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Laterality 2020: entering the next decade

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ABSTRACT
In the 2010s, significant progress has been made in several key areas of laterality research, including neuroimaging, genetics and comparative research. In the present article, we discuss which trends are likely to shape laterality research in the 2020s. These include, but are not limited to: (1) Finding laterality-specific solutions to the replication crisis. (2) Integrating non-W.E.I.R.D. (Western, Educated, Industrialized, Rich, and Democratic) samples into laterality research to a larger extent. (3). Combining meta-analysis and large-scale databank studies to come to unbiased conclusions about true effects. (4) Understanding altered laterality in different psychiatric and neurodevelopmental disorders. (5) Exploring the relevance of laterality research for the treatment of psychiatric and neurodevelopmental disorders. (6) Investigating the molecular correlates of environmental factors that affect laterality. (7) Bridging the gap between laterality research in human subjects and non-human model species. (8) Utilizing "next-generation" neuroimaging in laterality research. (9) Integrating graph-theory and machine learning into laterality research. (10) Enhancing ecological validity in laterality research using mobile EEG and smartphone-based data collection. These trends will likely shape the next decade of laterality research by opening the way for novel questions, enhancing collaborations and boosting the reliability and validity of research findings in our field.

Introduction

The 2010s have been a decade of tremendous advances in laterality research. Large scale neuroimaging studies in the ENIGMA consortium (Kong et al., 2018) and genome-wide association studies in the UK Biobank datasets (Wiberg et al., 2019) allowed for key insights into the neurogenetics of human lateralization. Moreover, the UK Biobank dataset has also been utilized

to investigate early life factors on hemispheric asymmetries (De Kovel, Carrión-Castillo, & Francks, 2019). In clinical laterality research, a more critical and balanced perspective on the issue whether atypical asymmetries are a cause, correlate or consequences of mental disorders has been brought forward (Bishop, 2013).

In comparative laterality research we saw the first use of unilateral embryonic gene manipulation to investigate the establishment of functional lateralization in rodents (Li et al., 2013), substantial advances in our understanding of the genetic pathways shaping laterality in zebrafish (Hüsken & Carl, 2013) and an increasing focus on how laterality research can help to interpret animal emotions (Siniscalchi, Lusito, Vallortigara, & Quaranta, 2013). Moreover, the 2010s saw the establishment of using magnetic resonance imaging to investigate laterality in-vivo in birds and other animals (Jonckers, Güntürkün, De Groof, Van der Linden, & Bingman, 2015). Since MRI is one of the key techniques to investigate functional laterality in humans, this development hopefully will lead to stronger connections between laterality research in human subjects and laterality research in non-human model species in the future. Last, but not least, there has been a push towards an integration of laterality findings across different species including both vertebrates (Karenina, Giljov, Ingram, Rowntree, & Malashichev, 2017; Rogers, Vallortigara, & Andrew, 2013; Ströckens, Güntürkün, & Ocklenburg, 2013) and invertebrates (Frasnelli, 2013).

Despite these tremendous advances, a number of key challenges remain. Some of them are specific for laterality research, while others are general trends in neuroscience. Here, we will give our own personal views on these challenges and how we might address them as a research community. We hope that our list will facilitate discussion and foster future research. We welcome other researchers to comment on this article and share their own views on what they perceive are the major issues in laterality research that need to be addressed in the next decade.

Finding laterality-specific solutions to the replication crisis

Psychological research has come under criticism in the last decade due to the inability to replicate numerous research findings. Research on the validity and reliability has shown that the probability of a research finding to be true is affected by a variety of factors such as the sample size, effect size, number of tested relationships, flexibility in study design among others (Button et al., 2013; Ioannidis, 2005).

One of the major contributors to the so-called "replication crisis" is a systematic publication bias that transcends disciplines. The bias is that studies that presumably find novel and significant results are more likely being published than studies finding a null-result (e.g., Kühberger, Fritz, & Scherndl, 2014). Certainly, this issue needs to be addressed outside of the lab. As

summarized in a statement by representatives of the American Psychological Association, the strong competition for jobs and grants coupled with the apparent necessity of getting significant results encourages problematic research practices (Gonzales & Cunningham, 2015). To tackle this issue, some journals have implemented the pre-registration of studies. In this publication scheme, researchers submit their research rationale, hypotheses, design and analytic strategy to the journal for peer review before beginning the study. If the proposed study is accepted at this stage, the study will be published regardless of the novelty of the research finding. Therefore, pre-registration is expected to increase theory-driven research with stronger methodology and a decline of the false-positive publication bias (Gonzales & Cunningham, 2015).

Albeit the pre-registration of studies is highly encouraged, this option may not be applicable under all circumstances. However, as outlined above, the publication bias is not the only issue. The general possibility that different studies may find different results leads to much confusion and controversy within scientific fields and laterality research is no exception. Research on sex differences in asymmetries, for example, shows a variety of more or less stable results (Hirnstein, Hugdahl, & Hausmann, 2019). While meta-analyses created a consensus that males are more likely to show left-handedness than females (Papadatou-Pastou, Martin, Munafò, & Jones, 2008; Sommer, Aleman, Somers, Boks, & Kahn, 2008), the size of this sex difference is moderated by the assessment of handedness (Papadatou-Pastou et al., 2008). As pointed out by Papadatou-Pastou (2018), various conceptualizations of handedness exist in the literature such as the distinction between hand preference and skill, the classification of handedness as a binary or discrete variable, as well as the distinction between consistent and non-consistent handedness. Furthermore, even studies that use the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), the common measurement of handedness, show heterogeneity in the way it is used and/or reported (Edlin et al., 2015). Naturally, potential sources of discrepancy in the literature enumerate with more intricate research questions. Therefore, it is of little surprise that questions such as the cortical foundation of handedness are not yet answered unequivocally.

While diversity in research practices and operationalization is a necessary motor for innovation, we believe that the report of study results can be improved. As outlined above, potential problems come from in-transparent method sections, the omission of information (e.g., excluded subjects) and a general lack of consensus on how to use certain tools. Borrowing from other fields such as preclinical research (Steward & Balice-Gordon, 2014) or guidelines for reporting certain methods (fMRI, Poldrack et al., 2008), the laterality community may thus benefit from addressing methodological heterogeneities by proposing a consensus statement as well as methodological papers on best practices.

