due to MDDs high prevalence and associated mortality risk (Kessler et al., 2003). This disorder is characterized by negative affect, anhedonia, feelings of hopelessness and changes in activity and appetite.

MDD has also been linked to changes in gray matter structure. Region of interest studies have repeatedly shown volume reductions in frontal and orbito-frontal cortex, caudate, putamen and hippocampus as well as an excess of white matter lesion volumes (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012) while voxel-based morphometry studies have identified reductions in the dorsal frontomedial cortex, the cingulate cortex and the amygdala (Sacher et al., 2012).

Aberrant activation patterns in response to tasks concerning emotion regulation and attention have been in focus in the context of MDD: in the cognitive neurobiological model of depression, changes in information processing and cognitive representations have been associated with changes in activation of underlying structures giving rise to depressive symptoms (Disner, Beevers, Haigh, & Beck, 2011). Here, increased ACC and mPFC activity lead to negative thought patterns, while increased amygdala and hippocampus activity and decreased dlPFC and vmPFC lead to and sustain biased attention, information processing and memory retrieval. Altered emotion processing and motivation in MDD have been linked to changes in the medial prefrontal limbic network and the reward network respectively (Kupfer, Frank, & Phillips, 2012). MDD has been associated with changes in functional connectivity, especially in the default mode network (DMN). Patients with MDD show increased connectivity within the anterior DMN, between the anterior DMN and the salience network and decreased connectivity between the anterior and posterior DMN and the posterior DMN and central executive network (Mulders, van Eijndhoven, Schene, Beckmann, & Tendolkar, 2015).

Changes in asymmetries have not been in the focus in the study of MDD so far. The strongest evidence for altered asymmetry in MDD comes from EEG studies. Here, patients with MDD show reduced asymmetry in frontal alpha power during resting state (Thibodeau et al., 2006). Alpha band power has been used as a marker for the absence of brain activity (Pfurtscheller, Stancák, & Neuper, 1996). Thus, this change in MDD could be due to reduced left frontal or increased right frontal activity in depression. According to the valence hypothesis, the left hemisphere is associated with positive affect and the right hemisphere is associated with negative affect (Davidson & Hugdahl, 1996; Silberman & Weingartner, 1986). Thus, this change in asymmetry could be linked to the changed mood in MDD (Thibodeau et al., 2006).

These substantial differences between MDD patients and healthy controls in functional asymmetries are not necessarily reflected by similar differences in structural asymmetries in grey matter. A recent study by De Kovel et al. (2019) and De Kovel, Carrión-Castillo, et al. (2019) focused on MDD-related changes in structural asymmetry as reflected by cortical thickness and surface area of 34 cerebral cortical regions. The analysis performed on the ENIGMA consortium data could not identify any significant differences in these macrostructural asymmetries between MDD patients and controls. This indicates that asymmetries of cortical thickness and surface are unrelated to changes in functional lateralization in MDD. Unfortunately, there is little published data on asymmetries in gray matter microstructure or white matter structural asymmetries (e.g., Kieseppä et al., 2010), but these might be promising venues for future research.

2.5. *Posttraumatic stress disorder*

Posttraumatic stress disorder (PTSD) can be a result of exposure to trauma, an event that involves actual or perceived threat to one's health resulting in a feeling of intense fear and helplessness (American Psychiatric Association, 2014). The disorder involves symptoms of reliving the traumatic event like flashbacks, symptoms of changed attentional states like hyperarousal and avoidance of stimuli associated with the

traumatic event. Most studies investigating the effects of trauma and PTSD on neurological changes focus on the hippocampus and the amygdala as these two structures are implicated in the main symptom groups of this disorder (Ahmed-Leitao, Spies, van den Heuvel, & Seedat, 2016). Here, patients show volume reductions in the bilateral hippocampus and the bilateral ACC (O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015). Changes in amygdala volume were inconclusive in adults with different types of trauma. Only in patients with PTSD resulting from childhood maltreatment, both hippocampal and amygdala volumes are bilaterally reduced compared to healthy controls (Ahmed-Leitao et al., 2016). This militates for the hypothesis that PTSD from childhood maltreatment composes a distinct subtype of PTSD as these patients also show a less favorable course of treatment and higher symptom severity (Teicher & Samson, 2013). As outcome of maltreatment is dependent on type, timing and severity, this indicates an epigenetic modification of stress response and brain development during childhood (Danese & McEwen, 2012). Moreover, patients display decreased white matter integrity in the ACC, the cingulum, the precentral gyrus, left frontal gyrus, internal capsule and midbrain (Ayling, Aghajani, Fouche, & van der Wee, 2012).

Alterations in PTSD are not limited to structural changes: patients show hyperresponsiveness in the amygdala and hyporesponsiveness in the rostral and ventral medial PFC (Hughes & Shin, 2011). However, changes in asymmetrical organization have been sparsely investigated. Some studies found increased right-sided parietal EEG resting state activation (Kemp et al., 2010), which were attributed to anxious arousal (Metzger et al., 2004) while other studies have not found changes in EEG resting state activity (Gordon, Palmer, & Cooper, 2010). In general, changes in asymmetry are not well studied in the context of PTSD although this perspective might contribute to the field, as there is evidence for functional differences between left and right hippocampus (Burgess, Maguire, & O'Keefe, 2002).