Particularly actions that fall under the label of "open science" are promising for overcoming factors that contribute to the crisis, such as small sample sizes and methodological differences. Across fields, there is a strong impulse for sharing data and code in order to increase reproducibility. Open science initiatives such as the human connectome project (HCP, Van Essen et al., 2013) or the UK biobank (Sudlow et al., 2015) make it possible for different researchers to work on the same dataset and create reproducible studies. Importantly, initiatives such as the "PRIME-DE Global Collaboration Workshop and Consortium" make sure that data and code sharing can be done on the scale of research communities, with the aim of increasing reproducibility and advancing a particular field of research (Milham et al., 2020).

For laterality research, it is inspiring to see that the intention of increasing transparency and reproducibility in research is strongly supported by many leading scientists in the field. This includes the editorial board of *Laterality*. The new roadmap for the journal, published in 2020 included new guidelines for clear reporting of methodology and analysis, the introduction of registered reports as a new article type and a clear commitment to data sharing (Grimshaw, Hausmann, & Rogers, 2020).

Integrating non-W.E.I.R.D. samples into laterality research to a larger extent

An issue that is related to the replication crisis is the fact that in general, there is an overrepresentation of participants from the so-called W.E.I.R.D. (Western, Educated, Industrialized, Rich, and Democratic) societies in psychological and neuroscientific research (Henrich, Heine, & Norenzayan, 2010). Scientists often assume that basing their conclusions on data generated in this sample is unproblematic and that results obtained in these participants are representative across all human cultures. However, it has been shown that W.E.I.R.D. participants are not comparable to many other human populations. They are – in fact – particularly unusual and very unrepresentative for humans in general in a number of psychological and biological domains, implying that one should be careful to make any conclusions about human behaviour in general based on data gathered in these samples (Henrich et al., 2010).

While the overrepresentation of participants from W.E.I.R.D. societies and the resulting underrepresentation of participants from all other societies in psychological and neuroscientific research is a general problem in these fields, laterality research might be affected particularly strongly by it. Several papers have shown that there is sometimes strong geographical variation in hemispheric asymmetries (for a review see Raymond & Pontier, 2004). For example, in contrast to most Western countries, it has been shown that there is strong cultural pressure against use of the left hand in some African countries like Malawi. In this study, 87.6% of teachers and guardians of

schoolchildren indicated that they are convinced that left-handers should be forced to change the hand they use for writing (Zverev, 2006). Consequently, there are lower rates of left-handedness in Malawi than in Western countries. One study in a sample of 512 Malawian schoolchildren found that the overall prevalence of left-handedness was 3.9%. 5.7% of pupils were mixed-handed and 90.4% right-handed (Zverev, 2004). A systematic analysis of handedness data from 81 studies from 14 countries also found a significant effect of the country (Raymond & Pontier, 2004).

This geographical variation in handedness might also indicate geographical variation in other forms of hemispheric asymmetries, as handedness is correlated with other forms of hemispheric asymmetries such as language lateralization (Somers et al., 2015), albeit weakly (Packheiser et al., 2020c).

Thus, testing mainly samples from W.E.I.R.D. societies generates a multitude of issues in laterality research. We rely for example on phenotypic distributions determined in W.E.I.R.D. societies when judging whether there is an increased amount of atypical asymmetries in a clinical sample or in a group with a specific genotype. Therefore, large transcultural multicenter studies are essential for laterality research in the next decade in order to gain accurate phenotyping and be able to estimate frequencies of atypical lateralization in specific samples reliably. Moreover, replication of existing results in underrepresented cultural groups is equally essential in order to get unbiased estimates of laterality phenotype distributions. The first attempts to solve this issue in laterality research have been made. For example, Karim et al. (2017) investigated lateral preferences during kissing that had previously been reported in Western samples (Ocklenburg & Güntürkün, 2009) in a non-W.E.I.R.D. patriarchal conservative Muslim society with the explicit aim to further laterality research in non-W.E.I.R.D. participants. In this study, kissing preferences were tested in 48 Bangladeshi heterosexual married couples. While a general right-sided preference was replicated in this sample, there were some specific cultural effects like a male bias in kiss initiation that showed the importance of taking influences of societal learning or cultural norms into account in laterality research. Other studies have tested research questions related to laterality in non-W.E.I.R.D. participants because they were aimed at specific samples, e.g., families with an overrepresentation of left-handedness that were from specific non-W.E.I.R.D. societies (Kavaklioglu, Ajmal, Hameed, & Francks, 2016). In general, laterality research in the next decade needs to become more inclusive of participants with diverse cultural backgrounds to avoid being affected by cultural biases.

Combining meta-analysis and large-scale databank studies to come to unbiased conclusions about true effects

One of the core problems of the replication crisis in psychology and neuroscience is the large number of studies with low sample sizes resulting in

low statistical power (Button et al., 2013; Ioannidis, 2005). Combined with the file drawer problem, e.g., the fact that most researchers (and editors!) tend to prefer publishing significant results, this issue leads to the unfortunate situation that there is an overabundance of significant results that often do not replicate. Like many other fields in psychology and neuroscience, laterality research is almost certainly affected by this problem, especially since lateral phenotypes are heavily skewed in the population requiring very large sample sizes to represent individuals with atypical phenotypes such as left-handedness with sufficient power (Tran, Stieger, & Voracek, 2014). Unsurprisingly, there have been cases in the past, in which an initial laterality study publishes a strong significant effect that subsequent studies do not find. For example, a recent study aimed at replicating nine different studies investigating the lateralization of visual information processing with near-identical setups and found mixed results regarding the replicability of published data (Brederoo, Nieuwenstein, Cornelissen, & Lorist, 2019). Here, the authors reported that they were successfully able to replicate visual field asymmetries in the processing of faces, emotional expressions, global and local information, words, and spatial attention. The evidence was less convincing for asymmetries in processing of high and low spatial frequencies and there was no evidence for asymmetries in the categorical perception of color and shape oddballs, as well as in the judgment of categorical and coordinate spatial relations.

When it comes to solutions for the replication crisis, increasing statistical power by analyzing effects in large samples is one of the key approaches. There are essentially two ways how this can be achieved. On the one hand, meta-analyses can be used to statistically combine published (and sometimes non-published) datasets and increase statistical power by increasing the number of investigated subjects. On the other hand, large-scale multicenter databank studies can be used to increase statistical power in a single study with a large n. Both approaches have been used in laterality research in the last decade. For example, meta-analysis has been used to investigate the relation of handedness and intelligence (Ntolka & Papadatou-Pastou, 2018), the rate of non-right-handedness in autism (Markou, Ahtam, & Papadatou-Pastou, 2017) and side preferences in cradling (Packheiser, Schmitz, Berretz, Papadatou-Pastou, & Ocklenburg, 2019b). Moreover, meta-analysis has also been used in comparative laterality research, e.g., for investigating paw preferences in cats and dogs (Ocklenburg, Isparta, Peterburs, & Papadatou-Pastou, 2019). As these papers represent reliable baselines for further research in the field, it can only be hoped that in the next decade, more scientists use both classic meta-analysis and meta-analytic approaches for imaging data like activation likelihood estimation (ALE) meta-analysis (Minkova et al., 2017) to investigate diverse laterality questions.