3. Both genes and environment affect the ontogenesis of hemispheric asymmetries

The healthy brain and body display a series of typical structural and functional asymmetries (Kong et al., 2018). How do these asymmetries come about?

Bodily asymmetries are determined during early embryogenesis when asymmetric *Nodal* signaling leads to left-sided expression of *Pitx2* and thus asymmetric organ development further downstream (Hirokawa, Tanaka, Okada, & Takeda, 2006). However, the origins of hemispheric asymmetries remain elusive. Early intrauterine development of structural (Abu-Rustum, Ziade, & Abu-Rustum, 2013) and functional asymmetries (Hepper et al., 1998; Ververs, Vries, van Geijn, & Hopkins, 1994) suggests a genetic component. While hemispheric asymmetries like handedness were initially thought to be determined monogenetically (Annett, 2001; McManus, 1999), this theory was clearly refuted by all handedness GWAS (Armour, Davison, & McManus, 2014; De Kovel & Francks, 2019; Eriksson et al., 2010).

If a single gene would determine handedness, it should explain a large amount of variance in the phenotypic data. However, all published GWAS either failed to show any significant effects or found significant effects for multiple loci that explained only small amounts of variance.

Nevertheless, there are genetic influences on hemispheric asymmetries. Strong evidence for a genetic influence on handedness comes from large scale twin studies: In their 2009 study on over 25000 twin families, (Medland et al., 2009) estimated about 24% of variance in handedness to be accounted for by shared additive genetic effects while 76% of variance was accounted for by non-shared environmental influences. Nevertheless, the specific genes that influence this behavioral asymmetry are still debated. Several genes have been proposed to underlie this association. For example, *LRRTM1* (Francks et al., 2007), *SETDB1* and *SETDB2* (Arning et al., 2015; Crespi, Read, & Hurd, 2018; Ocklenburg, Arning et al., 2016) as well as *AR* (Arning et al., 2015; Hampson & Sankar, 2012; Medland et al., 2005) have been associated with handedness. The gene *PCSK6* involved in the development of visceral asymmetries has been associated with relative hand skill (Arning et al., 2013; Scerri et al., 2011) as well as gray matter asymmetry in frontal and temporal cortex (Berretz et al., 2019). Brandler and Paracchini (2014) proposed that genes involved in the Nodal cascade and ciliogenesis control both determination of visceral asymmetry as well as the development of brain mid-line structures which in turn influence functional asymmetries.

That being said, a recent study of the UK Biobank could not replicate findings on previous candidate genes (De Kovel & Francks, 2019). However, the study produced several novel loci, like *MAP2*, a large inversion haploblock spanning the genes *STH*, *KANSL1*, *ARL17B*, *ARL17A*, *LRRC37A*, *LRRC37A2* and *NSF*, he non-coding RNA-gene *LINC00381*, *HCG27* and *DCAF12L1*, whose causative role remains to be resolved. Since most of these genes are involved in brain development and neurogenesis, they could also play a role in the development of structural and/or functional asymmetries in the brain.

However, the contribution of single gene effects for heritability might be too subtle to be reliably identified even in large scale studies as any gene with a regulatory variant can contribute to phenotype ontogenesis by not only influencing the phenotype directly but also influencing other genes across the genome (Boyle, Li, & Pritchard, 2017). In light of this, gene ontology groups constitute a promising approach, identifying biological pathways involved in anatomical structure development, pattern specification and biological regulation to be associated with handedness (Schmitz, Lor, Klose, Güntürkün, & Ocklenburg, 2017). Moreover, epigenetic regulation constitutes a mechanism by which phenotype ontogenesis can be influenced without changes in genomic variation but by environmental influences.

The largest published work on the impact of non-genetic factors on hemispheric asymmetries investigated the impact of early life factors on handedness using the UK Biobank cohort (De Kovel, Carrión-Castillo, & Francks, 2019). Here, the authors found that year, month and location of birth affected the probability of being left-handed. This suggests that cultural effects, for example via direct instructions or observational learning, influence the probability of

becoming left-handed (Laland, 2008; Laland, Kumm, van Horn, & Feldman, 1995). The effect of year of birth is likely caused by forced relearning of right-handedness in left-handed children up to the 1970s. Additionally, hand preference was affected by birthweight, being part of a multiple birth, breastfeeding, and sex, with each effect remaining significant after accounting for all others. Interestingly, several of these factors are related to early life stress (De Kovel et al., 2019). As with maternal age (Bailey & McKeever, 2004) and stress during pregnancy (Searleman, Porac, & Coren, 1989), less beneficial conditions are associated with an increase in left-handedness. These influences will be later discussed in more detail.