Unfortunately, meta-analyses have two main methodological issues (Egger, Smith, & Sterne, 2001). On the one hand, their results can be affected by publication bias. If significant studies have a higher chance of getting published than studies that did not observe significant effects, then meta-analyses are likely to overestimate the size of observed effects. Non-significant studies with low effect sizes often escape the attention of researchers conducting meta-analyses as they are rarely published. While this problem can to some extent be counteracted by identifying researchers working in the field and contacting them to ask for unpublished datasets, it likely affects many meta-analyses to some extent. The other major problem of meta-analyses has been termed the "garbage in, garbage out" issue and refers to the fact that biases and methodological issues at the level of the individual studies that are fed into the meta-analysis can affect the reliability of the results of the meta-analysis. Thus, if only low-quality studies are integrated in the meta-analysis, the meta-analysis delivers low-quality results.

A second way to increase statistical power in laterality research, neuroscience and psychology, in general, are large-scale multicenter databank studies. For example, the UK biobank dataset contains data on subjects' handedness and several different genetic and neuroimaging phenotypes and has successfully been used in laterality studies in the last decade (Wiberg et al., 2019). Moreover, the ENIGMA consortium has worked on laterality and has for example published a study on cortical brain asymmetries in more than 17,000 subjects (Kong et al., 2018). These studies allow for better control of study parameters and quality than meta-analysis, but have problems of their own, such as integrating imaging data that has been recorded on different MRI scanner or the coordination of up to several dozen study sites, not to mention the potentially very high costs of collecting and analyzing data from tens of thousands of subjects. We are convinced that in the next decade, laterality research will follow the general trend in neuroscience away from small samples, single-center empirical studies towards larger and more integrative studies. By using both meta-analyses of existing datasets and collection of new and larger datasets to replicate published effects and investigate new questions, we are sure laterality research can make an important step towards greater replicability in the 2020s.

Understanding altered laterality in different psychiatric and neurodevelopmental disorders

Many psychiatric and neurodevelopmental disorders are accompanied by changes to typical lateralization patterns in both structural and functional hemispheric asymmetries. Several of these altered asymmetries have been associated with symptoms of depression, schizophrenia, autism spectrum disorders (ASD) and dyslexia.

In patients with major depressive disorder (MDD), asymmetries in frontal alpha power have been shown to be reduced during resting state EEG measurements (Thibodeau, Jorgensen, & Kim, 2006). Since alpha power is indicative of inhibition (Pfurtscheller, Stancak Jr, & Neuper, 1996), this reduced asymmetry could be linked to depressive mood and altered emotional processing (Davidson & Hugdahl, 1996). Individuals with schizophrenia also show altered hemispheric asymmetries patterns that have been related to auditory verbal hallucinations (Ocklenburg, Westerhausen, Hirnstein, & Hugdahl, 2013). On the structural level, these patients exhibit a reduction in asymmetries of the planum temporale (Sommer, Ramsey, & Kahn, 2001), a brain region strongly implicated in language processing. These changes in structural asymmetry are accompanied by decreased functional language lateralization (Ocklenburg, Beste, Arning, Peterburs, & Güntürkün, 2014) as well as increased positive symptomatology (Geoffroy et al., 2014). Similar to changes in schizophrenia, neurobiological alterations in autism have been linked to language networks and motor functions. Compared to healthy controls, children with ASD display a rightward shift in volume and connectivity in the motor system leading to greater right-hemispheric involvement in motor-related function. This has been proposed to underlie behavioural motor abnormalities seen in ASD (Floris & Howells, 2018). Moreover, these individuals show atypical asymmetries in the language system (Gage et al., 2009) which are linked to impaired language function (De Fossé et al., 2004). Finally, dyslexic individuals also show structural (Altarelli et al., 2014) and functional changes (Norton, Beach, & Gabrieli, 2015) in language lateralization. Moreover, they exhibit altered connectivity in the language system due to which dyslexia has been labeled a disconnection syndrome (Peterson & Pennington, 2012).

Psychiatric and neurodevelopmental disorders have furthermore been associated with higher rates of atypical handedness (see Papadatou-Pastou et al., 2019 for a meta-analysis) and atypical footedness (see Packheiser et al., 2020b for a meta-analysis). One major challenge for laterality research in the 2020s will be to understand why all of these ontogenetically diverse disorders show somewhat similar phenotypes when it comes to hemispheric asymmetries and to identify the factor that links them (if any such factor exists). Moreover, whether altered asymmetries cause symptoms of these disorders or are an epiphenomenon of changed neurobiological processes implicated in these pathologies as well as further factors influencing both lateralization patterns and psychiatric and neurodevelopmental disorders is still debated. One of these factors could be a shared genetic foundation of these disorders and atypical lateralization. A recent genome-wide association study (GWAS) conducted on the UK Biobank cohort found a link between left-handedness, brain development and structural connectivity patterns associated with the pathogenesis of psychiatric diseases on the locus rs199512

(Wiberg et al., 2019). Also, environmental factors have been implicated in the ontogeny of disorders and atypical lateralization. A model proposed by Berretz, Wolf, Güntürkün, and Ocklenburg (2020) for example highlighted the importance of stress in the context of both and argued that increased rates of early life and chronic stress could be the missing link between psycho-pathologies and atypical lateralization patterns. Future research in the 2020s should therefore further explore the association and causal relationship between psychiatric and neurodevelopmental disorders and changes in typical lateralization patterns while keeping in mind environmental and genetic influences that could mediate between both.

Exploring the relevance of laterality research for the treatment of psychiatric and neurodevelopmental disorders

As outlined in the previous paragraph, many psychiatric and neurodevelopmental disorders are associated with increased rates of atypical lateralization patterns. Some authors have suggested that this association might be relevant in the context of psychotherapy (Banmen, 1983). Evidence in favor of this hypothesis comes for example from a recent study by Weinland, Mühle, Kornhuber, and Lenz (2019). They investigated 200 early-abstinent alcohol-dependent patients and found that crossed eye/hand laterality and left-eyedness were related to a reduced risk for alcohol-dependency relapses. Forbes et al. (2006) conducted another study on the relation between lateral biases and the outcome of PTSD treatment. 150 Vietnam veterans were subjected to cognitive–behavioral therapy to reduce PTSD symptoms. In individuals with mixed-handedness, therapy was however less effective compared to left- and right-handers. In line with these results, Kishon et al. (2015) investigated the influence of language lateralization on treatment outcome in depression. Here, patients with stronger language lateralization to the left hemisphere responded better to cognitive behavioral therapy compared to individuals with bilateral language lateralization. These studies provide first indications that psychotherapy outcome might be affected by laterality patterns in patients. However, there have been to our knowledge no other studies investigating the relationship between laterality and psychotherapy so far. Furthermore, the underlying neurobiological mechanisms influencing this relationship are currently unknown and have not been investigated.

In the context of psychotherapy, it has also been suggested that a laterality perspective could enhance the effectiveness of treatment (Schore, 2019). The author highlights the importance of the right hemisphere in holistic emotional and social processing which play a role in relational outcomes of psychotherapy (Schore, 2014). Banmen (1983) argued that classical approaches to psychotherapy like cognitive–behavioral therapy are strongly left-hemispheric oriented as these approaches are based on verbal interaction and logic, and

may thus neglect the potential of the right-hemisphere for psychotherapy. Thus, treatment in psychotherapy should specifically target right-hemispheric activation to optimize treatment outcomes (e.g., Banmen, 1983; Schore, 2019).

This approach is reminiscent of the early idea of hemisphericity, namely that a preferred mode of cognitive processing implies predominant activity of either hemisphere linking this to personality and psychiatric disorders. However, the concept that the right hemisphere as the seat of primary process thinking and repression (Galin, 1974) has been harshly criticized (Beaumont, Young, & McManus, 1984) and does not reflect current opinions in laterality research (McManus, 2019). Moreover, the empirical foundation for treatment ideas by Schore (2014) is sparse and largely remains on the theoretical level. It is unclear whether hemisphere-specific psychotherapy is an effective or even feasible strategy to help patients with psychiatric and neurodevelopmental disorders. Furthermore, it is highly debated whether such a strict hemispheric dissociation for social and emotional processing applies.

A substantial body of evidence suggests that the right hemisphere is dominant in emotional processing (see Demaree, Everhart, Youngstrom, & Harrison, 2005 for review). In contrast, several studies have also indicated that positive emotions are processed in the left hemisphere, whereas only negative emotions are processed in the right hemisphere, especially for the experience of emotion (see Davidson, 2003 and Alves, Fukusima, & Aznar-Casanova, 2008 for review). If this valence-specific hypothesis applies, the feasibility of a specific right-hemispheric activation becomes even more questionable. Moreover, research that is more recent suggests that both the right hemisphere and the valence hypothesis are partly correct, but that they reflect different facets of the emotion processing system and only apply to specific brain regions (Killgore & Yurgelun-Todd, 2007).

Despite these issues, some support for hemisphere-specific intervention has come from a line of evidence investigating the potential of neurofeedback for clinical applications (Masterpasqua & Healey, 2003). Neurofeedback refers to techniques during which cortical activity is monitored and modulated with the goal of influencing symptoms of psychological disorders. In the context of laterality, neurofeedback studies have strongly focused on frontal EEG alpha asymmetries that are associated with Major Depressive Disorder (Thibodeau et al., 2006). Here, neurofeedback-induced changes in frontal alpha asymmetry have been shown to alleviate symptoms of depression and anxiety (Mennella, Patron, & Palomba, 2017; Wang et al., 2019). These positive effects have been related to changes in decreased negative affect (Mennella et al., 2017) and improved working memory performance (Escolano et al., 2014). On the contrary, increased right frontal activity through neurofeedback has been shown to diminish adaptive coping and lack of reduction of subjective stress (Quaedflieg et al., 2016). Similar studies have been performed for

ADHD showing that normalization of frontal alpha asymmetry was associated with improved inhibitory control (Deiber et al., 2020).

In conclusion, many open questions regarding laterality and psychotherapeutic treatment remain to be answered. Since many studies on the topic of laterality claim its importance in psychotherapy, more research is needed in the 2020s to support the validity of these claims. Unless more empirical evidence is generated supporting the influence of laterality on treatment and its outcomes, these claims should be treated with caution as they are presently rather unsubstantiated. A promising approach constitutes research on the influence of neurofeedback of EEG asymmetries. These studies indicate the potential of changes in asymmetry for therapeutic use. In this context, studies with larger samples and other psychiatric disorders are needed to evaluate the specificity and helpfulness of this approach. Moreover, other EEG asymmetries than frontal alpha power need to be investigated (Chen & Lin, 2020).

Ontogenesis and modulation of hemispheric asymmetries: genetic, epigenetic and endocrinological factors

One of the core questions in laterality research is how genetic and non-genetic factors interact during the ontogenesis of hemispheric asymmetries. Related to that is the question, which factors modulate hemispheric asymmetries over the lifetime. In a seminal laterality paper from the late 2000s, Medland et al. (2009) found that additive genetic effects accounted for 23.64% of the variance in handedness data, while non-shared environmental influence accounted for the remaining 76.36%. This highlights the importance of non-genetic factors for the ontogenesis of hemispheric asymmetries (Güntürkün & Ocklenburg, 2017), an idea that is also strongly supported by comparative research. For example, several studies reported that functional and structural asymmetries in chicken and pigeons are strongly influenced by light stimulation (Manns & Ströckens, 2014; Rogers, 1982, 1996). At the end of 2010s, De Kovel et al. (2019) published a seminal paper that used the UK Biobank dataset to investigate the role of early life factors for the ontogenesis of handedness in humans. They found that the probability of being a left-hander was significantly affected by the year and location of birth, birth weight, being part of a birth with multiple children, season of birth, breastfeeding, and sex. Both the Medland et al. (2009) and De Kovel et al. (2019) study highlight the importance of non-genetic factors for the ontogenesis of hemispheric asymmetries. However, there are several open questions in this field that need to be investigated in the 2020s. For example, the early life factors that have been found to influence handedness in the De Kovel et al. (2019) paper had only minimal predictive value for handedness, despite being statistically significant. These findings hints to the possibility

that other factors not assessed in the UK Biobank dataset might also be relevant and need to be investigated in the coming decade. For example, it has been suggested that a more in-depth look at stress experiences in early and later life might be of interest in this context (Ocklenburg, Korte, Peterburs, Wolf, & Güntürkün, 2016).