4. Genetic overlap: disorders and asymmetry

The psychiatric and neurodevelopmental disorders described above are associated with a higher probability of atypical hemispheric asymmetries. If this shared phenotype were to be determined by a common genetic factor, one would expect genetic overlap between the different disorders as well as between the disorders and asymmetry ontogenesis.

Indeed, schizophrenia, MDD, bipolar disorder, anxiety disorder and ADHD show significant genetic correlation with each other with an average genetic correlation = .40 indicating shared heritability for these disorders (Anttila et al., 2018). An earlier study also examined common genetic components across different disorders and identified several loci associated with ASD, ADHD, MDD, bipolar disorder, and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Here, intronic SNPs in *ITIH3* and *AS3MT* as well as SNPs in *CACNA1C* and *CACNB2* reached genome-wide significance. The latter two are involved in calcium channel functioning. Looking not only at genetic variation but also at the transcriptome, another recent study revealed a significant overlap among ASD, schizophrenia and bipolar disorder as well as schizophrenia, bipolar disorder and MDD (Gandal et al., 2018). This overlap appeared in genetic modules enriched for glia cell differentiation and fatty-acid metabolism pathways as well as G protein–coupled receptors, cytokine–cytokine interactions, and hormone activity pathways indicating an influence of transcription of genes involved in synaptic regulation, astrocyte function and HPA regulation.

However, there is no evidence that the shared genetic variation among these disorders also influences hemispheric asymmetries. There is, however, some evidence that some of the genetic loci linked to hemispheric asymmetries are also implicated in one or more of the disorders discussed in this paper.

In order to systematically investigate these overlaps, we determined for each of the major loci associated with hemispheric asymmetries whether or not any published papers suggested that they might also be related to one of the investigated disorders (see Table 1). Different genes previously associated with handedness also show an association with different disorders. The genetic influence on all of these disorders is highly complex and the relationship with asymmetry-related genes is ambiguous.

In general, Table 1 shows that some of the genes implicated in the ontogenesis of hemispheric asymmetries might also be relevant for one or more neurodevelopmental or psychiatric disorders. Importantly, those effects are mostly specific to single disorders and none of the discussed genes have been related to all of the discussed disorders, making it unlikely the there is a genetic factor that can completely explain the reduction of asymmetries in several different disorders.

As ASD are a heterogeneous group of disorders, genetic components influencing the behavioral phenotype are also complex. Several disorders have been associated with a behavioral phenotype that fulfills the diagnostic criteria of ASD. For example, subgroups with Fragile X Syndrome, Rett Syndrome, PTEN Macrocephaly Syndrome and various metabolic conditions fulfill diagnostic criteria for ASD (Miles, 2011). Other genetic risk factors include changes in *SHANK3*, which influences development and function of synapses, and *TPTH2*, affecting the serotonergic system, among others (Waye & Cheng, 2018).

Regarding the asymmetry-related genes, *LRRTM1* (Sousa et al., 2010), *PCSK6* (Robinson et al., 2016), *SETDB1* (Cukier et al., 2012), *AR* (Chen & van Horn, 2017), *COMT* (Karam et al., 2013), *MAP2* (Pescucci et al., 2003) have been related to ASD or autism-like traits. As the autism phenotype often shows in different disorders, it is important to view these overlaps with caution.

In the etiology of developmental dyslexia, a strong role has been ascribed to genes underlying neuronal migration. According to this hypothesis, the abnormalities in structure and function mentioned above result from a failure of neurons from the ventricular zone of the cortex to migrate upwards (Galaburda, LoTurco, Ramus, Fitch, & Rosen, 2006). However, the genes commonly associated with dyslexia, *DYX1C1*, *DCDC2*, *KIAA0319* and *ROBO1*, have recently been questioned to be involved in neuronal migration, rendering this hypothesis unlikely (Guidi et al., 2018). Hence, the developmental factors leading to impaired asymmetries in developmental dyslexia are still unclear. It has been suggested that the development of dyslexia is not influenced by genes involved in neuronal migration but rather by genes involved in left–right axis determination. In this context, the gene *PCSK6* has been in the focus of research: Studies could show an association between variation in PCSK6 and relative hand skill in dyslexia (Scerri et al., 2011) which have been replicated in other dyslexia samples as well as the general population (Brandler et al., 2013).

As most neurodevelopmental disorders, schizophrenia is proposed to be highly polygenic in nature with several copy number variants, de novo mutations and distinct genetic loci associated with this disorder. In a large-scale study with nearly 37000 patients, 108 genetic loci reached genome-wide significance (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Although these loci are widespread across the genome, there is evidence for convergence on biological processes like synaptic communication and immune and inflammatory processes (Owen et al., 2016). Especially genes involved in glutamatergic synapses have been implicated in the regulation of dopaminergic function, which is aberrant in schizophrenia (Howes, McCutcheon, Owen, & Murray, 2017). Moreover, the disorder

Table 1 – Genes that have been associated with handedness and are implicated in the ontogenesis of different disorder. The two left columns show the gene and study that showed an association with handedness. The right column displays exemplary studies demonstrating an association of the gene with the respective disorder.