Another open question is which molecular processes mediate between environmental factors and functional and structural hemispheric asymmetries in both humans and animals. Schmitz, Metz, Güntürkün, and Ocklenburg (2017) suggested that epigenetic processes like CpG island methylation in nervous tissue, histone modification or transcriptional regulation by micro-RNAs might be relevant in this context. Indeed, there are some preliminary findings that point in this direction. For example, it has been found the methylation of CpG sites in the promoter region of *LRRTM1*, a candidate gene for handedness, was associated with more mixed-handedness (Leach, Prefontaine, Hurd, & Crespi, 2014). Methylation of CpG sites in the promoter regions of genes asymmetrically expressed in the fetal brain or spinal cord has also been associated with handedness variation (Schmitz, Kumsta, Moser, Güntürkün, & Ocklenburg, 2018). Most recently, Li et al. (2020) reported that neurons of the human prefrontal cortex exhibit hemispheric differences in DNA methylation. Specifically, they found that the left hemisphere had higher DNA methylation levels compared to the right hemisphere. Overall, 82.7% of significant cytosines showing a leftward asymmetry. Functionally, most of the genes that showed asymmetric epigenetic regulations were involved in the development of the nervous system and in brain diseases. While Li et al. (2020) did not investigate the relationship between these epigenetic asymmetries and functional or structural hemispheric asymmetries, this interesting finding certainly deserves more investigation in the context of the ontogenesis of hemispheric asymmetries. In general, large-scale studies in humans are needed to further investigate the link between peripheral markers of epigenetic processes in the central nervous system (such as CpG site methylation in saliva or blood samples) and hemispheric asymmetries in humans. However, due to the tissue-specificity and time-sensitivity of some epigenetic processes like histone modification, comparative research in animal model species will be essential in order to advance this field. Here, light-induced modulation of hemispheric asymmetries in birds might prove to be a meaningful model system.

In spite of early ontogenetic affects, many forms of hemispheric asymmetries are not completely fixed over the lifetime of an organism but fluctuate to some extent. For example, already in the 2000s, Hausmann & Güntürkün hypothesized that functional hemispheric asymmetries may be affected by sex hormone levels. Their so-called progesterone-mediated interhemispheric decoupling hypothesis (Hausmann & Güntürkün, 2000) assumes that the dominant hemisphere inhibits the non-dominant hemisphere via GABAergic

interneurons at the axon terminals of the glutamatergic callosal fibers. Hence, excitatory signals that traverse the corpus callosum can lead to an inhibition of the target region in the other hemisphere. This mechanism, however, is mediated by cycle phase dependent fluctuations in progesterone, which affects both glutamatergic and GABAergic receptors. Indeed, there is ample evidence linking progesterone to changes in hemispheric asymmetries (Fernández et al., 2003; Hausmann, Becker, Gather, & Güntürkün, 2002). Later studies extended this framework of the influence of hormonal changes of hemispheric asymmetries to estradiol (Hausmann, 2005, 2017; Weis et al., 2008) and possibly testosterone (Pletzer, Jäger, & Hawelka, 2019). Therefore, factors beyond genes and epigenetics influence functional hemispheric asymmetries.

Recently, the potential influence of other steroid hormones on hemispheric asymmetries has come into focus. A preliminary study by Brüne, Nadolny, Güntürkün, and Wolf (2013) could show that acute stress and the related increase in cortisol induced hemispheric asymmetries in an emotional face recognition task. However, factors of consideration are not limited to acute stress, because the effect of stress hormones on asymmetries may be influenced by levels of prenatal stress (Jones, Osmond, Godfrey, & Phillips, 2011). Concordantly a study with rats by Sullivan and Dufresne (2006) showed that typically right-lateralized control of the hypothalamus-pituitary-adrenocortical axis was disrupted by early life stress leading to deficits in stress regulation. As the underlying mechanisms are still elusive, future research should further investigate the influence of cortisol in hemispheric asymmetries. In this context it would also be worthwhile to explore the effects of other stress hormones like epinephrine and norepinephrine as well as binding hormones like oxytocin and their interplay. Animal models would allow for a direct manipulation of hormones.

Bridging the gap between laterality research in human subjects and non-human model species

We have come a long way from the times during which many laterality researchers were convinced that only humans show hemispheric asymmetries. Nowadays, laterality is seen as a general phenomenon across all of bilateralia, including both vertebrates and invertebrates (Frasnelli, 2013; Frasnelli, Vallortigara, & Rogers, 2012; Marie et al., 2018; Ocklenburg et al., 2019; Sun & Walsh, 2006). While the ubiquity of studies investigating laterality in diverse animal species was certainly an important progress in laterality research in the 2010s, there still is a major issue in this field. Often, studies in a specific species are somewhat isolated and not much connection to other animal species or human findings are made. Thus, it is one of the major challenges

for laterality research in the 2020s to bridge the gap between different species.

Investigating laterality across species comes with several advantages. For instance, knowledge about laterality and asymmetries in other species may inform about the evolutionary trajectory of this phenomenon. For instance, a recent DWI tractography study demonstrated a novel relationship between asymmetries in visuospatial attention and the lateralization of the superior colliculi connectivity in humans (Sreenivasan & Sridharan, 2019). Intriguingly, this result pattern is reminiscent of asymmetries in visually guided responses (e.g., lungfish; Lippolis, Joss, & Rogers, 2009) and anatomical asymmetries in mesencephalic structures (e.g., zebrafish; Dreosti, Llopis, Carl, Yaksi, & Wilson, 2014) of phylogenetically older species. As outlined in Friedrich, Thiebaut de Schotten, Forkel, Stacho, and Howells (2020), the similarity in both behavioral and anatomical asymmetries suggests a deeply rooted evolutionary history of this structure–function asymmetry.

A further strong point of investigating laterality beyond humans is that model species allow for more direct manipulation and recording of the neural substrates that may contribute to laterality. Pigeons and chicks, for example, have been demonstrated to be excellent model organisms to study cerebral asymmetries as their visual system is strongly lateralized (Ocklenburg & Güntürkün, 2017; Rogers, 1990; Rogers, Zucca, & Vallortigara, 2004; Vallortigara, Regolin, & Pagni, 1999). The lateralized visual system emerges from the asymmetric exposure of light to the eyes in the egg (Güntürkün & Ocklenburg, 2017; Rogers, 1990). Here, the left eye is light deprived since it is occluded by the pigeon's own body while the right eye is oriented towards the translucent eggshell resulting in a pronounced structural and functional asymmetry in downstream visual brain areas (Güntürkün, 1997). In pigeons for example, the left hemisphere specializes in categorization and visual discrimination whereas the right hemisphere is dominant in the processing of attentional shifts or spatial information (Diekamp, Regolin, Güntürkün, & Vallortigara, 2005; Yamazaki, Aust, Huber, Hausmann, & Güntürkün, 2007). Similarly, chicks demonstrate a left-hemisphere advantage for visual discrimination (Gaston & Gaston, 1984) and a right-hemisphere advantage in spatial orientation (Rashid & Andrew, 1989) as well as in the processing and recognition of conspecifics (Vallortigara, 1992; Vallortigara & Andrew, 1994). These asymmetries can be easily manipulated by incubating the animals in the dark completely abolishing the visual asymmetry that can be observed in light-incubated birds both on the structural and functional level (Letzner, Patzke, Verhaal, & Manns, 2015; Manns & Güntürkün, 1999; 2003; Rogers, 1982). Thus, the causal role of light exposure can be assessed through a simple intervention.

Animal models are also indispensable to study the causal roles of genes in asymmetry. Several genetic loci have been identified using large-scale GWAS

in humans associated with handedness (Armour, Davison, & McManus, 2014; De Kovel & Francks, 2019; Wiberg et al., 2019). However, it is impossible to study the causal effects of these genes on handedness systematically in humans. In mice however, genes or gene transcription factors can be knocked out or knocked down to identify how the removal influences a behavioral phenotype (Houdebine, 2007). Li et al. (2013) for example knocked down the Lim domain only 4 (LMO4) transcription factor that has been identified to be asymmetrically expressed in fetal brain tissue (Sun et al., 2005) in a transgenic mouse strain and found that it significantly altered the laterality of paw preferences in these mice. Furthermore, optogenetic interventions can be applied to identify causal roles of brain structures and their lateralization using temporally precise light-induced manipulations of neurons (Rogers & Vallortigara, 2017). For example, optogenetic activation of left- and right-hemispheric CA3 neurons revealed lateralization of long-term potentiation (LTP) as high frequency stimulation of the left hemisphere resulting in stronger LTP compared to the right hemisphere (Shipton et al., 2014). Behaviourally, silencing CA3 neurons in the left hippocampus resulted in reduced performance in a spatial discrimination task in mice whereas silencing of the right hemisphere did not affect the number of correct responses (Shipton et al., 2014). Overall, we believe that the use of animal models and the plethora of methodological possibilities associated with them will be crucial to understand the mechanistic role of environmental or genetic factors in the ontogenesis of lateral phenotypes.

An important question in future lateralization research will also concern how lateralization patterns between species or even classes of animals are associated with another. While lateralization of the brain and body is widespread in the animal kingdom (Ströckens et al., 2013), it remains unclear whether these asymmetries are grounded in a common evolutionary advantage or are specific to an organism's ecological niche. Similar to human lateralization patterns such as language or handedness, behavioral population level asymmetries have been found in large varieties of invertebrate (Frasnelli et al., 2012) and vertebrate species (Ströckens et al., 2013). However, humans usually demonstrate more pronounced asymmetries at the population level and as such, these lateralization patterns might be unique. Unfortunately, comparative cross-species laterality studies are still rare, but a small body of research has been gathered in recent years. For example, it has been shown that for detection of predators on the left side and visual discrimination on the right side, results are fairly consistent across a number of vertebrate species (MacNeilage, Rogers, & Vallortigara, 2009; Vallortigara & Rogers, 2005). However, for most fields of laterality, comparative cross-species are still lacking. The next decade should therefore focus on this question at hand to understand the evolutionary role of lateralization comprehensively. One particularly important aspect would be to conduct more studies in

which the same lateralized behavior is investigated in a number of closely related species (e.g., different primates) in order to better trace evolutionary trajectories in laterality phylogenesis.

Investigating laterality in non-human animals not only allows to assess the topic from a comparative/evolutionary perspective but also to gain insight into mechanisms of human laterality by using animal models. However, laterality research on humans and non-human animals represents two largely separate bodies of literature, with little-to-no intellectual overlap.

While the body of literature on hemispheric asymmetries in non-human species is growing, comparative research needs to address the issues contributing to the interpretational gap between human and animal research. Within the bigger field of comparative cognition, it is known that valid interpretations require "species-fair" tasks and test batteries (Beran, 2018; Shaw & Schmelz, 2017). Ideally, the manifestation of cognitive abilities should be tested across taxa, across contexts and with multiple converging tasks to gain a more robust understanding of a species cognitive profile and the evolutionary trajectory of cognitive phenomena (Beran, Parrish, Perdue, & Washburn, 2014).

Similarly, advancing our understanding of anatomical similarities and differences across species requires a shared framework that allows comparing anatomical features despite fundamental differences in brain architecture. In particular, MRI has been proven useful as a common-ground investigation tool that is applicable across species. Comparative imaging certainly comes with its own set of challenges (Thiebaut & Zilles, 2019) but allows for innovative approaches to engage the common-space-problem. For instance, shared connectivity blueprints have been proposed to identify homologous areas between human and macaque brains (Mars et al., 2018). As other fields work on solutions to these problems, laterality research needs to be aware of these endeavors and integrate them into future studies.

Utilizing recent advances in neuroimaging for laterality research

Laterality research investigates different levels of asymmetries including functional asymmetries (such as behavior, physiological signals, or gene expression) as well as structural or anatomical asymmetries. Due to its non-invasiveness, MRI is the most widely used apparatus for investigating functional and structural variation in the human brain. It is commonly known that MRI protocols can be tuned to investigate grey or white matter. For instance, MRI sequences that differentiate gray and white matter can be utilized to model cortical thickness or volume (Ashburner & Friston, 2000; Fischl & Dale, 2000). Beyond the interest of gray matter, diffusion-weighted tensor imaging (DTI) has proven useful for modeling the trajectory of white

matter fiber bundles (Catani & Thiebaut de Schotten, 2012). While modeling the spatial layout of white matter tracts can be called a qualitative analysis, diffusion metrics that are based on a simple diffusion tensor model (e.g., DTI) have also been used for qualitative analyses. Fractional anisotropy (FA), for example, is often seen as a surrogate measure of white matter integrity, despite its lack of specificity for the underlying biological tissue (Beaulieu, 2014).