Gene	Study	Phenotype	Association with disorder
LRRTM1	Annett and Turner (1974)	Hand skill	Dyslexia: potentially (Ludwig et al., 2009) ASD: potentially (Sousa et al., 2010) MDD: no PTSD: no Schizophrenia: yes (Francks et al., 2007)
PCSK6	Arning et al. (2013)	Hand preference	Dyslexia: Yes (Scerri et al., 2011) ASD: potentially (Robinson, Hurd, Read, & Crespi, 2016) MDD: no PTSD: no Schizophrenia: potentially (Robinson et al., 2016)
SETDB1	Ocklenburg, Arning et al. (2016)	Hand preference	Dyslexia: no ASD: yes (Cukier et al., 2012) MDD: no PTSD: no Schizophrenia: yes (Chase et al., 2015)
SETDB2	Ocklenburg, Arning et al. (2016)	Hand preference	Dyslexia: no ASD: no MDD: no PTSD: no Schizophrenia: no
AR	Arning et al. (2015)	Hand preference	Dyslexia: no ASD: yes (Chen & van Horn, 2017) MDD: no PTSD: no Schizophrenia: no
COMT	Savitz, van der Merwe, Solms, and Ramesar (2007)	Hand skill	Dyslexia: no ASD: yes (Karam et al., 2013) MDD: yes (Otsuka et al., 2019) PTSD: yes (Haxhibeqiri et al., 2019) Schizophrenia: yes (Debost et al., 2017)
MAP2	de Kovel & Francks (2019)	Writing hand	Dyslexia: no ASD: yes (Pescucci et al., 2003) MDD: potentially (Daftary et al., 2017) PTSD: no Schizophrenia: yes (Rosoklija et al., 2005)
HCG27	de Kovel & Francks (2019)	Writing hand	Dyslexia: no ASD: no MDD: no PTSD: no Schizophrenia: no
DCAF12L1	de Kovel & Francks (2019)	Writing hand	Dyslexia: no ASD: no MDD: no PTSD: no Schizophrenia: no

shows a considerable overlap in this polygenic variation with bipolar disorder (International Schizophrenia Consortium, 2009). Regarding the asymmetry-related genes, *LRRTM1* (Francks et al., 2007), *PCSK6* (Robinson et al., 2016), *COMT* (Debost et al., 2017) and *MAP2* (Rosoklija et al., 2005) also have potentially been implicated in schizophrenia. However, these effects might be weak, as none of these four genes are within the 108 loci that reached genome-wide significance for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

While genome-wide association study (GWAS) in MDD had difficulties in identifying significant loci (Levinson et al., 2014), a recent study by Wray et al. (2018) discovered 44 independent loci associated with depression in a meta-analysis of eight MDD and major depression cohorts. The authors identified 153 significant genes, whereof about a third was incorporated in the major histocompatibility complex and thus associated with immune functioning. Others were mainly associated with calcium, glutamate and dopaminergic signaling. Regarding asymmetry-related genes, *COMT* (Otsuka et al., 2019) and *MAP2* (Daftary et al., 2017) have been associated with MDD. Yet, these genes have not reached genome-wide significance in GWAS related to MDD so the effect are rather weak.

PTSD is the only disorder in the diagnostic and statistical manual of mental disorders that includes the cause for the disorder in the diagnostic criteria (American Psychiatric Association, 2014). Thus, the focus in etiology of PTSD has

been on environmental factors of trauma and personality factors influencing trauma processing. However, the susceptibility to trauma is heritable (True et al., 1993; Wolf, Mitchell, Koenen, & Miller, 2014). A recent large scale study by Duncan et al. (2018) estimated the genetic-based heritability in European-American women to be 29%. Despite that, no single-nucleotide polymorphism reached significance. With regard to asymmetry-related genes, only *COMT* (Haxhibeqiri et al., 2019) has been associated with PTSD. However, the association is not evident on a genome-wide level (Duncan et al., 2018).

While genes involved in cilia formation have been associated with visceral left–right axis determination and neurodevelopmental and psychiatric disorders show changes in asymmetry, there is no evidence for a link between cilia function and neurodevelopmental disorders. In a recent review on this topic, Trulioff, Ermakov, and Malashichev (2017) conclude that the link between proteins connected to cilia function and neurodevelopmental disorders is conveyed via influences on neuronal migration, neurite outgrowth and cellular and interneuron signaling rather than mechanisms underlying visceral asymmetry. This indicates that another, non-genetic factor common to these disorders might contribute to changes in asymmetry.

Taken together, there is evidence for a genetic overlap between different neurodevelopmental and psychiatric disorders. There is also evidence that some of the potential genetic determinants of hemispheric asymmetries are also potentially affecting one or more disorders. A recent paper on the UK Biobank cohort examined the link between handedness, brain structure and genetic background (Wiberg et al., 2019). The study demonstrated a link between left-handedness, genes involved in brain development, microtubules and brain patterning and structural connectivity in white matter tracts connecting language-related areas. Here, the genetic locus rs199512 was also associated with pathogenesis of psychiatric diseases. This indicates that shared genetic variations contribute to lateralization, handedness and certain neurodevelopmental disorders.

However, there is no clear evidence that any number of genetic loci overlap between all investigated disorders and hemispheric asymmetries and explain a considerable amount of phenotypic variance. Thus, it is highly unlikely that genetic overlap is the reason why atypical lateralization is so common in many neurodevelopmental and psychiatric disorders.

5. Stress affects the emergence of different disorders

As discussed earlier, many psychiatric and developmental disorders share some genetic basis. However, these genes have not been implicated in the development of hemispheric asymmetries. This poses the question as to how these disorders come to show changes in hemispheric asymmetries. If the influence is not purely genetic, the development of these disorders has to be influenced by another mechanism that is common to all these disorders. Here, earlier research has suggested stress as a major component in the development of mental illness.

5.1. *Stress*

The body is equipped with two different systems that respond to stress. The sympathetic adrenomedullary system is part of the sympathetic nervous system and secretes epinephrine and norepinephrine from the adrenal medulla. This fast-acting stress response is part of the fight or flight response (Cannon, 1929) and influences the sympathetic arm of the autonomous nervous system, regulating for example heart rate and blood pressure. The other system is the Hypothalamic-pituitary-adrenal (HPA) axis (Joëls & Baram, 2009; Kloet, Joëls, & Holsboer, 2005). Secretion of corticotrophin-releasing-hormone (CRH) from paraventricular cells in the hypothalamus (PVN) leads to release of adrenocorticotropic hormone (ACTH) from the pituitary (Gunnar & Quevedo, 2007). ACTH stimulates the release of cortisol from the adrenal cortex, which in turn interacts with mineralocorticoid and glucocorticoid receptors in various types of tissues (Joëls, Karst, DeRijk, & Kloet, 2008).

5.2. *Changes in HPA-axis activity in mental disorders*

Many developmental and psychiatric disorders are accompanied by changes in stress reactivity and basic cortisol levels. In ASD, patients show a greater circadian dysregulation and more day to day variability in cortisol levels indicating a heightened sensitivity for the influence of daily stressors compared to healthy controls (Taylor & Corbett, 2014). Moreover, patients show a slower response and recovery from stress as well as hyperreactivity to social interaction and aversive stimulation.

Most patients with schizophrenia also show a blunted cortisol response to stress induction (Zorn et al., 2017) but elevated baseline cortisol levels and exhibit an enlarged pituitary supporting hypercortisolism compared to healthy controls (Beards et al., 2013; Borges, Gayer-Anderson, & Mondelli, 2013; Walker, Mittal, & Tessner, 2008). These changes in cortisol secretion likely contribute to poor physical health and premature mortality seen in patients with schizophrenia (Bradley & Dinan, 2010). The link between altered cortisol levels and schizophrenia has been strengthened by the observation that HPA activation influences dopamine level changes seen in schizophrenia and antipsychotic treatment reduces cortisol and symptoms in psychosis (Holtzman et al., 2013).

MDD has been frequently connected with changes in HPA activity. Baseline cortisol levels are chronically elevated in depression (Jacobson, 2014) and patients show elevated hair cortisol measures indicating chronic stress (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). The empirical evidence for sex differences in HPA activity is somewhat heterogeneous, however, a recent meta-analysis that analyzed 308 currently depressed patients and 219 remitted patients from 14 studies showed that HPA reactivity to stress induction shows a blunted response in women and an elevated response in men (Zorn et al., 2017). However, changes in cortisol levels seem to be related to specific subtypes of depression, with hyperactivity of the HPA-axis only seen in melancholic and psychotic depression (Wolf, 2008). These changes in HPA-axis activity has been ascribed to exaggerated

CRH drive and/or altered MR/GR balance (Schlosser, Wolf, & Wingenfeld, 2011). This is in accord with the notion that MR stimulation exerts beneficial effects in young MDD patients (Wingenfeld & Otte, 2019). MDD patients also do not show typical reactions in response to cortisol administration with no effects on memory retrieval or inhibitory control (Wingenfeld & Wolf, 2015). Moreover, chronically elevated cortisol levels have been associated with reduced hippocampal volumes often seen in depression (Dohm, Redlich, Zwitserlood, & Dannlowski, 2017). It has been hypothesized that this association is mediated by the influence of glucocorticoids on brain derived neurotrophic factor and other growth factors, which levels are decreased by stress and normalized by antidepressant treatment (Duman & Monteggia, 2006; Holsboer, 2000, 2001). This coincides with the observation, that MDD patients show a heightened cortisol awakening response which is reduced by antidepressant treatment restoring memory function (Hinkelmann et al., 2013; Wingenfeld & Wolf, 2011).