Recent years yielded a variety of new imaging protocols and analyzing techniques that promise better-tailored models for specific tissue properties. For instance, techniques such as magnetization ratio or myelin water imaging are designed to estimate cortical and subcortical myelination (see Heath, Hurley, Johansen-Berg, & Sampaio-Baptista, 2018). Novel imaging methods such as Neurite Orientation Dispersion and Density Imaging (NODDI; Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012) and AxCaliber (Assaf, Blumenfeld-Katzir, Yovel, & Basser, 2008) are sensitive for investigating neurite density and axon diameter, respectively. Other methods are promising for quantifying myelin content, such as computing the myelin water fraction (Prasloski et al., 2012) or the T1w/T2w ratio (Glasser & Van Essen, 2011). Importantly, multimodal studies show that different methods are complementary (Billiet et al., 2015) and link to different parts of the variance in the FA signal (Friedrich, Fraenz, et al., 2020).

To this date, only a small number of studies utilized these technological innovations in a laterality framework. NODDI, in particular, brought some intriguing insight into regional asymmetries of neuron density in the cortex (Schmitz, Fraenz, et al., 2019). It was also proven useful for investigating the neural basis in lateralized cognition such as pre-lexical speech asymmetries that manifest during dichotic listening (Ocklenburg, Friedrich, et al., 2018). The neural foundation of other lateralized tasks is, however, still understudied with regards to the tools listed above. One potential avenue that may lead to new insight includes multi-modal investigations of structural asymmetries in white matter tracts that are crucial for the realization of lateralized functions. For instance, a characterization of various microstructural properties of the left and right arcuate fasciculus may yield a new understanding of defining architectural asymmetries. However, there is an apparent lack of studies that investigate hemispheric differences in white matter tracts, or differentiate between the left and right side of a given tract (Forkel, Friedrich, Thiebaut de Schotten, & Howells, 2020), thus leaving plenty of room for further investigation.

Besides structural imaging, technology to quantify brain function is also steadily moving forward. Further advancements in Ultra high-field MRI (7 Tesla and beyond), and other imaging modalities such as magnetic encephalography (MEG) or ultrasound imaging can be expected, which is accompanied by an increase of novel research questions. One example is the increasing literature of layer-fMRI studies, which enable investigating

feedforward and feedback responses from laminar activation profiles (for review see Lawrence, Formisano, Muckli, & de Lange, 2019). While the layer-fMRI field is still in its infancy, visions such as investigating hemispheric asymmetries in layer-specific activation patterns, for instance in the planum temporale during speech listening, easily come to mind. We are confident that upcoming technical innovations will allow us to delve deeper into the neural foundation of lateralized cognition.

Integrating network neuroscience and machine learning into laterality research

The general perspective on brain functional mapping has evolved with our growing understanding of the brain's complexity. The initial debate on this matter started with holism vs. localism in the eighteenth century and continued with localism vs. connectionism at the beginning of the nineteenth century. Today, the majority of cognitive neuroscientists would agree that functions are distributed across a mosaic of cortical and subcortical neural tissue, which in turn represent functional networks. These networks are investigable in both functional and structural domains and on different levels of resolution. On the microscale, local ensembles of neurons interact in close proximity via their direct neurite pathways. Similarly, on the mesoscale, functionally or anatomically defined brain areas covary in their activation pattern and are connected via long-range white matter bundles. However, in spite of the general consensus that most functions are based on neural networks, the vast majority of laterality research appears to be targeting certain areas or fiber tracts, thus neglecting the network perspective on brain functions.

The change in perspective made novel analyses necessary. Instead of analyzing linear or non-linear relations between a number of variables (as is the case in classical statistics), network neuroscience utilizes graph-theory to investigate features of the entire network. This kind of study has provided an interesting insight into the fundamental differences between the two hemispheres' architecture. For instance, investigating the structural topology of the left and right hemisphere separately evince that the left hemisphere is more efficiently wired compared to the right hemisphere (Caeyenberghs & Leemans, 2014). Concordantly, the two hemispheres differ in their functional interaction with one another: The left hemisphere shows higher intra-hemispheric functional connectivity, while the right hemisphere shows more inter-hemispheric functional connectivity (Gotts et al., 2013). Thus, these studies suggest architectural differences in the general processing strategies of the two cerebral hemispheres.

Another more recent change in the neuroscientific landscape is the rise of machine learning algorithms to solve several technical issues. Due to the constantly increasing amount of data, conventional preprocessing and analyzing

approaches are pushed to their limits. In neuroimaging and clinical radiology, Machine learning and deep learning, in particular, have proven useful for pre-processing steps including artifact detection and image normalization as well as in diagnostic tasks such as classification, risk assessment, prognosis and prediction of therapy responses (Zhu et al., 2019). Deep learning neural net-works can also be used as models of cognitive processes. For instance, the success or failure of a task-performing model may represent a proof of prin-ciple for a potential computational mechanism (Storrs & Kriegeskorte, 2019). While this presents machine learning as a means of hypothesis testing, this method can be used beyond a hypothesis-driven framework as a data-driven approach. This can create new hypotheses, which can later be vali-dated in experimental setups (Vu et al., 2018). Machine learning is especially well suited for predicting phenotypes based on imaging data. For instance, a recent study by Weis et al. (2020) successfully trained a classifier to predict the sex of unknown participants based on their patterns of resting-state functional connectivity. Here, brain areas that were previously associated with sex differences showed the highest classification accuracies, which bridges the gap between the novel method and literature knowledge. In similar fashion, it is possible to design studies for predicting handedness (or other lateralized phenotypes) based on brain anatomy or function. Such studies may in turn reveal novel targets for investigating the neural basis of handedness in an experimental setting. To this date, laterality research seldom utilizes novel analyzing approaches such as graph theory and particularly machine learning. We are hopeful that this will change in the near future.

Enhancing ecological validity in laterality research using mobile EEG and smartphone-based data collection

A significant shortcoming in laterality research for the investigation of motor lateralization in the brain pertains to the low ecological validity of the measurements. To assess cerebral motor asymmetries for example, partici-pants are typically asked to move as little as possible, either because they are lying in an fMRI scanner or because they are connected to a stationary EEG. This is obviously problematic as motor asymmetries can only be measured using tasks that have a range of motion suitable for a spatially con-strained environment. The most common tasks to assess cerebral motor asymmetries thus involve finger tapping for handedness or foot-stomping for footedness (e.g., Kapreli et al., 2006; Rocca & Filippi, 2010; Schmitz, Packhei-ser, et al., 2019; Turesky, Olulade, Luetje, & Eden, 2018). The drawback of these tasks is that they represent rather unnatural movements that almost never occur in real-life settings considerably calling into question how well the results from such studies generalize to everyday hand or foot movements.

A similar issue arises for the investigation of emotional lateralization. The most prominent method to induce emotions in fMRI scanners or EEGs is by showing movies, pictures or music to the participants that elicit positive and negative affect (Gross & Levenson, 1995; Hausmann, Hodgetts, & Eerola, 2016; Hewig et al., 2005; Uhrig et al., 2016). By application of this method, a large number of studies were conducted to study asymmetries in emotional processing (e.g., Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Güntekin, Femir, Gölbaşı, Tülay, & Başar, 2017; Tandle, Jog, Dharmadhi-kari, & Jaiswal, 2016). However, despite the vast number of studies using behavioral, neurophysiological and neuroimaging means to study emotional lateralization in the brain, there is still no conclusive understanding of this phenomenon (Demaree et al., 2005). A possible reason for the inconclusive-ness in the field relates to this method of emotional induction as it has little to do with real-life emotions (with the exception of disgust). Emotions such as fear or love cannot be properly measured if they are merely passively per-ceived since emotions are inherently connected to behavioral action. Prete, Capotosto, Zappasodi, Laeng, and Tommasi (2015) for example noted that emotional lateralization might substantially differ during decision-making as compared to mere perceptual processing. We believe that understanding emotional processing and its lateralization in the brain requires future studies to bring more ecological settings to the table. Only if the neural cor-relates of emotions are measured when they are experienced (and acted upon!) in more natural environments can we understand their neural underpinnings.

One possible solution to the presented issues is the application of mobile EEGs (De Vos & Debener, 2014; Gramann et al., 2011) or mobile fNIRS (Holtzer et al., 2011; Quaresima & Ferrari, 2019) that can identify brain activity patterns directly or indirectly in freely moving participants and in more natural environ-ments. A recent mobile EEG study demonstrated that lateralization patterns in both the alpha and beta frequency band can distinguish between left- and right-handers as well as left- and right-footers on the neurophysiological level during the execution of natural movements (Packheiser et al., 2020a). Similar studies could be conducted in the context of emotional lateralization when participants perceive and express emotions naturally. Future research should therefore embrace these novel techniques to replicate findings acquired from laboratory studies in real-life settings.

Another blindspot in asymmetry research has been that studies on latera-lized motor functions have almost exclusively investigated hand or feet pre-ferences since these are well known to be lateralized in humans (Hammond, 2002; Kim et al., 1993). However, humans demonstrate a variety of lateralized social behaviours such as hugging, kissing or cradling (Forrester, Davis, Mareschal, Malatesta, & Todd, 2019; Malatesta, Marzoli, & Tommasi, 2020; Ocklenburg & Güntürkün, 2009; Packheiser et al., 2019a; Packheiser

et al., 2019c; Turnbull, Stein, & Lucas, 1995). An interesting opportunity for future research of motor lateralization could therefore be to study a broader range of lateralized human behavior to identify if motor asymmetries across lateral biases share a common neural basis. A key advantage of studying these social behaviors is that they not only encompass motor behavior but can also be conducted in various emotional states (Ocklenburg, Packheiser, et al., 2018). If an individual's brain activity is recorded during for example kissing or cradling, it allows for the measurement of true affection towards the partner or the child. Thus, these human social behavior provide a prime example of how to study enacted emotions in ecologically valid environments which is arguably much more difficult for emotions such as fear due to ethical concerns. Furthermore, studying lateralized social behavior allows for the investigation of motor and emotional lateralization in the very same experiment with the identical participants. To this day, the relationship of different lateral phenotypes remains rather unclear, not only among motor biases such as handedness, footedness and eyedness (Brown & Taylor, 1988), but especially between motor and emotional lateralization (Bourne, 2008). Using behavioral phenotypes that test multiple lateral biases simultaneously could potentially illuminate possible shared underlying biological mechanisms of lateralization.

Finally, laterality research should also dive into novel ways of data acquisition allowing for the online assessment of behavior while participants engage in their everyday environment. Due to the widespread use of smartphones, researchers should invest in creating apps to move out of the laboratory and back into the field. This would not only potentially increase the ecological validity of research, it would most likely also result in much larger samples that allow for a more precise estimation of effects in the population. Bless et al. (2015) for example used a dichotic listening app to study more than 4000 participants from various cultural backgrounds. It has to be mentioned that the use of apps for data generation comes with several drawbacks such as a lack of control of experimental conditions. As Bless et al. (2015) note however, these might be addressed using strict exclusion criteria as well as precise instructions for the participants to reduce noise in the data. We therefore believe that smartphone-based data acquisition provides a valuable opportunity for future research in laterality.

Conclusion

In the last decade, tremendous advances have been made in laterality research, but many open questions remain. In the present article, we have highlighted ten different trends and challenges that will likely shape the next decade in laterality research. The first three points were (1) finding laterality-specific solutions to the replication crisis, (2) integrating non-W.E.I.R.D.

samples into laterality research to a larger extent, and (3) combining meta-analysis and large-scale databank studies to come to unbiased conclusions about true effects. These three points refer to ensuring replicable research findings that are not limited to very specific populations (e.g., undergrad psychology students). These trends will hopefully result in a greater integration of the principles of open science in future laterality studies, as well as more international multi-center studies and more meta-research. The next two points we raised were (4) understanding altered laterality in different psychiatric and neurodevelopmental disorders and (5) exploring the relevance of laterality research for the treatment of psychiatric and neurodevelopmental disorders. These trends call for a larger amount of applied studies that combine basic research with clinical application. In addition, they will hopefully spark a larger interest in transdiagnostic approaches in laterality research focused on altered hemispheric asymmetries in neurodevelopmental and psychiatric disorders. The next two points were (6) investigating the molecular correlates of environmental factors that affect laterality and (7) bridging the gap between laterality research in human subjects and non-human model species. These call for a greater amount of studies that directly compare laterality phenotypes and molecular factors affecting them in human volunteers and non-human model species. Empirical studies testing more than one species using test procedures that are ecologically meaningful for each species are an essential tool in this context. The last three points were (8) utilizing "next-generation" neuroimaging in laterality research, (9) integrating graph-theory and machine learning into laterality research and (10) enhancing ecological validity in laterality research using mobile EEG and smartphone-based data collection. These refer to the utilization of recent methodological developments in laterality research. We conclude that a single lab can hardly tackle any of these challenges alone. Only by addressing them collectively as a transdisciplinary research community, we can further our understanding of left and right in the nervous system.

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