Patients with PTSD show elevated CRH and ACTH levels while basal cortisol levels are lower (Yehuda, 2002), probably due to increased glucocorticoid feedback sensitivity (Jacobson, 2014; Morris, Compas, & Garber, 2012).

5.3. *The influence of stress on the developing organism*

5.3.1. *Influence of stress on development of disorders*

Stress has been proposed to be the most potent factor in the vulnerability to mental illness (Kinney, Munir, Crowley, & Miller, 2008).

The exposure to prenatal stress leads to reprogramming of the HPA-axis in offspring later in life (Lupien, McEwen, Gunnar, & Heim, 2009; Meaney & Szyf, 2005; O'Donnell & Meaney, 2017). Maternal cortisol levels have been proposed to impact offspring by general modulation of the developing fetal nervous system, specific effects on nervous system subcomponents and alterations in serotonin and dopamine transmitter systems (Huizink & de Rooij, 2018). Although the influence of maternal glucocorticoids on the developing embryo is attenuated by placental 11β-HSD2, repeated stress exposure reduces its activity leaving the fetus susceptible for the influence of glucocorticoids (Mairesse et al., 2007). These maternal glucocorticoids change brain developmental processes and thus alter later HPA function: early life stress leads to attenuated HPA-axis regulation at the level of the PVN, amygdala and hippocampus leading to reduced negative feedback resulting in the HPA-axis overactivation in different mental disorders (van Bodegom, Homberg, & Heckens, 2017). Moreover, prenatal stress leads to epigenetic changes in HPA-axis pathway-related genes that could mediate exposure-phenotype associations (Cao-Lei et al., 2017). These glucocorticoids exert tissue-specific effects on gene expression in the embryo altering later HPA reactivity (Bale et al., 2010). Another possible mechanism involves stress related changes in the placenta and intrauterine environment leading to altered brain development (for a comprehensive review see Babenko, Kovalchuk, & Metz, 2015). This indicates that changes in HPA-axis regulation and activity are essential to the development and perpetuation of several neurodevelopmental and psychiatric disorders.

The influence of stress in the developing organism is not limited to intrauterine effects. Early life stress has been shown to influence stress sensitivity via epigenetic changes in the glucocorticoid receptor gene (McGowan et al., 2009). Quality of maternal care affects DNA methylation, acetylation and transcription factor binding to GR promoter region (Weaver et al., 2004) leading to altered behavioral and physiological coping responses in offspring. Postnatal stress and childhood maltreatment further induce experience-dependent changes in structure and function of the nervous system (Teicher, Samson, Anderson, & Ohashi, 2016). In genetically vulnerable individuals, these maltreatment-induced changes may lead to the development of psychopathy (Belsky & Pluess, 2013). It is important to note that the influence of stress on the developing nervous system is dependent in the timing an severity of the stressor with the strongest effects on structures that are affected by neurodevelopmental changes at the time (Lupien et al., 2009). Stress during adulthood seems to affect the integrity of the hippocampus and the medial PFC, leading to hypoactivity and dendritic atrophy, while the amygdala shows hyperactivity and hypertrophy as a result of chronic stress (Wolf, 2017).

5.3.2. *Influence of stress on hemispheric asymmetries*

Taken together, stress is a potent influence factor in the ontogenesis of all the discussed psychiatric and neurodevelopmental disorders. It therefore is a strong candidate to cause phenotypic similarities like reduced hemispheric asymmetries in patients affected from these disorders.

But does it also directly affect hemispheric asymmetries? Indeed, there is evidence from studies in both human participants and non-human model organisms alike suggesting that various forms of stress affect functional and structural hemispheric asymmetries in the vertebrate brain (Ocklenburg, Korte, Peterburs, Wolf, & Güntürkün, 2016). Jones, Osmond, Godfrey, and Phillips (2011) investigated the effects of acute stress on hemispheric asymmetries by subjecting children to the Trier Social Stress Test (TSST). In this study, acute stress led to more lateralized cerebral blood flow in children with higher prenatal stress. Furthermore, acute stress has been shown to enhance right-hemispheric activity in response to stress (Gruzelier & Phelan, 1991). Brüne, Nadolny, Güntürkün, and Wolf (2013) could show that acute stress induced hemispheric asymmetries in an emotional face recognition task, indicating a stronger activation of the right hemisphere as well. In general, acute and chronic stress seems to lead to a greater activation of the right hemisphere as well as reducing inhibitory effects over the corpus callosum (Ocklenburg, Korte et al., 2016).

Using neuroimaging techniques, asymmetrical reaction patterns to stress have been found. Here, the right ventral prefrontal cortex has been associated with the response to stress (Wang et al., 2005). On the structural level, smaller volumes of the left anterior cingulate cortex have been implicated in HPA-axis dysregulation (MacLullich et al., 2006).

The influence of early life stress has been primarily investigated in the context of handedness. The early insult theory postulates that left-handedness pathologically results from stress during birth (Bakan, Dibb, & Reed, 1973). In follow-up studies, these results were however only found in

subsamples and of a weaker effect (Coren, 1995; Coren & Porac, 1980; Leiber & Axelrod, 1981). Furthermore, a large number of studies could not replicate this result as they found no relation between birth stress and handedness (Annett & Ockwell, 1980; Bailey & McKeever, 2004; Ehrlichman, Zoccolotti, & Owen, 1982; Van der Elst et al., 2011) so the relation between these two phenomena is still unclear.

As discussed above, handedness has been associated with lower birthweight, being part of a multiple birth and being breast-fed. These factors are markers of suboptimal prenatal development: in their review of the Fetal Origins of mental Healthy hypothesis, O'Donnell and Meaney (2017) propose that maternal adversity influences intrauterine factors which in turn program neural systems underlying cognitive-emotional function. These affect the development of psychiatric and neurodevelopmental illness. It might be possible that these intrauterine factors also affect the development of hemispheric asymmetries adversely through epigenetic regulation (Schmitz, Güntürkün, & Ocklenburg, 2019). There are different mechanisms by which epigenetic effects of stress on hemispheric asymmetries could be inherited. Germ line epigenetic inheritance implies an environmental factor influencing the mother, which directly passes on these epigenetic changes to their children (Crews, 2008). In experience-dependent inheritance, the mothers' behavior leads to epigenetic changes in children that in turn induces the same behavior in offspring towards their offspring (Danchin et al., 2011). Lastly, gene-dependent inheritance implies that a genetic factor increases the likelihood of an environmental factor to occur that influences epigenetic changes in offspring (Coren, 1995; Schmitz et al., 2019). These effects might account for the shared additive genetic-based effects seen in twin studies. It has been shown that maternal stress as well as birth complications influence handedness ontogenesis (Schmitz, Metz, Güntürkün, & Ocklenburg, 2017).

6. Conclusion

As previously described, stress seems to be an important factor in the development of psychiatric and neurodevelopmental disorders. As a causative factor, it might disrupt the typical brain development leading to structural and functional alterations seen in these disorders. We propose that early life stress, like intrauterine and birth stress, as well as chronic elevation of the HPA-axis not only increases the risk for psychiatric and neurodevelopmental disorders but also changes structural and functional hemispheric asymmetries (see Fig. 1). These influences can come about via several possible mechanisms. These are not mutually exclusive but rather complementary. Moreover, the presence of these atypical patterns in individuals free of the disorders mentioned above does not necessarily disagree with our proposal. Rather it highlights the multifaceted nature of neurodevelopmental and psychiatric disorders: the ontogenesis of these disorders in association with hemispheric asymmetries and stress is multifactorial with all factors increasing the probability of development of said disorders. Vulnerability to stress presents a risk factor for the

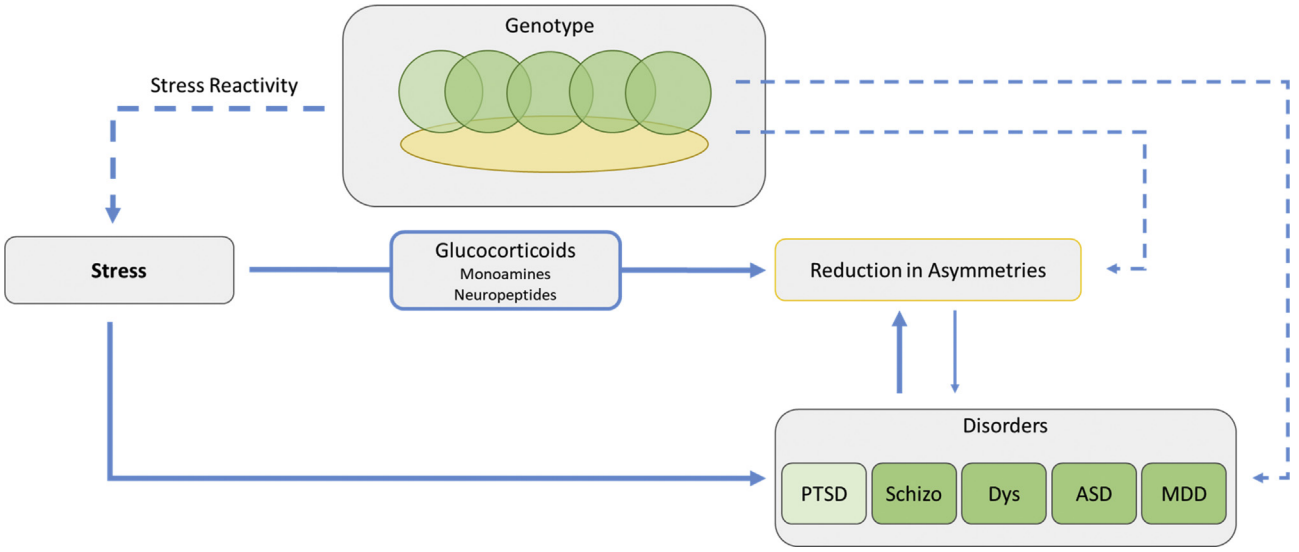

Fig. 1 – The influence of stress on psychiatric and neurodevelopmental disorders and hemispheric asymmetries. Stress as an environmental factor influences the risk for the development of different disorders as well as the development of hemispheric asymmetries. Different forms of stress, like intrauterine and chronic stress lead to a reduction in asymmetries often seen in psychiatric disorders. Stress also influences the development of disorder separately. Genetic differences influence the development of hemispheric asymmetries and the development of psychiatric disorders. Between these genes, partial overlap is possible so that a few genes influence both phenotypes. With regard to the disorders mentioned in the review, PTSD presents an outlier, as it is the only disorder that is not accompanies by heightened cortisol levels. It would be of interest to investigate changes in hemispheric asymmetries with this regard.

development of disorders as well as changes in typical asymmetry patters, however, other vulnerability and protective factors may influence illness outcomes.

It needs to be considered that some genes might influence both the sensitivity of stress system and the development of hemispheric asymmetries, which is known as partial pleiotropy (Ocklenburg et al., 2014). A more direct influence of stress on the development of hemispheric asymmetries might derive from intrauterine effects of maternal stress and early life stress on the stress system and disease development. In their Fetal Origins of mental Healthy hypothesis, O'Donnell and Meaney (2017) propose that maternal adversity influences intrauterine factors which in turn program neural systems underlying cognitive-emotional function. These affect the development of psychiatric and neurodevelopmental illness. It might be possible that these intrauterine factors also affect the development of hemispheric asymmetries adversely through epigenetic regulation (Schmitz et al., 2019). As discussed above, there is evidence that maternal stress plays a role in the development of handedness (Schmitz, Metz et al., 2017).

Pathological changes in the stress system as well as hemispheric asymmetries due to these early influences may lead to further dysregulation and disorganization. The resulting changes in HPA reactivity and basal cortisol secretion could acutely influence hemispheric asymmetries. There is evidence that fluctuating steroid hormones change functional hemispheric asymmetries (e.g., Brüne et al., 2013; Ocklenburg, Korte et al., 2016). It has been suggested that hormonal changes affect information transfer via the corpus callosum (Hausmann & Güntürkün, 2000). As the corpus callosum expresses glucocorticoid receptors (Yu, Romero, Gomez-Sanchez, & Gomez-Sanchez, 2002), acute stress and the resulting increase in free glucocorticoids could influence the transmission of inhibitory cross-hemispheric transfer. The resulting dysfunction could lead to further dysregulation, thus maintaining the disordered state.

It needs to be emphasized that the effect of stress on hemispheric asymmetries could depend on the timing of the stressor. While intrauterine and early postpartum stress might have an organizing effect on brain development during sensitive periods, acute or chronic stress could influence changes in functional asymmetries that could also deviate from changes induced due to early life influences. Depending on onset and type of stressor, influences on the nervous system may vary in type, degree and direction. Here, early intrauterine stress might have more of an effect on structural changes in the developing nervous system, while chronic stress later in life may stronger influence functional aspects.

Moreover, stress could have a differential influence on the left and the right hemisphere, which themselves have differential regulatory influence on the HPA axis. In an animal model, Sullivan and Dufresne (2006) could show that early life stress lead to a non-lateralized influence of mesocortical dopamine inhibition in the HPA axis, while rats that were not stressed during early life development showed rightward lateralization of HPA axis control. This shows that deficits in lateralization lead to deficits in stress regulation, which is dependent on early life adversity.

Another aspect that needs to be considered is that the effect of stress on alterations in hemispheric asymmetries could be symptom group specific with the result that different disorders might display varying changes in asymmetry depending on other disorder factors. There is evidence that changes in asymmetries do not lead to neurodevelopmental disorders but rather result from impaired cognitive systems (Bishop, 2013). These impairments could result from disorder specific changes in brain development and give rise to different alterations in asymmetry. These changes again could lead to a positive feedback loop with dysfunction seen in the respective disorders.

7. Outlook and testable predictions for future studies

Further research is needed to investigate the direct influence of glucocorticoids on hemispheric asymmetries. Our model suggests that early life stress leads to structural and functional changes in hemispheric asymmetries seen in psychiatric and neurodevelopmental disorders. Further, chronic as well as acute elevations in glucocorticoid levels also influence the corpus callosum and the two hemispheres leading to changes in hemispheric asymmetries. It is also intriguing to investigate the nature of hemispheric asymmetries in PTSD, as there has been little interest in this aspect of the disorder. Moreover, PTSD is the only disorder we discussed that is not accompanied by a chronic elevation in glucocorticoid levels. This makes it a good opportunity to elucidate the relationship between stress and hemispheric asymmetries. Further, the influence of other stress mediators like CRH, noradrenaline and dopamine on hemispheric asymmetries needs to be investigated as the stress response is a complex process that could affect hemispheric asymmetries through different agents. Future studies are needed to gain deeper insight into underlying mechanisms and possible drug targets.

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Declaration of Competing interest

The authors declare no conflict of interest.

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